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Association between Salted Seafood Consumption and Biliary Tract Cancer in Patients Living in the Island Regions of Tokyo: Ecological Study Using Population-based Cancer Registry Data

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Abstract

Background: Although salted seafood is a known carcinogen for intestinal tract cancer, its effects on biliary tract cancer remain unclear. We examined salted seafood consumption's associations with biliary tract cancer on islands in Tokyo, where large salted seafood amounts are consumed. **Methods:** Due to the island region's small population, we applied age standardization using an indirect method based on Tokyo's population as the standard population. The standardized incidence ratio was calculated using Tokyo Metropolitan Cancer Registry data from 2013 to 2018. The salted seafood amount consumed was obtained from a nutritional survey conducted on the islands. Spearman's correlation coefficient was calculated between the salted seafood amount consumed and biliary tract cancer's incidence among the islands. **Results:** Six islands were included in this study (Oshima, Niijima, Kouzushima, Miyakejima, Hachijojima, and Ogasawara). The standardized incidence ratio was high in the islands (1.24). Of the six islands, Niijima (1.56) and Hachijojima (1.60) had high standardized incidence ratios, whereas Miyakejima (0.62) and Ogasawara (0.61) had low standardized incidence ratios. We found a positive correlation between the salted seafood amount consumed and biliary tract cancer's standardized incidence ratio (r=0.797, p=0.058). **Conclusion:** Our ecological study suggests that salted seafood consumption may be a risk factor for biliary tract cancer. Further research, including animal studies and case-control studies conducted on the islands of Tokyo, is needed to clarify the association between salted seafood consumption and the incidence of biliary tract cancer.

Keywords: biliary tract neoplasms- diet- dimethylnitrosamine- carcinogen- risk factors

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Introduction

Biliary tract cancers, including intrahepatic, perihilar, and distal cholangiocarcinoma, and gallbladder cancer, are malignant tumors of the bile duct epithelium [1]. The prognosis of biliary tract cancer remains extremely poor; the 5-year survival rate of cholangiocarcinoma is approximately 10% [2-4], and that of gallbladder cancer is only 5% [5, 6]. Early detection is sometimes difficult because the disease progresses rapidly without symptoms [7]. Therefore, primary prevention is crucial in reducing the number of deaths from biliary tract cancer, and identifying the associated risk factors is essential to advancing this effort [8].

The incidence of biliary tract cancer varies widely by region, and environmental factors, especially diet, are important risk factors [9]. Food-related disease states such as obesity and diabetes, metabolic syndrome, alcohol consumption, and smoking have been suggested as risk factors for cholangiocarcinoma [3, 4, 10, 11]. Associations between dietary factors, such as the consumption of betel nuts, processed meat, and fewer vegetables, and cholangiocarcinoma have also been suggested, although the findings are inconsistent [8, 11]. Risk factors for gallbladder cancer such as obesity, smoking and diet are also inconsistent [10, 12].

Nitroso compounds are known carcinogens associated with gastrointestinal cancers such as stomach and colon cancers, and they induce DNA damage by promoting DNA alkylation [13, 14]. While numerous studies have explored the association between nitroso compounds and gastrointestinal cancers [13, 15], evidence of the relationship between exposure to nitroso compounds and biliary tract cancer remains limited. Nitroso compounds are synthesized endogenously in the body and are also ingested from diet, tobacco, and drinking water [13, 15]. Nitrosamines, a type of nitroso compound, are found primarily in cured meat products, smoked products, beer, whiskey, and salted seafood [13-15] and are more abundant in Asian than in Western diets [15]. Given the

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high incidence of biliary tract cancer in Asia [5, 9], we hypothesized that the intake of nitrosamine-rich foods is associated with the incidence of biliary tract cancer.

Several small islands are located approximately 100–1000 km south of central Tokyo. Hiroo Hospital in Tokyo is the core hospital (base hospital) of the emergency medical care system for the island regions, established by the Welfare and Public Health Bureau, and services many patients from the islands. According to the hospital cancer registry, 25 patients with biliary tract cancer from the islands were treated at Hiroo Hospital during the four-year period from April 2016 to March 2020, (crude incidence rate: 23.6/100,000, Tokyo crude incidence rate in 2016: 15.9/100,000; p=0.063). If biliary tract cancer patients from the islands who visited hospitals other than Hiroo Hospital were included, an even higher incidence rate would be expected. Each island on the islands of Tokyo has its own distinct environment, which has led to the development of unique local cultures and diets. The consumption of salted seafood products, such as kusaya and shiokara, is particularly common [16, 17]. Kusaya is salted and dried fish product made exclusively on the islands of Tokyo. It is prepared by dipping fish intermittently and repeatedly over hundreds of years in a brine solution called kusaya-eki, followed by sun-drying [16]. Shiokara is made by fermenting seafood, especially squid, during salting. Japanese salted seafood products contain volatile N-nitrosamines, which reportedly increase during cooking [18] and are consumed daily. Thus, we hypothesized that biliary tract cancer would be more prevalent among patients from the islands of Tokyo.

Therefore, to investigate the possibility that the consumption of nitrosamine-rich foods may increase the risk for biliary tract cancer, we conducted an ecological study on the association between salted seafood products and biliary tract cancer in patients from the island regions.

Materials and Methods

Study design

We conducted an ecological survey on the incidence of biliary tract cancer and the intake of salted seafood products in the island regions of Tokyo from 2013 to 2018. Intrahepatic (International Classification of Disease (ICD)-10 code: C22.1), perihilar (C24.8), and distal cholangiocarcinomas (C24.0) and gallbladder cancer (C23) were defined as biliary tract cancers. Duodenal papillary carcinoma (C24.1) was excluded as it may be histologically derived from the intestinal tract or pancreaticobiliary tract and histologically distinct from cholangiocarcinoma and gallbladder cancer [19]. The diagnosis of biliary tract cancer in Japan is made at all hospitals in accordance with clinical practice guidelines for management of biliary tract cancers [20]. Pathological diagnosis via biliary cytology or biopsy is recommended, though sensitivity is low (59%), and false-negative cases do occur to some extent [20]. When pathology does not confirm the diagnosis, a comprehensive assessment is made based on imaging (e.g., abdominal ultrasound, CT, MRI) and blood tests. There is no difference in diagnostic methods between island regions and the cancer registry. There are nine inhabited islands in the island region of Tokyo, and those with a population of less than 1,000 were excluded due to the small population size.

Biliary tract cancer incidence

The demographics of the islands and Tokyo, including the total population, the number of out-migrants, and the number of in-migrants, were obtained from a demographic survey based on the Basic Resident Registry for the years 2013-2018 [21]. This survey provides data and demographic trends (number of births, deaths, and transfers in and out) on the population each year between January 1 and December 31 based on the Basic Resident Registers. The average age for each island and Tokyo was obtained from the 2015 Population Census of Japan [22]. The Population Census is Japan's most important national statistical survey, covering all people and households in the country and is conducted every five years. We obtained data on the annual number of biliary tract cancer cases, their corresponding ages, and survival information (including year of death for deceased cases) for each island and all regions of Tokyo. This data was sourced from the Tokyo Metropolitan Area Population-Based Cancer Registry for 2013-2015 and the National Population-Based Cancer Registry for 2016-2018. The Tokyo Metropolitan Regional Cancer Registry was launched in 2012 and collects, compiles, and records information on cancers diagnosed in Tokyo [23]. The national cancer registry was established in 2016 and a government initiative requires all cancer information from all hospitals in Japan to be collected, compiled, and recorded in a database [24].

The crude incidence rate was calculated in person-years. The number of person-years of observation was calculated as one person-year for those who did not move or develop biliary tract cancer. Patients who developed biliary tract cancer in 2013 or later and were alive the following year or later were excluded from the person-years of observation. Since the date of relocation or the precise onset of cancer was unknown, the incidence rate was calculated using 0.5 person-years, assuming onset at six months [25]. For each island, the incidence rate per 100,000 persons was calculated by dividing the total number of persons who developed biliary tract cancer during the six years from 2013 to 2018 by the total person-years of observation to minimize bias as much as possible due to the small population size. We applied age standardization using an indirect method based on the Tokyo population as the standard population because of the small population of the islands. The five-year age-specific incidence rates from 2013 to 2018 in Tokyo were used to calculate the expected number of incidences and, subsequently, the standardized incidence ratios for each island. Due to the small number of patients on the islands, gender was not evaluated.

Salted seafood intake

Daily salt intake, seafood intake, and salt content of fish were obtained from the Island Nutrition Survey conducted by the Public Health Centers in 2016, targeting residents aged 20 years and older [26]. On Oshima, Hachijojima, Miyakejima, and Kouzushima, twenty percent of the population was randomly selected by sex and age from the Basic Resident Registry. Due to the small population, fifty percent of the population of the islands of Shikinejima, Niijima, and Ogasawara, and 100 percent of the population of the islands of Toshima, Mikurajima, and Aogashima were included in the study. As a result, 5038 participants were included in the food survey. The survey items were validated using self-administered dietary history questionnaires (BDHQ) [27]. The BDHQ is a simplified version of the Dietary History Questionnaire developed to quantify the eating habits of adults living in Japan over a one-month period [27].

Data on the daily intake of salted seafood products was unavailable, so the average amount of salt contained in the seafood was used as a proxy for the amount of salted seafood products, as raw fish contains little salt [28]. The nutritional intake status in Tokyo was obtained from data from the National Nutrition Survey of 2016 [29]. This is a published annual survey on the physical condition, nutritional intake, and lifestyle of stratified, randomly selected households and household members [30].

Statistical analyses

Spearman's correlation coefficient was calculated to estimate the association between the standardized incidence ratio of biliary tract cancer and the amount of salt in seafood. Scatter plots were drawn based on a standardized incidence ratio in relation to the amount of salt contained in the seafood per island. All data analyses were performed using Stata 16.1 (Collage Station, TX, 2022).

Results

Initially, the environmental conditions, population demographics, and medical resources of the six islands were assessed (Table 1). The number of physicians per 1,000 population per island ranged from 0.86 (Oshima, nearest island to Tokyo) to 1.55 (Ogasawara, farthest island from Tokyo), with no significant difference (p=0.36). The highest amount of salt contained in seafood was found in Niijima and Kouzushima (1.5 g/day), and the lowest in Ogasawara (1.0 g/day), which was higher than the average amount of salt contained in seafood in Tokyo (0.6 g/day).

Between 2013 and 2018, a total of 51 patients were diagnosed with biliary tract cancer across the six islands (Table 2). The mean crude incidence rate of the six islands was 31.8/100,000 person-years, significantly higher than the mean crude incidence rate in Tokyo (16.7/100,000 person-years) (p<0.001). Also, the standardized incidence ratio was high in the island regions (1.24). Among the six islands, Niijima (1.56), Kouzushima (1.16), and Hachijojima (1.60) showed high standardized incidence ratios using the Tokyo population as the standard population, while Miyakejima (0.62) and Ogasawara (0.61) showed low standardized incidence ratios.

A scatter plot illustrating the relationship between the salt content in seafood and the standardized incidence of biliary tract cancer demonstrated a linear correlation (Figure 1). Spearman's rank correlation coefficients

Table 1. Characteristics of Six Islands

	Area(km^2)	Distance from Tokyo(km)	Access(min)		Population[1]	Average age	Medical environment		Nutritional intake status(g/day)		
			By air	By ship			Number of hospitals	Number of doctors	salt intake[2]	seafood intake[2]	salt contained in seafood
Oshima	90.8	120	25	105	8178	51.1	1	7	11.8	96.1	1.4
Niijima	27.5	145	35	140	2818	53.0	2	4	11.5	99.5	1.5
Kouzushima	18.6	167	45	225	1927	47.8	1	2	11.8	98.9	1.5
Miyakejima	55.4	173	50	360	2618	54.1	1	3	11.0	85.2	1.2
Hachijojima	69.1	281	55	620	7834	52.1	2	8	11.5	93.3	1.4
Ogasawara	104.4	978	-	1440	2587	40.9	2	4	10.7	72.5	1.0
Tokyo	2190.1	-	-	-	13415349	44.7	-	-	9.9	58.6	0.6

[1], Population as of 2016; [2], The mean for salt and seafood intake

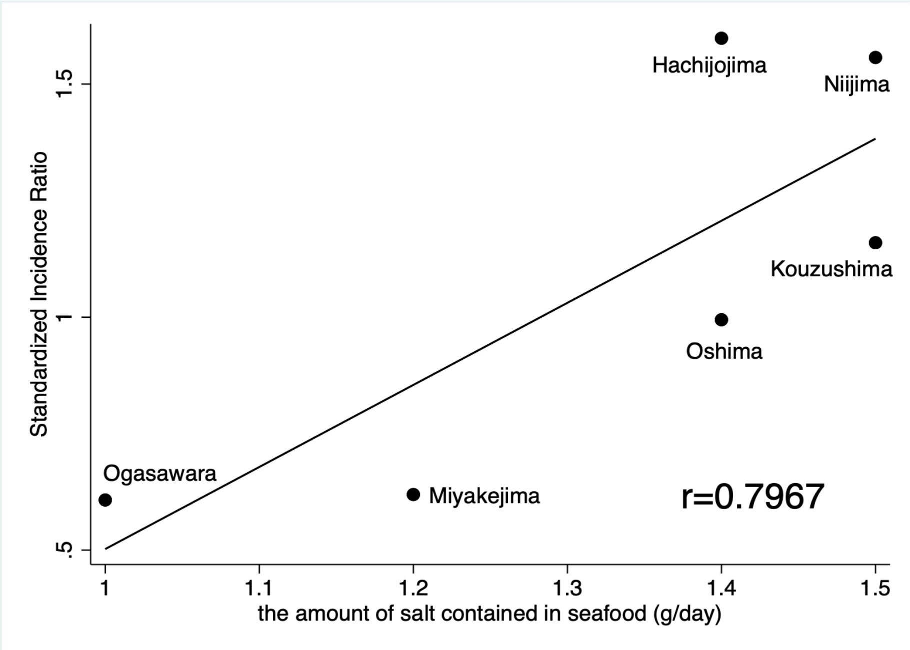

Figure 1. Correlation between Amount of Salt Contained in Seafood and Standardized Incidence Ratio of each Island Region. Since salt is rarely found in raw fish and is mainly obtained from processed (salted) products, we used the amount of salt contained in seafood as a proxy for the intake of salted seafood products.

Table 2. Characteristics of Patients in Six Islands

	Oshima	Niijima	Kouzushima	Miyakejima	Hachijojima	Ogasawara	All islands
Number of patients	13	8	3	3	21	1	51
Male(%)	9 (69.2)	5 (62.5)	0 (0)	2 (66.7)	13 (61.9)	1 (100)	31 (60.8)
Age (mean)	76.1 (10.9)	73.5 (12.4)	69.7 (26.6)	74.0 (6.9)	78.3 (10.9)	69.0	76.1 (12.1)
Person-years	48693.0	16961.5	11538.0	15813.0	46861.5	15568.0	162244.5
Crude incidence rate[1]	26.7	47.2	26.0	19.0	44.8	6.4	31.8
Standardized incidence ratio[2]	0.99	1.56	1.16	0.62	1.60	0.61	1.24

[1], per 100,000 person-years; [2], Standardized incidence ratio was calculated indirectly using the population of Tokyo as the standard population

between salt intake, seafood intake, amount of salt contained in seafood, and the standardized incidence ratio of biliary tract cancer are shown in Table 3. There was a positive but not significant correlation between salt content in seafood and the standardized incidence ratio of biliary tract cancer (r=0.797, p=0.058).

Discussion

This study examined the association between the intake of salted seafood products and biliary tract cancer in patients living in the island regions of Tokyo. We found a positive correlation between the amount of salt in seafood and biliary tract cancer, although at an ecological level. The lack of significant difference could be due to the small number of cases in this study (number of islands: 6), which may have resulted in a lack of power.

Salted seafood is a potential carcinogen; however, the consumption of salt or seafood itself does not increase the risk of cancer [14, 31, 32]. Salted seafood, such as Chinese-style salted fish, contains high levels of carcinogenic nitroso compounds, which are considered a risk factor for nasopharyngeal cancer and are listed as Group 1 carcinogens by the International Agency for Research on Cancer [33]. Exposure to nitroso compounds during childhood has been implicated in carcinogenesis, and furthermore, prolonged or repeated exposure has been reported to increase the risk of cancer [34].

Table 3. Spearman's Rank Correlation Coefficient

	Standardized incidence ratio	Salt intake	Seafood intake	Amount of salt c ontained in seafood
Standardized incidence ratio	1.000			
Salt intake	0.634	1.000		
Seafood intake	0.745	0.931*	1.000	
Amount of salt contained in seafood	0.797	0.922*	0.993*	1.000

*p<0.01

Previous studies have reported an association between salted seafood and gastric and colorectal cancer [17, 35]; however, the association between salted seafood and biliary tract cancer had rarely been reported and remained controversial [36, 37]. A case-control study in China showed that salted meat and salted fish were associated with an increased risk of gallbladder cancer (odds ratio: 1.18, 95% confidence interval: 1.02-1.37) and cholangiocarcinoma (odds ratio:1.19, 95% confidence interval:1.01-1.39) [37]. On the other hand, in a case-control study in Niigata, Japan, consumption of salted seafood reduced the risk of biliary tract cancer (odds ratio: 0.43, 95% confidence interval 0.24-0.76) [36]. One possible reason for the divergence between the positive correlation for China and the Tokyo Islands and the inverse correlation for Niigata could be the difference in the type of salted seafood products. In Niigata, shiokara (a dish made with squid and fish roe) is commonly eaten [38], but its dimethylnitrosamine content is relatively low, at approximately 3.5 μg/kg [18]. On the other hand, the amount of dimethylnitrosamine in Chinese-style salted seafood products was reported to be 373 μg/kg [39]. Chinese-style salted fish is a fermented food made by salting fish, semi-fermenting them, and drying them in the sun [39], similar to the preparation method of kusaya and its distinctive fermented smell, which is consumed on the islands of Tokyo [16]. It has been reported that kusaya-eki contains high levels of dimethylamine (26-77 mg/L) [40, 41], a precursor of dimethylnitrosamine [42], which is much higher than the average level of dimethylamine in Japanese dried fish (14 mg/kg) [43]. The dimethylnitrosamine content in Japanese dried fish is reported to range from 0.6 to 9.9 μg/kg when uncooked and from 3.3 to 37.5 μg/kg when boiled with city gas [18]. Although the dimethylnitrosamine content in kusaya has not been reported, it is speculated that kusaya may contain higher concentrations of nitrosamines than Japanese dried fish.

Several limitations are recognized in this paper. First, this was an ecological study using island-specific data, and the actual intake of salted seafood was unknown (i.e., ecological fallacy). Ecological studies are used when individual-level data are unavailable or when examining population-level effects of exposure to a disease [44]. They are an efficient means of generating hypotheses before conducting more costly individual-level studies and are well-established for suggesting possible epidemiological associations [45]. However, individual-level studies are warranted to investigate the association between the intake of salted seafood and the incidence of biliary tract cancer, including childhood intake of salted seafood and years of residence in the region. Second, it is unclear whether there are any other known risks or genetic factors. We did not adjust for lifestyle and epidemiological factors other than age, such as BMI, smoking, or alcohol consumption, and could not rule out the possibility that factors other than salted seafood products were involved. Third, because the amount of nitroso compounds ingested was not measured, further clarification is needed on whether nitroso compounds are really the cause of the higher incidence rate. In the future, it will be necessary to measure the amount of nitroso compounds contained in the salted seafood consumed on the islands. Fourth, this study included only six islands and 51 patients. This limited sample size may reduce the statistical power of the study and its ability to detect significant associations, highlighting the need to accumulate more cases. Fifth, in this study, salt content in seafood was used as a proxy for actual salted seafood consumption. This indirect measure may not accurately capture individual consumption patterns or account for variations in the types of salted seafood consumed and their preparation methods. Sixth, because dietary intake data rely on dietary surveys and self-reported information, recall bias and misclassification may occur, potentially affecting the accuracy of reported associations.

Larger studies with a greater number of accumulated cases are needed to further confirm the association between the consumption of salted seafood products and the incidence of biliary tract cancer. Animal studies using Chinese-style salted fish, a known risk factor for nasopharyngeal cancer, have demonstrated carcinogenesis when fed to rats [46]. Similar animal studies using salted seafood products such as kusaya, which is commonly consumed on the islands of Tokyo, are needed. Additionally, since the incidence rate of biliary tract cancer is low, conducting cohort studies is challenging, making a case-control study in the islands of Tokyo warranted. The average per capita intake of salted seafood products in Tokyo was reported to be 14.9 g /day (standard deviation 29.0) [29]. Assuming that the intake of salted fish products is twice that of Tokyo on the islands, approximately N=120 (60 biliary tract cancers, 60 controls) would be required (α error 0.05, power 0.8). In this study, 51 biliary tract cancers were identified over 6 years, and based on the sample size, a case-control study on islands is feasible.

We found a marginal but positive correlation between the amount of salt in seafood and biliary tract cancer, although this was observed at an ecological level. Our results suggest that salted seafood consumption may be a risk factor for biliary tract cancer. Further animal studies and case-control studies are needed to clarify the association between the consumption of salted seafood products and the incidence of biliary tract cancer.

Author Contribution Statement

Eiko Okamoto: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, and writing of the original draft. Yuri Ito: Methodology, supervision, writing-review and editing. Shuhei Terada: Formal analysis, writing of the original draft. Takeo Fujiwara: Conceptualization, formal analysis, methodology, project administration, supervision, writing-review and editing

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Approval

This study was not approved by any scientific Body and it was not part of an approved student thesis.

Data availability

Only publicly available data were used in our study, and the data sources and handling of these data are described in Methods.

Study registration

This study was not registered in any registration dataset (for clinical trials, guidelines, or meta-analysis).

Ethics approval

This ecological study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Tokyo Metropolitan Hiroo Hospital (Approval Number: Jin-1).

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