Journal of Affective Disorders 129 (2011) 282–288

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Long chain n-3 fatty acids intake, fish consumption and suicide in a cohort of Japanese men and women — The Japan Public Health Center-based (JPHC) Prospective Study

Kalpana Poudel-Tandukar [a], Akiko Nanri [a], Motoki Iwasaki [b], Tetsuya Mizoue [a,*], Yumi Matsushita [a], Yoshihiko Takahashi [c], Mitsuhiko Noda [c], Manami Inoue [b], Shoichiro Tsugane [b,1]
and for the Japan Public Health Center-based Prospective Study Group

[a] Department of Epidemiology and International Health, International Clinical Research Center, National Center for Global Health and Medicine, Japan
[b] Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Japan
[c] Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Japan

ARTICLE INFO

Article history:
Received 28 December 2009
Received in revised form 30 June 2010
Accepted 17 July 2010
Available online 6 August 2010

Keywords:
Cohort study
Suicide
Fish consumption

ABSTRACT

Objective: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been implicated as protective against suicide. However, it is uncertain whether a higher intake of EPA and DHA or of fish, a major source of these nutrients, lowers suicidal risk among Japanese, whose fish consumption and suicide rate are both high. This study prospectively examined the relation between fish, EPA, or DHA intake and suicide among Japanese men and women.
Method: Subjects were 47,351 men and 54,156 women aged 40–69 years who participated in the JPHC Study, completed a food frequency questionnaire in 1995–1999, and were followed for death through December 2005. We used the Cox proportional hazards regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for suicide by quintile of intake.
Results: A total of 213 and 85 deaths from suicide were recorded during 403,019 and 473,351 person-years of follow-up for men and women, respectively. Higher intakes of fish, EPA, or DHA were not associated with a lower risk of suicide. Multivariate HRs (95% CI) of suicide death for the highest versus lowest quintile of fish consumption were 0.95 (0.60–1.49) and 1.20 (0.58–2.47) for men and women, respectively. A significantly increased risk of suicidal death was observed among women with very low intake of fish, with HRs (95% CI) for those in 0–5th percentile versus middle quintile of 3.41 (1.36–8.51).
Conclusions: Our overall result does not support a protective role of higher intake of fish, EPA, or DHA against suicide in Japanese men and women.

1. Introduction

The long chain n-3 polyunsaturated fatty acids (PUFA) found in oily fish such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been suggested to be protective against suicide (Freeman, 2000). One explanation for this is that low plasma EPA and DHA may adversely impact serotonergic and corticotrophic functions in the brain (Arato et al., 1989; Mann et al., 1996; Hibbeln et al., 1997, 2004). In particular, an increased risk of suicide has been linked to low

* Corresponding author. Department of Epidemiology and International Health, International Clinical Research Center, National Center for Global Health and Medicine, Toyama 1-21-1, Shinjuku-ku, Tokyo 162-8655, Japan. Tel.: +81 3 202 7181; fax: +81 3 3202 7364.
E-mail addresses: mizoue@ri.ncgm.go.jp (T. Mizoue), stsugane@ncc.go.jp (S. Tsugane).
[1] Reprint requests: Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel.: +81 3 547 8579; fax: +81 3 3547 8578.

0165-0327/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2010.07.014

concentrations of the serotonergic metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Mann et al., 1996) and to high concentrations of corticotrophin-releasing factor in cerebral spinal fluid (Arato et al., 1989), both of which have been associated with low plasma EPA and DHA.

Studies have shown protective associations between the intake of fish, EPA, or DHA and suicide or suicidality (Hirayama, 1990; Huan et al., 2004). For example, suicide attempters consumed a smaller amount of fish (Li et al., 2009; Tanskanen et al., 2001) or polyunsaturated fatty acids (Zhang et al., 2005) and had lower levels of plasma EPA or DHA (Huan et al., 2004; De Vriese et al., 2004; Sublette et al., 2006) than non-attempters. One randomized-controlled trial (Hallahan et al., 2007) showed that EPA + DHA supplementation reduced suicidality. However, evidence for these associations in a population in which both the fish intake and suicide rate is high is limited (Hirayama, 1990; Hakkarainen et al., 2004). In a 17-year follow-up of 256,118 Japanese, those who ate fish daily had a lower risk of suicide compared to those who ate fish less than daily, albeit that this finding may have been limited by a lack of adjustment for confounding variables (Hirayama, 1990). This observation among Japanese was not corroborated in a Finnish cohort, in which the risk of suicide was not associated with the intake of fish, EPA or DHA (Hakkarainen et al., 2004).

We hypothesized that a higher intake of fish, EPA or DHA is associated with a lower risk of suicide. We considered that an investigation in Japan, in which one person takes their own life every 15 min on average (Mc Curry, 2008) and where people consume an average of 5–8 times more EPA + DHA than people in the United States (Sugano and Hirahara, 2000; Kris-Etherton et al., 2000), might provide useful information about the role of these nutrients in mental health. Here, we investigated the association between fish, EPA, or DHA intake and suicide in a cohort of Japanese men and women.

2. Method

2.1. Study subjects

The Japan Public Health Center-based (JPHC) Study was prospectively conducted in Cohort I (1990) and Cohort II (1993) of Japanese residents in 11 public health centers areas. The study design has been described in detail previously (Tsugane and Sobue, 2001). Among the eligible study population at a 5-year follow-up survey (136,605), 103,768 responded to the survey, yielding a response rate of 76%. We excluded subjects who did not have information on diet or fatty acid intake (1197) and those who reported energy intake outside of the mean ± 3 SD by sex (1064). We included 101,507 subjects in our analysis.

2.2. Lifestyle, anthropometry and dietary assessment

The study participants completed a self-administered five-year follow-up questionnaire which included queries on diet, lifestyle and anthropometric parameters. A food frequency questionnaire (FFQ) was used to assess the intake of 147 foods, including 19 fish questions. Each participant was asked how often s/he had consumed each food during the previous year. For each food item, the subjects indicated their mean frequency of consumption in terms of the specified serving size by checking one of nine frequency categories ranging from "never," to "7 or more times/day." Portion sizes were specified into less than half, the same, and more than 1.5 times a normal serving. Consumption of each food was calculated by multiplying the frequency score of consumption by portion size. The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items.

We assigned specific values for each of 19 fish to calculate dietary intake of n-3 PUFA (Kobayashi et al., 2003). For reproducibility, sex-specific Spearman correlation coefficients between the two FFQs administered one year apart in Cohorts I and II ranged from 0.34 to 0.54 for energy-adjusted total fish and n-3 PUFA intake (Sasaki et al., 2003a; Ishihara et al., 2003). The Spearman correlation coefficients between questionnaire and dietary records for energy-adjusted fish intake in men and women were 0.32 and 0.32, respectively, for cohort I (Sasaki et al., 2003b), and 0.27 and 0.23, respectively, for cohort II (Ishihara et al., 2003) and between dietary intake and serum concentrations for EPA and DHA were 0.44 and 0.32, respectively ($p \leq 0.01$) among subsamples of Cohort 1 (Kobayashi et al., 2003).

2.3. Follow-up and identification of suicide

Cohort I was followed from 1995 and Cohort II from 1998, until December 31, 2005. Changes in residence, including survival, were obtained annually using the residential registry. The status of subjects who had moved out of the study area was assessed through the municipal office to which they had moved. Mortality data for persons in the residential registry are forwarded to the Ministry of Health, Labour and Welfare (MHLW) and are coded for inclusion in the National Vital Statistics. Residential registration and death registration are required by the Basic Residential Register Law and Family Register Law, respectively, and the registries are thought to be complete.

Information on deaths for subjects who remained in their original area was obtained from their primary health center (PHC), and for subjects who died after moving from their original PHC area from death certificates maintained by the MHLW, Japan. Information on the cause of death was obtained from the death certificate, provided by the MHLW, Japan with the permission of the Ministry of Internal Affairs and Communications. Death from suicide was defined according to the International Classification of Diseases, 10th Revision (ICD-10), as codes X60–X84.

2.4. Statistical analyses

The number of person-years in the follow-up period was calculated from the response date to the five-year follow-up to the date of death or December 31, 2005, whichever came first. Hazard ratios and 95% confidence intervals (CI) were calculated for the categories of energy-adjusted fish, EPA, and DHA intake in quintiles, with the lowest consumption category as the reference, using Cox proportional hazards models and adjusting for confounding variables. Further, HRs (95% CI) were calculated for the lowest intake categories (0–5th percentile), with the middle quintile category as the reference. A regression residual method was used for energy adjustment of fish, EPA, and DHA intake (Willett and Stampfer, 1986). In the multivariate model, we adjusted for age, area, BMI, alcohol consumption, smoking, physical activity, living alone, history of chronic disease, drug use, stress, and unemployment. We tested trends across quintiles of fish, EPA, and DHA intake using ordinal numbers 0–4 assigned to quintile categories. All reported *p* values are two-sided, and significance level was set at $p<0.05$. All statistical analyses were performed with SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

3. Results

A total of 213 and 85 suicide cases were recorded during 403,019 and 473,351 person-years of follow-up in men and women, respectively. As shown in Table 1, there were significant differences in demographic and lifestyle characteristics and nutrients intake across quintiles of fish intake in both sexes, except for self-reported stress.

Tables 2 and 3 show the association between quintiles of fish, EPA and DHA intake and suicide by sex. The multivariate-adjusted HRs (95% CI) of a suicide for successive quintiles of fish intake in men were 1 (reference), 1.19 (0.79–1.79), 0.96 (0.62–1.49), 0.95 (0.61–1.48) and 0.95 (0.60–1.49), and in women were 1 (reference), 1.24 (0.60–2.58), 0.99 (0.46–2.15), 1.39 (0.68–2.83) and 1.20 (0.58–2.47). No significant inverse association was observed between the intake of EPA and DHA, either alone or in combination, and suicide in both sexes.

We compared suicide risk in subjects with fish, EPA or DHA intake in the 0–5th percentile with that of the middle quintile. HRs (95% CI) of suicide for subjects in the 0–5th percentile of fish, EPA, DHA, and EPA + DHA intake compared with those in the middle quintile in men were 0.98 (0.47–2.06), 0.71 (0.30–1.66), 0.90 (0.43–1.85), and 0.43 (0.17–1.09), respectively; and in women were 3.41 (1.36–8.51), 1.22 (0.37–4.05), 2.02 (0.79–5.16), and 2.05 (0.79–5.32), respectively.

In stratified analyses, no difference was seen in the relation between fish, EPA or DHA intake and suicide risk according to smoking, history of chronic disease or regular medication, and stress in either sex. HRs (95% CI) of suicide for the highest versus lowest quintile of EPA and DHA were 2.43 (1.08–5.45) and 3.41 (1.32–8.80), respectively, in male nondrinkers, whereas no such increase in risk was observed in male drinkers or in women regardless of drinking.

4. Discussion

This JPHC cohort study provided no evidence for an inverse relation between fish, EPA, or DHA intake and suicide risk. In women but not men, an increased risk of suicide was associated with very low fish intake. To our knowledge, this is

Table 1
Distribution of suicide risk factors and selected dietary variables in a cohort of Japanese men and women by quintile of fish intake.[a]

	Q1	Q2	Q3	Q4	Q5	Trend p[b]
Men (n = 47,351)						
Median intake (g/day)	32	56	77	103	153	
Age in years (mean)	56	55	56	57	58	<0.0001
Body mass index, mean (kg/m^2)	23.6	23.5	23.5	23.4	23.4	<0.0001
Current drinkers (%)	76.2	77.0	76.3	75.1	69.2	<0.0001
Current smokers (%)	47.1	46.3	47.7	46.3	44.5	0.001
Sports and physical exercise during leisure-time, ≥1 day/week (%)	40.4	42.8	42.1	40.7	37.6	<0.0001
Living alone, yes (%)	5.1	3.6	3.4	3.2	3.2	<0.0001
Past history of any chronic disease (%)	5.3	5.0	5.7	5.8	7.4	<0.0001
Current regular drug use prescribed by a doctor (%)	31.9	33.1	35.5	37.2	42.2	<0.0001
Self-reported stress, stressful (%)	79.6	81.0	80.2	81.1	79.3	0.65
Occupation, unemployed (%)	9.5	9.1	10.2	11.3	14.0	<0.0001
Mean daily total energy (kcal)	2288	2228	2201	2174	2053	<0.0001
Eicosapentaenoic acid (g/day)[a]	0.1	0.2	0.3	0.4	0.7	<0.0001
Docosahexaenoic acid (g/day)[a]	0.2	0.4	0.5	0.7	1.2	<0.0001
Arachidonic acid (g/day)[a]	0.1	0.1	0.1	0.1	0.2	<0.0001
Women (n = 54,156)						
Median intake (g/day)	32	55	75	98	142	
Age, mean (years)	56	56	56	57	58	<0.0001
Body mass index, mean (kg/m^2)	23.5	23.3	23.3	23.4	23.5	0.008
Current drinkers (%)	18.6	21.3	21.5	20.8	18.6	0.01
Current smokers (%)	6.5	6.0	5.5	5.4	5.7	0.002
Sports and physical exercise during leisure-time, ≥ 1 day/week (%)	32.0	33.9	33.4	33.2	29.8	0.0005
Living alone, yes (%)	8.5	6.7	5.8	5.9	6.3	<0.0001
Past history of any chronic disease (%)	3.0	2.8	3.1	3.2	3.4	0.02
Current regular drug use prescribed by a doctor (%)	34.6	33.7	35.0	37.7	40.5	<0.0001
Self-reported stress, stressful (%)	79.6	80.7	81.3	80.9	81.0	0.01
Occupation, unemployed (%)	8.7	8.4	8.4	9.1	9.6	0.003
Mean daily total energy (kcal)	1977	1912	1906	1882	1761	<0.0001
Eicosapentaenoic acid (g/day)[a]	0.1	0.2	0.3	0.4	0.6	<0.0001
Docosahexaenoic acid (g/day)[a]	0.2	0.4	0.5	0.7	1.1	<0.0001
Arachidonic acid (g/day)[a]	0.1	0.1	0.1	0.1	0.2	<0.0001

[a] Energy-adjusted for fish or fatty acid intake by the regression residual method.
[b] P for trend values were based on the Mantel–Haenszel chi-square test for categorical variables and linear regression analysis for continuous variables, with ordinal numbers 0–4 assigned to quintile categories of fish intake.

Table 2
Cox proportional hazard ratios and 95% confidence intervals for suicide according to quintile of fish [a] and fatty acids [a] intake among men ($n = 47{,}351$).

	Q1	Q2	Q3	Q4	Q5	Trend p [b]
Fish intake						
Median intake g/day	32.50	56.16	76.94	102.75	152.84	
No. of suicide	44	50	41	40	38	
No. of person-years	81,512	81,119	81,137	80,515	78,735	
HR1 (95% CI)	1.00 (reference)	1.11 (0.74–1.68)	0.90 (0.59–1.39)	0.88 (0.57–1.37)	0.87 (0.56–1.36)	0.31
HR2 (95% CI)	1.00 (reference)	1.19 (0.79–1.79)	0.96 (0.62–1.49)	0.95 (0.61–1.48)	0.95 (0.60–1.49)	0.52
EPA						
Median intake g/day	0.10	0.20	0.29	0.42	0.67	
No. of suicide	40	44	45	39	45	
No. of person-years	80,543	81,154	81,307	81,196	78,817	
HR1 (95% CI)	1.00 (reference)	1.05 (0.67–1.63)	1.06 (0.67–1.66)	0.91 (0.57–1.46)	1.12 (0.71–1.78)	0.84
HR2 (95% CI)	1.00 (reference)	1.11 (0.71–1.72)	1.13 (0.72–1.77)	0.99 (0.62–1.59)	1.22 (0.77–1.95)	0.57
DHA						
Median intake g/day	0.22	0.38	0.52	0.72	1.10	
No. of suicide	41	45	48	39	40	
No. of person-years	80,964	81,135	81,333	80,913	78,672	
HR1 (95% CI)	1.00 (reference)	1.07 (0.69–1.64)	1.13 (0.73–1.73)	0.92 (0.58–1.45)	0.99 (0.63–1.57)	0.75
HR2 (95% CI)	1.00 (reference)	1.11 (0.72–1.71)	1.19 (0.77–1.84)	0.99 (0.62–1.57)	1.07 (0.67–1.70)	0.98
EPA + DHA						
Median intake g/day	0.33	0.58	0.82	1.14	1.77	
No. of suicide	42	41	51	35	44	
No. of person-years	80,877	81,090	81,319	81,024	78,707	
HR1 (95% CI)	1.00 (reference)	0.94 (0.61–1.46)	1.16 (0.76–1.78)	0.79 (0.50–1.27)	1.06 (0.67–1.67)	0.95
HR2 (95% CI)	1.00 (reference)	0.99 (0.64–1.54)	1.23 (0.80–1.89)	0.86 (0.53–1.38)	1.15 (0.72–1.81)	0.77
AA/EPA						
Median intake g/day	0.22	0.30	0.40	0.55	1.10	
No. of suicide	45	54	41	34	39	
No. of person-years	79,705	80,531	82,178	79,907	80,697	
HR1 (95% CI)	1.00 (reference)	1.18 (0.79–1.75)	0.89 (0.58–1.36)	0.77 (0.49–1.22)	0.89 (0.55–1.45)	0.21
HR2 (95% CI)	1.00 (reference)	1.19 (0.80–1.77)	0.89 (0.58–1.37)	0.76 (0.48–1.20)	0.87 (0.54–1.41)	0.17

Eicosapentaenoic acid (EPA); Docosahexaenoic acid (DHA); Arachidonic acid (AA).
HR, hazard ratio; CI, confidence interval.
HR1: Age and area-adjusted model.
HR2: Multivariate model included age at baseline (continuous), body mass index (<21, 21–<23, 23–<25, 25–<27, or ≥27 kg/m^2), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/day), smoking (lifetime nonsmoker, former smoker, or current smoker with a consumption of <20 or ≥20 cigarettes/day), leisure-time physical activity (<1 day/month, 1–3 days/month, or >1 day/week), living alone (yes, no), past history of any chronic disease such as cancer, cerebrovascular disease, myocardial infarction, chronic liver disease, or renal disease (yes, no), current regular drug use prescribed by a doctor (yes, no), self-reported stress (mild, moderate, and severe), unemployment (yes, no), and area (PHCs).
[a] Energy-adjusted for fish or fatty acid intake by the regression residual method.
[b] Linear trends across quintiles of fish or fatty acids intake were tested using ordinal numbers 0–4 assigned to quintile categories.

the first prospective study to investigate the association between the intake of fish, EPA or DHA and suicide in a Japanese population using a validated FFQ with adjustment for confounding variables.

Two studies (Hirayama, 1990; Hakkarainen, 2004) have prospectively assessed the fish, EPA, and DHA intake in relation to suicide among high fish intake populations. The suicide risk was lower among persons who ate fish daily as compared to those who did so less than daily in a Japanese cohort (Hirayama, 1990). However, this result may have been limited by the lack of adjustment for confounding variables and use of a not-validated questionnaire. In contrast, a Finnish cohort study (Hakkarainen et al., 2004) found no link between fish, EPA or DHA intake and suicide, even with confounding variable adjustment. The median intake of fish (g/day) in this cohort (39) was nearly only half that of the present study (75), but nevertheless appeared higher than the intake in most Western countries (Kris-Etherton et al., 2000). The null finding in the present and Finnish studies suggests that a high fish intake does not reduce suicide among high fish intake populations.

We did find an increased risk of suicide in women whose intake of fish or EPA + DHA was very low. This suggests that suicide risk may be increased only in persons with an extremely low intake of fish or long chain n-3 PUFA. We assume that the fish consumed by our very low intake group might have been comparable to that by subjects in relatively low intake groups in countries with much lower fish consumption than Japan. In this context, our findings may be consistent with those from studies in the US (Zhang et al., 2005) and China (Huan et al., 2004), which found that suicide attempters consumed less polyunsaturated fatty acids or had lower levels of plasma EPA and DHA than non-attempters.

We found a significantly increased risk of suicide associated with very low fish intake in women, but not in men. To our knowledge, no previous study has reported such a gender difference. However, our finding is compatible with a result of a US study (Li et al., 2009), in which the number of fish servings consumed by suicide attempters was significantly lower than that of non-attempters in women but not in men. The particular mechanism for this gender difference is unclear, but studies have suggested that levels of PUFAs may determine the number and function of 5-HT (2A) promoter polymorphism (Maes and Smith, 1998), which has been associated with affective disorders in women but not in men (Enoch et al., 2001).

Table 3
Cox proportional hazard ratios and 95% confidence intervals for suicide according to quintile of fish [a] and fatty acids [a] intake among women.

	Q1	Q2	Q3	Q4	Q5	Trend p [b]
Fish intake						
Median intake g/day	32.29	55.38	74.86	97.97	142.09	
No. of suicide	13	17	14	21	20	
No. of person-years	94,143	94,673	94,661	94,796	95,076	
HR1 (95% CI)	1.00 (reference)	1.15 (0.55–2.39)	0.89 (0.41–1.92)	1.27 (0.62–2.58)	1.17 (0.57–2.40)	0.60
HR2 (95% CI)	1.00 (reference)	1.24 (0.60–2.58)	0.99 (0.46–2.15)	1.39 (0.66–2.83)	1.20 (0.58–2.47)	0.56
EPA						
Median intake g/day	0.10	0.20	0.29	0.41	0.64	
No. of suicide	14	12	21	21	17	
No. of person-years	93,293	94,198	94,732	95,811	95,315	
HR1 (95% CI)	1.00 (reference)	0.68 (0.31–1.51)	1.08 (0.52–2.21)	1.03 (0.50–2.13)	0.82 (0.38–1.75)	0.98
HR2 (95% CI)	1.00 (reference)	0.72 (0.32–1.60)	1.18 (0.57–2.41)	1.13 (0.55–2.34)	0.85 (0.39–1.81)	0.92
DHA						
Median intake g/day	0.21	0.37	0.51	0.69	1.03	
No. of suicide	16	13	19	16	21	
No. of person-years	93,542	94,310	94,760	95,603	95,134	
HR1 (95% CI)	1.00 (reference)	0.68 (0.32–1.44)	0.90 (0.45–1.79)	0.72 (0.35–1.49)	0.93 (0.47–1.85)	0.99
HR2 (95% CI)	1.00 (reference)	0.73 (0.34–1.53)	0.98 (0.49–1.96)	0.78 (0.38–1.61)	0.96 (0.48–1.91)	0.95
EPA + DHA						
Median intake g/day	0.32	0.57	0.80	1.10	1.66	
No. of suicide	15	14	20	17	19	
No. of person-years	93,343	94,341	94,680	95,771	95,214	
HR1 (95% CI)	1.00 (reference)	0.76 (0.36–1.60)	0.98 (0.49–1.98)	0.79 (0.38–1.65)	0.87 (0.42–1.78)	0.80
HR2 (95% CI)	1.00 (reference)	0.80 (0.38–1.69)	1.07 (0.53–2.16)	0.87 (0.41–1.80)	0.90 (0.44–1.84)	0.87
AA/EPA						
Median intake g/day	0.21	0.30	0.39	0.53	1.05	
No. of suicide	15	26	20	10	14	
No. of person-years	95,636	95,306	94,769	93,827	93,812	
HR1 (95% CI)	1.00 (reference)	1.81 (0.96–3.43)	1.47 (0.75–2.89)	0.83 (0.37–1.86)	1.50 (0.68–3.31)	0.98
HR2 (95% CI)	1.00 (reference)	1.93 (1.02–3.65)	1.58 (0.80–3.11)	0.87 (0.38–1.96)	1.51 (0.69–3.32)	0.96

Eicosapentaenoic acid (EPA); Docosahexaenoic acid (DHA); Arachidonic acid (AA).
HR, hazard ratio; CI, confidence interval.
HR1: Age- and area-adjusted model.
HR2: Multivariate model included age at baseline (continuous), body mass index (<21, 21–<23, 23–<25, 25–<27, or ≥27 kg/m^2), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/day), smoking (lifetime nonsmoker, former smoker, or current smoker with a consumption of <20 or ≥20 cigarettes/day), leisure-time physical activity (<1 day/month, 1–3 days/month, or >1 day/week), living alone (yes, no), past history of any chronic disease such as cancer, cerebrovascular disease, myocardial infarction, chronic liver disease, or renal disease (yes, no), current regular drug use prescribed by a doctor (yes, no), self-reported stress (mild, moderate, and severe), unemployment (yes, no), and area (PHCs).
[a] Energy-adjusted for fish or fatty acid intake by the regression residual method.
[b] Linear trends across quintiles of fish or fatty acids intake were tested using ordinal numbers 0–4 assigned to quintile categories.

Unexpectedly, we found a significantly increased risk of suicide in the highest EPA and DHA intake groups in male nondrinkers. The reason for this association remains unclear, and the possibility of chance cannot be ruled out. However, two cohort studies, in Finland (Hakkarainen et al., 2004) and Spain (Sanchez-Villegas et al., 2007), reported an elevated risk of mental disorders among persons in the highest fish, EPA or DHA consumption category. Given that an increased intake of fish can increase serum mercury concentrations (Bates et al., 2006) and that mercury compounds are a known risk factor for neurological disorders (Johansson et al., 2007; Wojcik et al., 2006), the increased risk of suicide among persons with a high fish intake might be attributable to the harmful effects of mercury in fish.

The major strengths of the present study are its population-based prospective design, large sample size, use of a validated questionnaire (FFQ), and adjustment for potential confounding variables. Several methodological limitations also warrant mention. First, the measurement of fish intake may not be sufficiently accurate and consistent to detect an association with suicide. However, the reproducibility of fish intake between baseline and 5-year follow-up was fairly good, and compatible with that reported in the Nurses' Health Study (Hu et al., 2002). Moreover, Iso et al. (Iso et al., 2006) found an inverse association between fish intake and heart disease based on the JPHC data, suggesting that our estimate of fish intake is reasonable in detecting an association if any. Second, our study cohort included subjects with a history of chronic disease or medication and stress, who may have altered dietary intake of fish, EPA or DHA. However, we found no significant difference in the association between fish intake and suicide in stratified analysis according to these variables, and moreover also adjusted for them in the model. The presence of depression at the time of baseline dietary assessment might have influenced both fish intake (decrease) and future suicidal risk (increase), and can thus modify the association. Unfortunately, depression status was not assessed in the JPHC study. Third, we could not obtain data on stressful life events including family member's death, divorce, and job loss during the study period, which might increase risk of suicide. Finally, our study subjects were middle aged population and they do not represent a random sample of the Japanese population, and caution is required in generalizing the present results to the young and elderly people.

In conclusion, this study provides no evidence to support the hypothesis that a high intake of fish, EPA, and DHA reduces the risk of suicide in Japanese men and women.

Role of funding source

This study is supported by grants-in-aid for cancer research and for the Third-Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan. The funding source had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflicts of interest

All of the authors read and approved the manuscript. None of the authors had a conflict of interest.

Acknowledgements

Members of the Japan Public Health Center-based Prospective Study Group (JPHC Study, principal investigator: S. Tsugane): S. Tsugane, M. Inoue, T. Sobue and T. Hanaoka, National Cancer Center, Tokyo, Japan; J. Ogata, S. Baba, T. Mannami, A. Okayama and Y. Kokubo, National Cardiovascular Center, Osaka, Japan; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Iwate, Japan; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi and N. Nagai, Akita Prefectural Yokote Public Health Center, Akita, Japan; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa and Y. Kobayashi, Nagano Prefectural Saku Public Health Center, Nagano, Japan; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa, Japan; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji and R. Saito, Katsushika Public Health Center, Tokyo, Japan; A. Murata, K. Minato, K. Motegi and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Ibaraki, Japan; K. Matsui, T. Abe, M. Katagiri and M. Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata, Japan; M. Doi, A. Terao, Y. Ishikawa and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi, Japan; H. Sueta, H. Doi, M. Urata, N. Okamoto and F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki, Japan; H. Sakiyama, N. Onga, H. Takaesu and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa, Japan; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii and M. Takano, Osaka Prefectural Suita Public Health Center, Osaka, Japan; Y. Tsubono, Tohoku University, Miyagi, Japan; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita, Japan; Y. Honda, K. Yamagishi, S. Sakurai and N. Tsuchiya, Tsukuba University, Ibaraki, Japan; M. Kabuto, National Institute for Environmental Studies, Ibaraki, Japan; M. Yamaguchi, Y. Matsumura, S. Sasaki and S. Watanabe, National Institute of Health and Nutrition, Tokyo, Japan; M. Akabane, Tokyo University of Agriculture, Tokyo, Japan; T. Kadowaki, Tokyo University, Tokyo, Japan; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo, Japan; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo, Japan; Y. Takashima and M. Yoshida, Kyorin University, Tokyo, Japan; K. Nakamura, Niigata University, Niigata, Japan; S. Matsushima and S. Natsukawa, Saku General Hospital, Nagano, Japan; H. Shimizu, Sakihae Institute, Gifu, Japan; H. Sugimura, Hamamatsu University, Shizuoka, Japan; S. Tominaga, Aichi Cancer Center Research Institute, Aichi, Japan; H. Iso, Osaka University, Osaka, Japan; M. Iida, W. Ajiki and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan; S. Sato, Chiba Prefectural Institute of Public Health, Chiba, Japan; E. Maruyama, Kobe University, Hyogo, Japan; M. Konishi, K. Okada and I. Saito, Ehime University, Ehime, Japan; N. Yasuda, Kochi University, Kochi, Japan; and S. Kono, Kyushu University, Fukuoka, Japan.

References

Arato, M., Banki, C.M., Bissette, G., Nemeroff, C.B., 1989. Elevated CSF CRF in suicide victims. Biol. Psychiatry 25, 355–359.

Bates, C.J., Prentice, A., Birch, M.C., Delves, H.T., Sinclair, K.A., 2006. Blood indices of selenium and mercury, and their correlations with fish intake, in young people living in Britain. Br. J. Nutr. 96, 523–531.

De Vriese, S.R., Christophe, A.B., Maes, M., 2004. In humans, the seasonal variation in poly-unsaturated fatty acids is related to the seasonal variation in violent suicide and serotonergic markers of violent suicide. Prostaglandins Leukot. Essent. Fatty Acids 71, 13–18.

Enoch, M.A., Greenberg, B.D., Murphy, D.L., Goldman, D., 2001. Sexually dimorphic relationship of a 5-HT2A promoter polymorphism with obsessive-compulsive disorder. Biol. Psychiatry 49, 385–388.

Freeman, M.P., 2000. Omega-3 fatty acids in psychiatry: a review. Ann. Clin. Psychiatry 12, 159–165.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., Lonnqvist, J., 2004. Is low dietary intake of omega-3 fatty acids associated with depression? Am. J. Psychiatr. 161, 567–569.

Hallahan, B., Hibbeln, J.R., Davis, J.M., Garland, M.R., 2007. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. Br. J. Psychiatry 190, 118–122.

Hibbeln, J.R., Umhau, J.C., George, D.T., Salem Jr., N., 1997. Do plasma polyunsaturates predict hostility and depression? World Rev. Nutr. Diet. 82, 175–186.

Hibbeln, J.R., Bissette, G., Umhau, J.C., George, D.T., 2004. Omega-3 status and cerebrospinal fluid corticotrophin releasing hormone in perpetrators of domestic violence. Biol. Psychiatry 56, 895–897.

Hirayama, T., 1990. Life-style and mortality: a large-scale census-based cohort study in Japan. In: Wahrendorf, J. (Ed.), Contribution to Epidemiology and Biostatistics, Volume 6. Karger, Basel.

Hu, F.B., Bronner, L., Willett, W.C., Stampfer, M.J., Rexrode, K.M., Albert, C.M., Hunter, D., Manson, J.E., 2002. Fish and omega-3 fatty acids intake and risk of coronary heart disease in women. JAMA 287, 1815–1821.

Huan, M., Hamazaki, K., Sun, Y., Itomura, M., Liu, H., Kang, W., Watanabe, S., Terasawa, K., Hamazaki, T., 2004. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. Biol. Psychiatry 56, 490–496.

Ishihara, J., Sobue, T., Yamamoto, S., Yoshimi, I., Sasaki, S., Kobayashi, M., Takahashi, T., Iitoi, Y., Akabane, M., Tsugane, S., 2003. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J. Epidemiol. 13, 134–147 suppl.

Iso, H., Kobayashi, M., Ishihara, J., Sasaki, S., Okada, K., Kita, Y., Kokubo, Y., Tsugane, S., 2006. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation 113, 195–202.

Johansson, C., Castoldi, A.F., Onishchenko, N., Manzo, L., Vahter, M., Ceccatelli, S., 2007. Neurobehavioural and molecular changes induced by methylmercury exposure during development. Neurotox. Res. 11, 241–260.

Kobayashi, M., Sasaki, S., Kawabata, T., Hasegawa, K., Tsugane, S., 2003. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess fatty acid intake: comparison with dietary records and serum phospholipid level. J. Epidemiol. 13 (suppl), 64–81.

Kris-Etherton, P.M., Taylor, D.S., Yu-Poth, S., Huth, P., Moriarty, K., Fishell, V., Hargrove, R.L., Zhao, G., Etherton, T.D., 2000. Polyunsaturated fatty acids in the food chain in the United States. Am. J. Clin. Nutr. 71 (suppl), 179–188.

Li, Y., Zhang, J., McKeown, R.E., 2009. Cross-sectional assessment of diet quality in individuals with a lifetime history of attempted suicide. Psychiatry Res. 165, 111–119.

Maes, M., Smith, R.S., 1998. Fatty acids, cytokines, and major depression. Biol. Psychiatry 43, 313–314.

Mann, J.J., Malone, K.M., Psych, M.R., Sweeney, J.A., Brown, R.P., Linnoila, M., Stanley, B., Stanley, M., 1996. Attempted suicide characteristics and

cerebrospinal fluid amine metabolites in depressed inpatients. Neuropsychopharmacology 15, 576–586.
Mc Curry, J., 2008. Japan to rethink suicide-prevention policies. Lancet 371, 372.
Sanchez-Villegas, A., Henríquez, P., Figueiras, A., Ortuño, F., Lahortiga, F., Martínez-González, M.A., 2007. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. Eur. J. Nutr. 46, 337–346.
Sasaki, S., Ishihara, J., Tsugane, S., 2003a. Reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess food and nutrient intake. J. Epidemiol. 13 (suppl), 115–124.
Sasaki, S., Kobayashi, M., Tsugane, S., 2003b. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for food groups. J. Epidemiol. 13 (suppl), 57–63.
Sublette, M.E., Hibbeln, J.R., Galfalvy, H., Oquendo, M.A., Mann, J.J., 2006. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am. J. Psychiatry 163, 1100–1102.
Sugano, M., Hirahara, F., 2000. Polyunsaturated fatty acids in the food chain in Japan. Am. J. Clin. Nutr. 71 (suppl), 189–196.
Tanskanen, A., Hibbeln, J.R., Hintikka, J., Haatainen, K., Honkalampi, K., Viinamäki, H., 2001. Fish consumption, depression, and suicidality in a general population. Arch. Gen. Psychiatry 58, 512–513.
Tsugane, S., Sobue, T., 2001. Baseline survey of JPHC study-design and participation rate. Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases. J. Epidemiol. 11, 24–29 suppl.
Willett, W., Stampfer, M.J., 1986. Total energy intake: implications for epidemiologic analyses. Am. J. Epidemiol. 124, 17–27.
Wojcik, D.P., Godfrey, M.E., Christie, D., Haley, B.E., 2006. Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994–2006). Neuro Endocrinol. Lett. 27, 4.
Zhang, J., Li, Y., Torres, M.E., 2005. How does a suicide attempter eat differently from others? Comparison of macronutrient intakes. Nutrition 21, 711–717.