



Fish Intake and Death From Pulmonary Embolisms Among Japanese Men and Women — The Japan Collaborative Cohort (JACC) Study —

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Background: Numerous studies have reported the association of cardiovascular risk factors with pulmonary embolism (PE), but the association of dietary factors, especially fish intake, with the risk of PE has not been fully established.

Methods and Results: Using a prospective design, we studied the risk of PE mortality in relation to fish intake in 90,791 community-dwelling men and women in Japan aged 40–79 years. The hazard ratios (HRs) and 95% confidence intervals (CIs) for PE death were estimated using the Cox proportional hazards model. Compared with participants in the lowest fresh fish intake group (<1 time/month), the HRs (95% CIs) for PE death for those in the other intake groups were 0.35 (0.08–1.59) for 1–2 times/month, 0.19 (0.05–0.69) for 1–2 times/week, 0.20 (0.06–0.74) for 3–4 times/week, and 0.18 (0.05–0.66) for fish intake every day. In addition to these findings, compared with the participants in the lowest 10% of ω 3 polyunsaturated fatty acid intake, those in the other groups had a 60–76% lower risk of PE death.

Conclusions: Fresh fish intake, even 1–2 times/week, is associated with a lower risk of death from PE among Japanese men and women.

Key Words: Diet; Epidemiology; Prospective cohort study; Risk factors; Venous thromboembolism

Pulmonary embolism (PE) is a common clinical condition with considerable associated morbidity and mortality, especially in Europe and North America: reported incidence rates for PE range from 45 to 65 per 100,000 person-years.^{1–4} Conversely, Asians have a strikingly lower prevalence of both deep venous thrombosis (DVT) and PE.^{5,6} In Japan, although the annual incidence rate of PE was estimated to be 12.6 per 100,000 persons in 2011,⁷ the number of patients with PE has increased 4.6-fold in the past 15 years.⁷

Dietary intake may be one plausible explanation for the differences in the morbidity and mortality rates of PE between Western countries and Japan. Previous epidemiological studies have shown that factor VIII coagulant activity (FVIIIc), von Willebrand factor (vWF), platelet aggregation, and homocysteine levels are associated with the incidence of DVT and PE,^{8,9} and these factors may be affected by dietary intake.¹⁰ In the Longitudinal Investigation of Thromboembolism Etiology (LITE) study of 14,962 middle-aged whites and blacks, red and processed meat and a Western diet pattern were positively

associated with the incidence of venous thromboembolism (VTE), while consumption of 4 or more servings of fruit and vegetables per day, or at least 1 serving of fish per week, was associated with lower incidence of VTE.¹¹ Because the average fish intake among the Japanese is 3–4-fold higher than that of Americans,¹² the low mortality rate from PE in the Japanese population may be attributable to a high intake of dietary fish. No observational study, however, has reported an association between diet and PE among Asians.

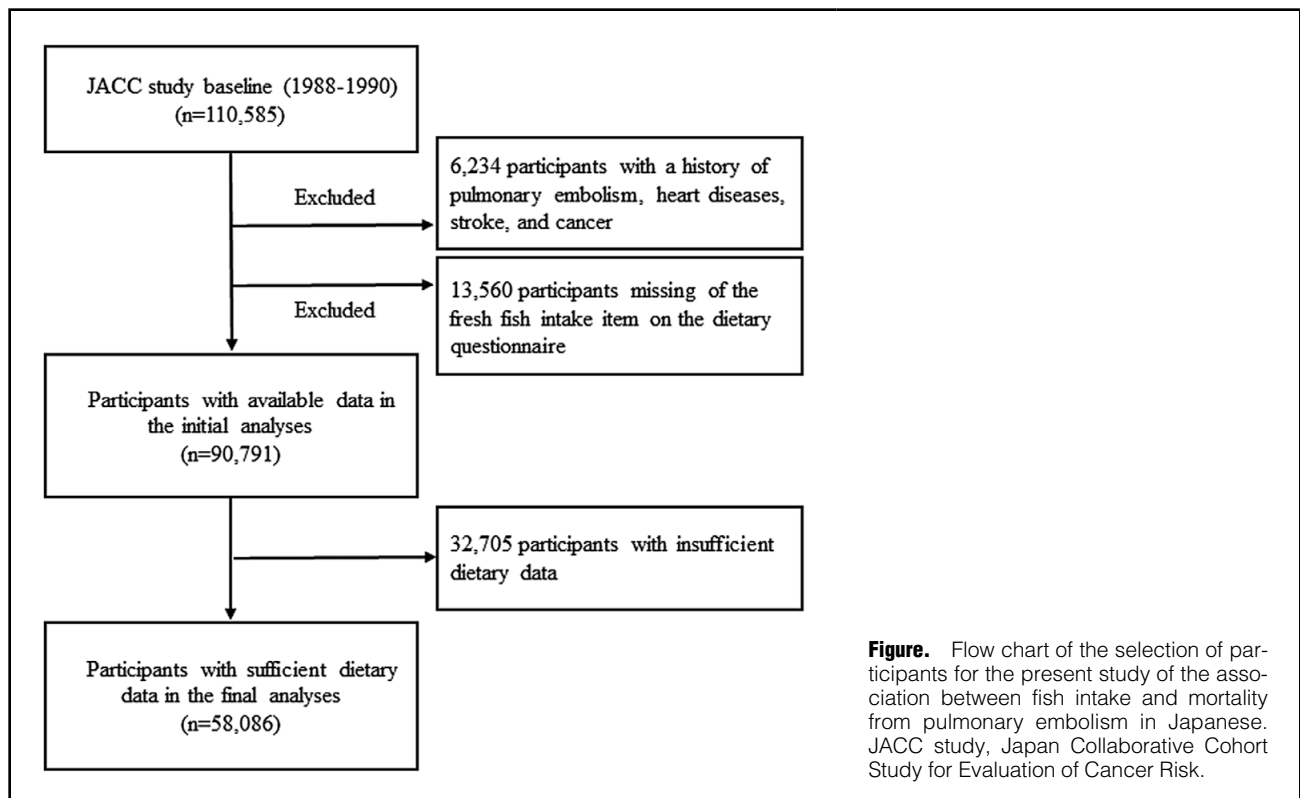
We therefore sought to examine the associations between dietary intake of fish and PE death using data from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC), a nationwide community-based follow-up study of cardiovascular disease with one of the largest subject cohorts in Asia. Our a priori hypothesis was that fish and/or ω 3 polyunsaturated fatty acid (PUFA) intake would be associated with a lower risk of PE death within a population with a high mean fish intake.

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Methods

Study Population and Design

The JACC study design and methods have been described in detail elsewhere.^{13,14} In brief, the JACC study comprised a nationwide community-based sample of 110,585 persons (46,395 men and 64,190 women) aged 40–79 years, from 45 administrative districts of Japan. In 22 of the 45 areas, all residents living in a given target area were regarded as study subjects, and participants completed self-administered questionnaires concerning their lifestyles and medical histories of previous cardiovascular disease or cancer during the baseline period (1988–1990). We excluded participants with a baseline history of PE, heart disease (ischemic heart disease, arrhythmia, heart failure, or unspecified heart disease), stroke, or cancer ($n=6,234$). We also excluded those missing the fresh fish intake item on the dietary questionnaire ($n=13,560$). The remaining 90,791 men and women were included in the initial analyses (**Figure**). Among the participants who were missing the fresh fish intake item, 7 died from PE during the follow-up period. There was no difference in the mortality rate for PE between the participants who did and did not report the fresh fish intake item. Written or explicit verbal informed consent was obtained before participants completed the questionnaire. In most communities, informed consent was obtained from each participant, except in a few study areas where informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders. The study design and informed consent procedures were approved by the Ethics Review Committee of Nagoya University School of Medicine.

Mortality Surveillance

In each community, investigators conducted a systematic review of death certificates. Registration of death is legally required in Japan and is believed to be consistent across the country. The cause and date of death among the study participants were identified by reviewing all death certificates in each area with the permission of the Director-General of the Prime Minister's Office (Ministry of Internal Affairs and Communications). Those who moved out of a study area were censored. We followed the subjects until the end of 2009, except in the 7 areas where follow-up was discontinued at the end of 1999 or 2003. The median follow-up period for the participants was 19.2 years. We used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) to identify the PE death (I26) endpoint.

Fish and ω 3 PUFA Intake

The frequency of intake of various food items was obtained at baseline by questionnaire. The food frequency questionnaire (FFQ) included 33 foods, with 4 fish items: fresh fish, kamaboko (steamed fish paste), dried or salted fish, and deep-fried foods or tempura (a common form of deep-fried fish or shellfish). Data regarding fruit, vegetable, and meat intake were also used for potential confounding dietary variables. The reproducibility and validity of the FFQ have been reported elsewhere.^{15–17} Five choices were presented for each item: rarely, 1–2 days/month, 1–2 days/week, 3–4 days/week, and almost every day. These choices were converted to scores of 0 (0/30 days), 0.05 (1.5/30 days), 0.214 (1.5/7 days), 0.5 (3.5/7 days), and 1 (30/30 days), respectively. The portion size was estimated by a previous

Table 1. Baseline Characteristics of Participants Who Did or Did Not Develop Incident Fatal PE (JACC)

Baseline characteristics [#]	Total (n=90,791)			Participants with sufficient dietary data (n=58,086)		
	PE (n=61)	No PE (n=90,730)	P value	PE (n=39)	No PE (n=58,047)	P value
Incidence rate (/100,000 person-years)	4.1			4.1		
Age (years)*	60.5	57.2	0.01	59.5	56.1	0.03
Sex (% women)**	57.2	58.2	0.87	61.3	60.5	0.93
Body mass index (kg/m ²)	23.2	22.8	0.22	23.4	22.8	0.23
Hypertension (%)	31.6	19.4	0.01	35.3	18.9	0.01
Diabetes mellitus (%)	5.9	4.6	0.62	7.1	4.2	0.37
Current smoker (%)	25.1	24.0	0.81	24.5	23.3	0.83
Current drinker (%)	43.7	46.8	0.58	39.6	44.4	0.50
Fresh fish intake (% rarely)	8.0	1.7	<0.001	7.5	1.5	0.002

Sample sizes vary somewhat among characteristics examined because of missing data. *Sex-adjusted, **age-adjusted, #age- and sex-adjusted. PE, pulmonary embolism.

validation study¹⁵ and assigned as 63 g for fresh fish, 20 g for steamed fish paste, 29 g for dried or salted fish, and 29 g for deep-fried fish, which was estimated as 26% of 113 g for deep-fried foods or tempura based on dietary records from the validation study.¹⁵ The consumption of fish (g/day) was calculated by multiplying the frequency scores and portion sizes and summing these across the 4 items.

The values for nutrient and fatty acid intake were estimated based on the 4th version of the Japan Food Table.¹⁵ The values of ω 3 PUFA, including non-long-chain ω 3 PUFA, assigned for 1 portion were the following: 1.009 g for fresh fish, 0.042 g for steamed fish paste, 0.544 g for dried or salted fish, 0.929 g for deep-fried foods or tempura, 0.357 g for fried vegetables, 0.230 g for boiled beans, and 0.184 g for miso soup. The total amount of nutrients consumed was calculated by multiplying the frequency scores and estimated nutrients for each portion and summing this across all 33 items. Data on fish oil supplementation were not available in the baseline survey, but supplement use was not common among Japanese adults. The details of the validation study and methods for the estimation of nutrient factors were also reported previously.¹⁵

Participants missing the fresh fish intake item and subjects missing more than 1 of the other 3 fish items were excluded when estimating fish or ω 3 PUFA intake. Furthermore, participants with a missing response to more than 4 of the 33 items on the FFQ were also excluded. The remaining eligible 58,086 participants (22,919 men and 35,167 women) were included in the final analysis. Energy adjustments were applied for dietary intakes using the nutrient residual model.¹⁸

Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m²), where weight and height were obtained from the baseline questionnaire. Histories of hypertension and diabetes were also derived from the baseline questionnaire.

Statistical Analysis

The age- and sex-adjusted mean or prevalence of baseline variables of interest were compared between participants with and without PE, using analysis of covariance (ANCOVA) or logistic regression models.¹⁹ For each participant, we calculated the person-years of follow-up from baseline between 1988 and 1990 to the first endpoint: death,

moving from the community, or the end of 2009. Mortality rates for PE were estimated according to frequency of fish intake and quintiles of intake of ω 3 PUFA. The hazard ratios (HRs) and 95% confidence intervals (CI) of PE death were estimated using a Cox proportional hazards model. We first estimated age- and sex-adjusted HRs for fresh fish intake and other factors previously associated with PE, including BMI (quintiles), history of hypertension and diabetes mellitus (yes or no), smoking status (never, former smoker, and current smoker of 1–19 or \geq 20 cigarettes/day), alcohol intake (never, former drinker, and current drinker of ethanol at 1–22, 23–45, 46–68, or \geq 69 g/day; with 23 g of ethanol corresponding to 1 'go', a traditional Japanese unit for volume), fruit, vegetable, and meat intake, and continuous values for total energy intake. In the multivariable-adjusted model, adjustments were made for age (years), sex, BMI, and other potential factors detected by the age- and sex-adjusted model. Furthermore, to explore competing risks,²⁰ subdistribution HRs were obtained using Cox regression models for PE death vs. cardiovascular and non-cardiovascular death (n=11,469). We used SAS version 9.4 (SAS Institute, Cary, NC, USA) for the analyses. All probability values for statistical tests were two-tailed, and values of P<0.05 were regarded as statistically significant.

Results

Among the 90,791 men and women followed for a median of 19.2 years, we documented 61 deaths caused by PE. **Table 1** shows the mean or prevalence of risk characteristics at baseline for fatal cases of PE and for the remaining study cohort from the total participants and participants with sufficient dietary data. The mean age and prevalence of hypertension were significantly higher among people who died of PE than in those who did not, but there were no significant differences in mean BMI, prevalence of diabetes mellitus, or current smoking or drinking status between the groups; these associations were essentially the same in both the total participants and participants with sufficient dietary data. There were no differences in baseline risk factors, such as hypertension and diabetes mellitus, between participants who responded to the FFQ and those who did not, although there were some differences in mean age between those who did and did not.

As there was no observed effect of sex on the association between fish or ω 3 PUFA intake and PE death, we combined men and women for further analyses. Among the 90,791 men and women, the age- and sex-adjusted HRs of PE death were reduced according to the frequency of fresh fish intake. Compared with the participants in the lowest fresh fish intake group (<1 time/month), the adjusted HRs (95% CI) of PE for those in the other groups were 0.28 (0.08–0.99) for 1–2 times/month, 0.23 (0.08–0.61) for 1–2 times/week, 0.19 (0.07–0.51) for 3–4 times/week, and 0.19 (0.07–0.54) for every day. Among the 58,086 men and women with sufficient dietary data, we observed an inverse association between fresh fish intake and the risk of dying from PE (Table 2). The age- and sex-adjusted HRs (95% CI) of PE for the participants in the 1–2 times/month, 1–2 times/week, 3–4 times/week, and daily fresh fish intake groups were 0.36 (0.08–1.60), 0.18 (0.05–0.65), 0.20 (0.05–0.70), and 0.19 (0.05–0.71), respectively, compared with those in the lowest fresh fish intake group (<1 time/month). The HRs were unchanged by additional adjustments of BMI, hypertension, and fruit intake. The HRs were also unchanged after further adjustments for

other potential confounding factors: area (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu) and residence (urban or rural). When we further analyzed the associations between fish intake and PE death, stratified by age group, the associations were somewhat stronger in the younger age group. Compared with those in the lowest fresh fish intake group (<1 time/month), the age- and sex-adjusted HRs (95% CI) of PE for the participants in the 1–2 times/month, 1–2 times/week, 3–4 times/week, and daily fresh fish intake groups were 0.37 (0.06–2.26), 0.07 (0.01–0.43), 0.11 (0.02–0.58), and 0.14 (0.03–0.71), respectively, for the age <60 years group, and 0.29 (0.02–4.61), 0.42 (0.05–3.46), 0.36 (0.04–2.99), and 0.27 (0.03–2.30), respectively, for the age \geq 60 years group.

Furthermore, the association between fresh fish intake and PE death was also unchanged in the competing risk analysis: the multivariable-adjusted subdistribution HRs (95% CI) of PE for the participants in the 1–2 times/month, 1–2 times/week, 3–4 times/week, and daily fresh fish intake groups were 0.36 (0.08–1.56), 0.18 (0.05–0.64), 0.19 (0.05–0.67), and 0.18 (0.05–0.66), respectively, compared with those in the lowest fresh fish intake group.

Variable	No. at risk	No. of cases	Person-years of follow-up	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)
Body mass index (kg/m²)					
Q1 (<20.31)	10,767	5	169,564	1	1
Q2 (20.31–21.91)	11,301	8	187,076	1.55 (0.51–4.74)	1.49 (0.49–4.56)
Q3 (21.91–23.34)	11,315	7	188,976	1.36 (0.43–4.30)	1.21 (0.38–3.84)
Q4 (23.34–25.11)	11,277	7	189,070	1.38 (0.44–4.38)	1.22 (0.38–3.86)
Q5 (\geq 25.11)	11,297	11	189,720	2.11 (0.73–6.09)	1.70 (0.58–4.96)
Hypertension					
No	47,127	24	790,163	1	1
Yes	10,959	15	167,072	2.39 (1.22–4.69)	2.32 (1.17–4.61)
Diabetes mellitus					
No	55,642	36	922,977	1	
Yes	2,444	3	34,258	2.02 (0.61–6.66)	
Smoking status					
Never/former	44,559	30	739,648	1	
Current	13,527	9	217,587	1.41 (0.55–3.63)	
Drinking status					
Never/former	31,424	23	517,259	1	
Current (ethanol <46 g/day)	17,596	7	292,419	0.60 (0.24–1.50)	
Current (ethanol \geq 46 g/day)	7,473	7	121,394	1.51 (0.50–4.53)	
Fresh fish intake					
Rarely	893	3	14,200	1	1
1–2 times/month	3,958	4	63,254	0.36 (0.08–1.60)	0.36 (0.08–1.61)
1–2 times/week	19,139	10	311,304	0.18 (0.05–0.65)	0.18 (0.05–0.65)
3–4 times/week	18,467	11	303,804	0.20 (0.05–0.70)	0.19 (0.05–0.67)
Every day	15,629	11	264,673	0.19 (0.05–0.71)	0.17 (0.05–0.64)
Dried or salted fish intake					
Rarely	5,469	6	81,568	1	
1–2 times/month	14,247	10	230,275	0.70 (0.26–1.95)	
1–2 times/week	22,200	14	372,297	0.56 (0.21–1.48)	
3–4 times/week	10,480	4	177,698	0.31 (0.09–1.11)	
Every day	5,054	5	86,063	0.70 (0.21–2.41)	

(Table 2 continued the next page.)

Variable	No. at risk	No. of cases	Person-years of follow-up	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)
Steamed fish paste intake					
Rarely	13,183	9	215,498	1	
1–2 times/month	18,739	12	309,846	1.11 (0.49–2.51)	
1–2 times/week	15,182	9	247,691	1.01 (0.42–2.44)	
3–4 times/week	5,256	4	86,645	1.20 (0.38–3.83)	
Every day	1,392	3	22,834	3.20 (0.87–11.8)	
Deep-fried fish intake					
Rarely	2,192	2	33,192	1	
1–2 times/month	14,422	11	231,031	1.18 (0.26–5.31)	
1–2 times/week	28,019	16	463,131	0.81 (0.19–3.52)	
3–4 times/week	10,396	8	177,353	0.98 (0.21–4.70)	
Every day	2,338	2	40,827	0.96 (0.13–7.14)	
Vegetable intake (g/day)					
Q1 (<54.6)	11,598	10	188,508	1	
Q2 (54.6–80.4)	11,599	4	191,580	0.38 (0.12–1.22)	
Q3 (80.4–108.0)	11,599	5	192,411	0.45 (0.15–1.33)	
Q4 (108.0–144.6)	11,599	8	193,491	0.68 (0.27–1.75)	
Q5 (≥144.6)	11,598	12	189,749	1.00 (0.42–2.34)	
Fruit intake (g/day)					
Q1 (<57.1)	11,615	6	188,666	1	1
Q2 (57.1–109.9)	11,616	5	192,391	0.82 (0.25–2.68)	0.86 (0.26–2.83)
Q3 (109.9–147.9)	11,616	5	193,885	0.80 (0.24–2.64)	0.88 (0.27–2.90)
Q4 (147.9–204.5)	11,616	7	191,779	1.15 (0.38–3.44)	1.26 (0.42–3.80)
Q5 (≥204.5)	11,615	16	190,386	2.75 (1.07–7.11)	2.96 (1.14–7.70)
Meat intake (g/day)					
Q1 (<12.7)	10,334	6	165,477	1	
Q2 (12.8–22.9)	11,302	10	184,849	1.57 (0.57–4.34)	
Q3 (22.9–33.0)	11,448	7	190,297	1.09 (0.36–3.28)	
Q4 (33.0–47.5)	11,568	5	191,194	0.79 (0.24–2.64)	
Q5 (≥47.5)	11,209	9	186,002	1.36 (0.46–4.03)	

Sample sizes vary somewhat among characteristics examined because of missing data. *Adjusted for age, sex, body mass index, history of hypertension, fish intake, and fruit intake. CIs, confidence intervals; HRs, hazard ratios; JACC study, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; PE, pulmonary embolism.

Table 3. Age-, Sex-Adjusted, and Multivariable-Adjusted HRs and 95% CIs of Death From PE According to ω3 PUFA Intake Among 58,086 Men and Women (JACC 1988–2009)						
Variable	Median (g/day)	No. at risk	No. of cases	Person-years of follow-up	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)
ω3 PUFA intake						
<10th	0.8	5,808	8	89,436	1	1
10th–19th	1.1	5,808	2	92,002	0.24 (0.05–1.12)	0.23 (0.05–1.08)
20th–39th	1.3	11,617	6	189,069	0.33 (0.11–0.94)	0.30 (0.10–0.88)
40th–59th	1.6	11,617	8	194,271	0.40 (0.15–1.07)	0.36 (0.13–0.98)
60th–79th	1.9	11,617	8	196,480	0.38 (0.14–1.02)	0.33 (0.12–0.89)
≥80th	2.4	11,617	7	195,948	0.31 (0.11–0.86)	0.26 (0.09–0.74)
<10th vs. ≥10th					0.34 (0.16–0.75)	0.31 (0.14–0.67)

*Adjusted for age, sex, body mass index, history of hypertension, and fruit intake. PUFA, polyunsaturated fatty acids. Other abbreviations as in Table 2.

Dried or salted fish intake also tended to be associated with a decreased risk of PE death, but the associations were not as marked as those seen with fresh fish intake. The HRs (95% CI) of PE death associated with frequency of dried or salted fish intake were 1.0 (<1 time/month: reference cohort), 0.70 (0.26–1.95) for 1–2 times/month, 0.56 (0.21–1.48) for 1–2 times/week, 0.31 (0.09–1.11) for

3–4 times/week, and 0.70 (0.21–2.41) for every day. There was no significant association between either steamed fish paste or deep-fried fish intake and the risk of PE death, and the highest quintile of fruit intake was associated with PE death risk (Table 2). Diabetes mellitus, smoking, drinking, self-reported BMI, and vegetable and meat intake were not related to the risk of dying from PE.

Table 3 presents the HRs of PE death according to dietary intake of ω 3 PUFA: ω 3 PUFA intake tended to be inversely associated with age- and sex-adjusted risk of PE death. Compared with participants in the lowest 10% of ω 3 PUFA intake, those in the other groups had a 60–76% lower risk of PE death, suggesting a threshold pattern effect; the age- and sex-adjusted HR of the \geq 10th vs. <10th percentiles was 0.34 (0.16–0.75). The association between ω 3 PUFA and PE death was virtually unchanged after adjustment for covariates. Furthermore, the association between ω 3 PUFA intake and PE death was unchanged in the competing risk analysis: the multivariable-adjusted subdistribution HRs (95% CI) of PE for the participants in the \geq 10th percentile was 0.31 (0.14–0.71), compared with those in the <10th percentile.

Discussion

This population-based prospective study found that a greater intake of fresh fish, even at a frequency of 1–2 times per week, was associated with a lower risk of PE death among Japanese men and women, and no such association with other dietary factors was found. Because the average fish intake of the Japanese population is high compared with that in Western countries, greater fish intake among Japanese may contribute in part to the low mortality rate for PE in Japan.

Fish intake is hypothesized to reduce DVT and PE risks by altering coagulation factors, although the data are very limited and there are few observational studies of fish intake and VTE.^{11,21–23} In the LITE study of 14,962 whites and blacks aged 45–64 years, eating \geq 0.1 servings of fish per day (or \geq 1 serving per week for quintiles 2–5) was associated with a 30–45% lower risk of VTE than eating <0.1 servings of fish per day. This suggests a threshold pattern effect, but not a linear trend (P for trend=0.30).¹¹ Conversely, compared with eating <2.5 servings per day of fruit and vegetables, eating \geq 2.5 servings per day was associated with a 27–53% lower risk of VTE, and a linear trend association was observed; HRs (95% CI) of VTE incidence across quintiles of fruit and vegetable intake were 1.0 (reference cohort), 0.73 (0.48–1.11), 0.57 (0.37–0.90), 0.47 (0.29–0.77), and 0.59 (0.36–0.99) (P for trend=0.03).¹¹ However, the Iowa Women's Health Study of 40,377 white (99%) women aged 55–69 years showed no significant association between dietary factors (such as fish, ω 3 PUFA, or fruit and vegetables) and risk of VTE.²¹ In the present study, we found \geq 1 serving of fresh fish per week was associated with reduced the risk of PE death; we also observed a threshold pattern effect in the association between fish and ω 3 PUFA intake and PE death. This finding is consistent with the LITE study. On the other hand, the highest quintile group of fruit intake had a higher risk of PE death, compared with lowest quintile group, in the present study. The estimated fruit intake included both fruit and fruit juice in the present study, and this may lead to the positive association between fruit intake and PE death because excessive fruit juice intake is associated with an increased risk of metabolic syndrome,²² which is a risk factor for VTE and PE.²³ Indeed, when we analyzed separately the associations of fruit intake and fruit juice intake with PE death, excessive fruit juice intake, but not fruit intake, was associated with increased risk of PE death. Compared with those in the lowest fruit juice intake group (<1 time/month), the age- and sex-adjusted HRs (95% CI) of PE for

the participants in the 1–2times/month, 1–2times/week, 3–4times/week, and daily fruit juice intake groups were 1.42 (0.48–4.23), 1.61 (0.60–4.34), 1.23 (0.39–3.89), and 3.05 (1.20–7.77), respectively.

Recently, 2 prospective studies reported on the associations of dietary intake with the incidence of VTE.^{24–26} In the Tromsø Study, a healthy dietary pattern, including fish, vegetables and fruit intake, was not associated with the incidence of VTE among 18,062 men and women aged 25–69 years in Norway, whereas this dietary pattern was associated with a 17% reduced risk of myocardial infarction.²⁴ Further, that study reported more recently that persons who ate fish \geq 3times/week had a 22% lower risk of VTE than those who consumed fish 1–1.9times/week, although statistical significance was borderline (multivariable HR 0.78; 95% CI 0.60, 1.01; P=0.06).²⁵ The Nurses' Health Study and Health Professionals Follow-up study reported that a "Western dietary pattern" with a high intake of red meat, dessert, sweets, French fries, and high-fat dairy products, was associated with an increased risk of VTE, although fat, fruits, vegetables, fish, and ω 3 fatty acid were not associated with incidence of VTE.²⁶ Because the average fish intake among the Japanese is 3–4-fold higher than that of Americans,^{12,27} the participants in the previous study tended to eat a lower volume of fish compared with the participants in our study, even if they were grouped within the highest quintile of fish intake. This may explain the discrepancy in the results between our study and previous studies in Western countries.

The mechanisms by which high fish intake might decrease the risk of PE have not been fully elucidated. However, the beneficial effects of fish and ω 3 PUFA intake on coronary artery disease (CAD) risk factors have been previously reported.^{12,28} Fish and ω 3 PUFA intake are associated with inhibited platelet aggregation, reduced blood viscosity, suppressed leukotriene (a lipid mediator for neutrophil and macrophage aggregation) formation, inhibited endothelial cell proliferation, and reduced insulin resistance, triglycerides, fibrinogen, and blood pressure levels.^{12,28} Most of these CAD risk factors could also increase the risk of PE, while some, such as blood pressure levels, may not be associated with PE risk. In the present study, the association between fresh fish intake and risk of PE death was stronger than that seen with dried or salted fish, steamed fish paste, or deep-fried fish intake. This seemed plausible because ω 3 PUFA intake in the present study was derived mainly from fresh fish.

One strength of the present study is that the JACC involved a large, nationwide, community-based Japanese cohort, which allowed us to examine the association of fish and ω 3 PUFA intake with PE for the first time in an Asian population. Another advantage of the present study was the wider distribution of fish intake compared with Western studies. This meant we could test the potential effect of very high fish or ω 3 PUFA intake, which cannot be reliably studied in Western populations.

Study Limitations

Several warrant consideration. First, as in most epidemiological studies, we evaluated dietary intake using a questionnaire. Although we used well-validated questionnaires to measure dietary intake, the use of a single assessment in this study could have resulted in misclassifying dietary variables, biasing our results towards the null. Additionally, the absolute amount of ω 3 PUFA intake in the present

study is probably underestimated. Although 26% of the participants responded “almost every day” to frequency of fish intake, we could not estimate how many times participants ate fish in a day.

Secondly, the number of PE cases in the present study was relatively small, because the outcome in this study was limited to fatal PE. In Japan, it has been reported that the case fatality rate of PE is almost 10–20%,^{7,29,30} and it depends on the severity of cases, such as massive or collapse cases. Therefore, the PE cases in the present study tended to be severe, and the findings may be confined to severe cases of PE. Because PE is confirmed by high-probability lung scanning, helical computed tomography, or pulmonary angiography, PE cases can be diagnosed only in highly specialized hospitals in Japan, although more than 90% of residents can be admitted to these hospitals within 60 min in emergency situations. Therefore, the number of PE deaths might be underestimated in the present study, although there was little possibility of overestimating the number of PE. As a result, we may have missed moderate or weak associations between other dietary factors and PE death because of low power. Thirdly, individuals with very low intake of fish might have specific lifestyles that increase the risk of PE. However, there were no apparent differences in lifestyle factors, such as excess alcohol intake and smoking status, according to the frequency of fish intake in the present study. Finally, we are unable to completely exclude the possibility of residual confounding factors from other factors, such as coagulofibrinolytic factors, lifestyle, hormone replacement, or family history.^{31–33}

Conclusions

In conclusion, increased fresh fish intake, even if only 1–2 times per week, was associated with a lower risk of PE death during a median follow-up of 19.2 years in this general population study in Japan. The low mortality rate from PE among the Japanese may be attributed to high fish intake.

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Conflict of Interest Statement

All authors have no conflicts of interest to disclose.

Author Contributions

T.O. conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. K.Y. analyzed and interpreted the data, and critically revised the manuscript. A.T. and H.I. conceived and designed the study, and critically revised the manuscript. All authors read and approved the final manuscript.

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