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ORIGINAL PAPER

Fish intake and risk of melanoma in the NIH-AARP diet and health study

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Abstract

Purpose Prior epidemiological studies evaluating the association between fish intake and melanoma risk have been few and inconsistent. Few studies distinguished different types of fish intake with risk of melanoma.

Methods We examined the associations between intake of total fish and specific types of fish and risk of melanoma among 491,367 participants in the NIH-AARP Diet and Health Study. We used multivariable-adjusted Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results During 6,611,941 person-years of follow-up with a median of 15.5 years, 5,034 cases of malignant melanoma and 3,284 cases of melanoma in situ were identified. There was a positive association between higher total fish intake and risk of malignant melanoma (HR = 1.22, 95% CI = 1.11–1.34 for top vs. bottom quintiles, $p_{trend} = 0.001$) and melanoma in situ (HR = 1.28, CI = 1.13–1.44 for top vs. bottom quintiles, $p_{trend} = 0.002$). The positive associations were consistent across several demographic and lifestyle factors. There were also positive associations between tuna intake and non-fried fish intake, and risk of malignant melanoma and melanoma in situ. However, fried fish intake was inversely associated with risk of malignant melanoma, but not melanoma in situ.

Conclusions We found that higher total fish intake, tuna intake, and non-fried fish intake were positively associated with risk of both malignant melanoma and melanoma in situ. Future studies are needed to investigate the potential biological mechanisms underlying these associations.

Keywords Melanoma · Fish intake · AARP · Survival analyses

Introduction

Melanoma is the fifth most common cancer among both men and women in the United States (US) [1]. It is estimated that 106,110 new cases of melanoma and 7,180 deaths from the disease will occur in 2021 [1]. Women have higher incidence rates of melanoma than men before age 50, but rates in men are higher than those in women after age 50 [1]. The major risk factors for melanoma include family history [2], the presence of atypical and multiple nevi [3], pigmentary traits [4], and ultraviolet radiation (UVR) exposure [5]. Epidemiological studies suggest that some dietary factors including coffee, citrus fruit, and alcohol may affect melanoma risk as well. [6–11].

Epidemiological studies evaluating the associations between fish intake and melanoma risk have been few and yielded inconsistent results. A few case–control studies found either inverse [13, 14] or no [15, 16] significant associations between fish intake and melanoma risk. Few studies have distinguished different types of fish intake [14–16].

A prospective study based on the US National Institute of Health (NIH)-AARP Diet and Health Study, the largest prospective cohort with dietary data and cancer outcomes

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in the US, evaluated fish intake and different types of cancer [12]. The study found that melanoma was the only type of cancer which was associated with higher fish intake. In the current study, we examined the associations between total fish intake, as well as specific types of fish intake, and the risk of melanoma in the NIH-AARP Diet and Health Study with extended follow-up.

Materials and methods

Study population

The NIH-AARP Diet and Health Study, described previously [17], is a large prospective cohort study initiated in 1995 and 1996. A baseline questionnaire was mailed to 3.5 million AARP members aged 50–71 who resided in one of the six states (California, Florida, Louisiana, New Jersey, North Carolina, or Pennsylvania) or two metropolitan areas (Atlanta, GA or Detroit, MI) with existing population-based cancer registries. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. Among 566,398 participants who completed the questionnaire and provided informed consent, we excluded individuals who reported a history of cancer ($n = 50{,}591$) prior to baseline; individuals who were proxy-responders ($n = 14{,}487$); individuals with extreme calorie intake ($n = 3{,}671$) at baseline, defined as more than three standard deviations beyond the mean intake on the log- transformed scale (i.e., calorie: < 426.6 kcal, or > 6,760.8 kcal); individuals who died, moved out of the study area, or were diagnosed with cancer by cancer registry data (not disclosed in self-reported cancer history) before study entry ($n = 2{,}082$); and individuals who were identified as having cancer through death reports ($n = 4{,}200$). The resulting analytic cohort consisted of 491,367 participants (293,052 men and 198,315 women).

Cohort follow-up and case ascertainment

In the NIH-AARP study, vital status was obtained by linkage to the National Death Index, and cancer diagnoses were updated via linkage to state cancer registries. Participants were followed from baseline until the date of their first melanoma diagnosis, the date of death, the end of study (31 December 2011), or the date the participants moved out of the registry area, whichever came first. Cutaneous melanoma was defined according to the International Classification of Disease for Oncology (ICD-O, 3rd edition) by anatomic site and histological code (C44.0–C44.9 with Histology 8720–8780). This classification includes melanoma in situ and malignant melanoma.

Exposure and covariate assessment

Dietary intakes were assessed at baseline using a 124-item food-frequency questionnaire (FFQ) developed and validated by the National Cancer Institute [18]. Participants were asked to report their intakes of foods and beverages over the past year in both frequency of intake (10 categories) and portion size (3 categories). Line items were linked to the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals to calculate nutrient and energy intakes [19]. Line items for fish differentiated fried fish or fish sticks, non-fried fish or seafood (such as flounder, cod, shrimp, clams, crabs, lobster and others), and canned tuna [18]. Canned tuna included water-packed tuna and oil-packed tuna. Total fish intake is measured by the sum of fried fish intake, non-fried fish intake, and tuna intake.

UVR exposure was estimated by noon-time ground-level erythemal dose measured in the month of July between 1978 and 2005, which links Total Ozone Mapping Spectrometer (TOMS) data (http://toms.gsfc.nasa.gov) to the latitude and longitude of census tract of residence at baseline. The details of this method have been described previously [20]. Other covariates include age (continuous), sex (male, female), education (≤ 11 years, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race (non-Hispanic White, non-Hispanic Black, Hispanic, others), body mass index (BMI) (kg/m^2, continuous), physical activities (defined as physical activities over the last 12 months lasting 20 min or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, ≥ 5 times per week), July erythemal UVR (≤ 180, > 180–188, > 188–236, and > 236 J/m^2), alcohol intake (grams/day, defined as average daily alcohol intake over the last 12 months from drinks of alcohol including beer, wine, and liquid; continuous), caffeinated coffee intake (grams/day, continuous), smoking history (never, former, or current smoker), and daily energy intake (kcal/day, continuous).

Statistical analysis

We described exposures and covariables by levels of different quintiles of total fish intake. We used Cox proportional hazards regression models with age as the underlying time metric to estimate hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) for total fish intake and specific types of fish intake (including tuna intake, fried fish intake, and non-fried fish intake) with

malignant melanoma and melanoma in situ. We used the baseline cohort distribution to determine fish intake quintiles (cut off: 20%, 40%, 60%, 80%) for HRs estimation. We tested the proportional hazards assumptions by graphing the Kaplan Meier survival function of different groups of fish intake, respectively. Consistent with proportional hazards, the graph resulted in parallel lines. We used SAS software, version 9.4 (SAS institute, Cary, NC) to conduct our analysis. All statistical tests were 2-sided and considered statistically significant at $p < 0.05$.

In the base multivariable models, we adjusted for age and sex. In the full multivariable models, we further included BMI, smoking status, race, education status, physical activity, family history of cancer, July erythemal UVR, alcohol drinking, caffeinated coffee intake, and daily calorie intake into the models. We used quintile1 as the reference to estimate hazard ratios for different types of fish intake. To evaluate the linear trend, we assigned participants the median value of their intake quintiles and entered these values as a continuous term in the regression models. To test for effect modification by sex (males or females), age at baseline (> 60 or ≤ 60), smoking status (never or ever), duration of follow-up (> 10 years or ≤ 10 years), education status (college or non-college), BMI (≥ 25 or < 25 kg/m^2), July erythemal UVR (> 188 J/m^2 or ≤ 188 J/m^2), history of non-melanoma skin cancer (yes or no), physical activity (< 1 time per week or ≥ 1 time per week), total vegetable intake (> 254 g/day or ≤ 254 g/day), and total fruit intake (> 293 g/day or ≤ 293 g/day) between the association of total fish intake and risk of malignant melanoma/melanoma in situ, we included a single cross-product term for each variable and total fish intake in separate models, and tested each cross-product term by likelihood ratio tests. We then ran the stratified analysis by the factors.

Results

During 6,611,941 person-years of follow-up, 5,034 cases of malignant melanoma (3,785 men and 1,249 women; 4,949 non-Hispanic White, 13 non-Hispanic Black, 21 Hispanic, 11 other race) and 3,284 cases of melanoma in situ (2,428 men and 856 women; 3,234 non-Hispanic White, 2 non-Hispanic Black, 15 Hispanic, and 3 other race) were identified. The median age at baseline was 62.0, and the median follow-up time was 15.5 years (IQR: 13.4–15.6 years). The median age of melanoma diagnosis was 70.8 during the follow-up period. At baseline, higher total fish intake was associated with higher BMI, younger age, male sex, higher education status, higher physical activity levels, higher alcoholic beverage intake, and higher total daily calorie intake (Table 1). Age, sex, smoking status, education status, physical activity, family history of cancer, alcoholic beverage intake, caffeinated coffee intake, and calorie intake were statistically significantly associated with malignant melanoma risk in age and sex-adjusted models (Supplemental Table 1).

Results of the analyses of total fish intake in relation to malignant melanoma and melanoma in situ are displayed in Table 2. In the age- and sex-adjusted models there were significant positive associations between total fish intake and risk of malignant melanoma (comparing fifth vs. first quintile, HR = 1.23, CI = 1.12–1.35, $p_{trend} < 0.001$) and melanoma in situ (HR = 1.29, CI = 1.15–1.44, $p_{trend} = 0.001$). After adjusting for other melanoma risk factors, we still observed a significant positive association between total fish intake with risk of malignant melanoma (HR = 1.22, CI = 1.11–1.34, $p_{trend} = 0.001$) and melanoma in situ (HR = 1.28, CI = 1.13–1.44, $p_{trend} = 0.002$). The associations were similar when we additionally adjusted for intakes of vegetables, fruits, and meats (data not shown).

Table 3 depicts the associations between the three types of fish intake (including tuna, fried fish, non-fried fish) and risk of malignant melanoma and melanoma in situ. Except for fried fish intake, the associations between the other types of fish intake and risk of melanoma were consistent with those of total fish intake and risk of melanoma. Higher intakes of tuna ($p_{trend} < 0.001$) and non-fried fish ($p_{trend} = 0.003$) were associated with an increased malignant melanoma risk. Higher intakes of tuna ($p_{trend} = 0.009$) and non-fried fish ($p_{trend} = 0.002$) were associated with increased risk of melanoma in situ. Sensitivity analyses among non-Hispanic Whites only for total fish and three specific types of fish intake and melanoma risk produced similar results (data not shown). Analyses excluding cancers that have occurred within the first 12 months of follow-up period yielded similar results (data not shown). Additional adjustment for self-reported non-melanoma skin cancer diagnosis did not change the results (data not shown).

We further stratified the associations between total fish intake and malignant melanoma/melanoma in situ by sex, cigarette smoking status, follow-up time, education, July erythemal UVR, BMI, age, history of non-melanoma skin cancer, and physical activity (Supplemental Tables 2 and 3). There was no evidence of interactions between each of the variables and total fish intake for malignant melanoma or melanoma in situ, which indicated that there was no difference in risk estimates between total fish intake and malignant melanoma or melanoma in situ across strata of sex, cigarette smoking status, follow-up time, education, July erythemal UVR, BMI, age, history of non-melanoma skin cancer, physical activity, total vegetable intake, or total fruit intake. The results were similar when we used sex-specific cutoffs for quintiles of fish intake and melanoma risk by sex (data not shown).

Table 1 Baseline characteristics by level of total fish intake in the NIH-AARP diet and health study ($n = 491,367$)

Characteristic	Total fish intake				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Intake range (g/d)	< 5.6	5.6–< 10.0	10.0–< 17.1	17.1–< 28.3	≥ 28.3
N (%)	98,147 (20.0)	98,383 (20.0)	97,558 (19.9)	98,695 (20.1)	98,584 (20.1)
Total fish intake, (g/d)[c]	3.2 (2.7)	8.0 (2.3)	12.9 (3.7)	22.4 (4.8)	42.8 (23.6)
Tuna intake, g/d	0.7 (2.0)	2.4 (4.2)	5.3 (3.4)	5.3 (10.1)	11.3 (10.3)
Fried fish, g/d	0.4 (1.0)	1.0 (2.4)	2.7 (6.2)	2.7 (7.3)	7.1 (18.6)
Non-fried fish, g/d	1.0 (2.4)	2.9 (2.5)	7.5 (4.8)	7.7 (13.6)	20.2 (40.3)
BMI, (kg/m^2)	26.7 (5.1)	26.9 (5.0)	27.3 (5.0)	27.1 (5.0)	27.6 (5.2)
Age, (y)	61.8 (5.4)	61.6 (5.4)	61.5 (5.4)	61.5 (5.4)	61.2 (5.4)
Sex					
Male	50,517 (51.5)	53,358 (54.2)	60,935 (62.5)	61,320 (62.1)	66,922 (67.9)
Female	47,630 (48.5)	45,025 (45.8)	36,623 (37.5)	37,375 (37.9)	31,662 (32.1)
Race and ethnicity					
Non-Hispanic white	88,609 (90.3)	90,320 (91.8)	89,766 (92.0)	90,721 (91.9)	88,667 (89.9)
Non-Hispanic black	3453 (3.5)	3356 (3.4)	3615 (3.7)	3785 (3.8)	5019 (5.1)
Hispanic	2539 (2.6)	1993 (2.0)	1648 (1.7)	1573 (1.6)	1689 (1.7)
Asian	1381 (1.4)	1077 (1.1)	1036 (1.1)	1137 (1.2)	1512 (1.5)
Pacific Islander	88 (0.1)	101 (0.1)	106 (0.1)	116 (0.1)	190 (0.2)
American Indian/Alaska Native	331 (0.3)	283 (0.3)	278 (0.3)	248 (0.3)	265 (0.3)
Unknown	1746 (1.8)	1253 (1.3)	1109 (1.1)	1115 (1.1)	1242 (1.3)
Smoking[b]					
Never smoker	37,010 (39.4)	35,083 (37.1)	33,103 (35.2)	34,166 (35.9)	33,529 (35.4)
Former smoker	44,645 (47.5)	47,528 (50.2)	48,959 (52.0)	50,016 (52.6)	50,363 (53.1)
Current smoker	12,408 (13.2)	12,082 (12.8)	12,029 (12.8)	10,908 (11.5)	10,905 (11.5)
Education[b]					
≤ 11 years	30,707 (32.5)	26,647 (27.9)	24,409 (25.7)	22,244 (23.1)	21,367 (22.3)
High school	10,266 (10.9)	10,265 (10.7)	9912 (10.4)	9200 (9.6)	8756 (9.1)
Some college	22,864 (24.2)	23,546 (24.6)	22,886 (24.1)	22,570 (23.5)	21,968 (22.9)
College and beyond	30,694 (32.5)	35,109 (36.7)	37,756 (39.8)	42,119 (43.8)	43,758 (45.7)
Physical activity[b]					
Never/rarely	21,985 (22.8)	18,811 (19.3)	16,817 (17.4)	15,476 (15.8)	15,034 (15.4)
1–3/mo	13,818 (14.3)	14,402 (14.8)	13,977 (14.5)	12,520 (12.8)	11,747 (12.0)
1–2/wk	19,425 (20.1)	21,323 (21.9)	21,946 (22.7)	21,625 (22.1)	21,268 (21.8)
3–4/wk	23,500 (24.3)	25,367 (26.1)	26,464 (27.4)	28,045 (28.7)	28,072(28.8)
5 + /wk	17,884 (18.5)	17,477 (18.0)	17,445 (18.1)	20,118 (20.6)	21,529 (22.1)
Family history of cancer[b]					
No	45,657 (49.2)	45,239 (48.4)	45,020 (48.6)	45,470 (48.5)	45,707 (49.0)
Yes	47,154 (50.8)	48,166 (51.6)	47,656 (51.4)	48,197 (51.5)	47,624 (51.0)
July erythemal UVR, (J/m^2)[a]					
≤ 180	43,589 (44.4)	42,252(43.0)	40,957 (42.0)	42,873 (43.4)	43,654 (44.3)
> 180–188	18,514 (18.9)	19,672 (20.0)	20,642 (21.2)	21,670 (22.0)	21,417 (21.7)
> 188–236	19,052 (19.4)	19,629 (20.0)	20,235 (20.7)	18,851 (19.1)	19,212(19.5)
> 236	16,992 (17.3)	16,830 (17.1)	15,724(16.1)	15,301 (15.5)	14,301 (14.5)
Alcoholic beverages, g/d	7.6 (61.4)	18.0 (103.7)	28.8 (136.5)	34.2 (149.8)	40.1 (168.5)
Caffeinated coffee, g/d	300.9 (957.5)	373.9 (957.5)	373.9 (957.5)	373.9 (957.5)	373.9 (957.5)
Calories, kcal/d	1538.2 (743.4)	1632.3 (704.7)	1831.5 (752.1)	1934.4 (781.3)	2315.8 (953.5)

[a]Median (IQR) for continuous variables without normal distribution (total fish intake, tuna intake, fried fish intake, non-fried fish intake, alcoholic beverages, and caffeinated coffee). Mean (SD) for continuous variables with normal distribution (BMI, calories). Count (percentage) for all the categorical variables. *NIH* National Institutes of Health; *UVR* ultraviolet radiation

[b]*n* does not bring to 491,367 because of missing data. Percentage of missing data (Smoking: 3.8%; Education: 2.9%; Physical activity: 1.1%; Family history of cancer: 5.2%)

[c]Total fish intake is the sum of total fish intake is the sum of non-fried fish intake, fried fish intake, and tuna intake

Table 2 Association of total fish intake with malignant melanoma and melanoma in situ in the NIH-AARP Diet and Health Study ($n = 491{,}367$)

	Median (g/day)	Malignant melanoma			Melanoma in situ		
		Cases	Age & sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[b]	Cases	Age & sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[a]
Total fish intake							
Q1	3.23	802	1 (reference)	1 (reference)	510	1 (reference)	1 (reference)
Q2	7.96	973	1.18 (1.08–1.30)	1.15 (1.05–1.26)	632	1.21 (1.07–1.36)	1.18 (1.05–1.32)
Q3	12.93	1035	1.21 (1.10–1.32)	1.18 (1.07–1.29)	693	1.28 (1.14–1.43)	1.25 (1.11–1.40)
Q4	22.38	1122	1.29 (1.18–1.41)	1.24 (1.13–1.36)	720	1.30 (1.16–1.46)	1.25 (1.11–1.40)
Q5	42.79	1102	1.23 (1.12–1.35)	1.22 (1.11–1.34)	729	1.29 (1.15–1.44)	1.28 (1.13–1.44)
p-trend			< 0.001	0.001		0.001	0.002

CI confidence interval

[a]Adjusted for age (continuous), sex (male, female), education (≤ 11 years, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race (non-Hispanic white, non-Hispanic black, Hispanic, others), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 min or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, ≥ 5 times per week), July erythemal UVR (≤ 180, > 180–188, > 188–236, and > 236 J/m^2), alcohol intake (defined as average daily alcohol intake over the last 12 months from drinks of alcohol including beer, wine, and liquid; continuous), caffeinated coffee intake (continuous), smoking history (never, former, or current smoker), and daily energy intake (continuous)

Discussion

In this large prospective cohort study, we examined the associations between fish intake and risk of incident melanoma (including malignant melanoma and melanoma in situ). We found that higher total fish intake was positively associated with risk of malignant melanoma and melanoma in situ. All of the intake categories were associated with statistically significant increased risks, with a linear dose–response relationship, for malignant melanoma and melanoma in situ. Similarly, higher tuna intake and non-fried fish intake were also associated with increased risk of malignant melanoma and melanoma in situ. The positive association between fish intake and risk of melanoma was consistent across several demographic and lifestyle factors. However, there was a negative association between fried fish intake and risk of malignant melanoma when comparing the fifth versus first quintile and the test for trend was marginally significant, suggesting the potential difference between intake of fried fish and other types of fish on the risk of melanoma.

Our findings on fish intake are consistent with results from the previous analysis of the cohort with 9 years of follow-up and smaller number of melanoma cases ($n = 2{,}960$) [12], which focused on fish intake and all types of cancer and where melanoma was the only type of cancer that was positively associated with fish intake. Compared to this, our study further adjusted for risk factors relating to skin cancer, distinguished between different types of fish intake, and conducted stratified analyses with extended follow-up and additional melanoma cases as well as evaluation of melanoma in situ.

Our findings may be explained by contaminants in fish, such as polychlorinated biphenyls, dioxins, arsenic and mercury [21–23]. Higher fish intake is associated with higher level of body burden of each of these contaminants [24–27], which are associated with higher risk of skin cancer [28–38]. Previous epidemiological studies suggested positive associations between plasma levels of polychlorinated biphenyls, dietary polychlorinated biphenyls, and their risk of melanoma [28, 29], between arsenic exposure and risk of skin cancer [30–33], and between mercury exposure and risk of melanoma [34]. A few studies in occupational settings reported a positive association between occupational mercury exposure and risk of melanoma [35, 36]. One cross-sectional study observed a positive association between blood mercury levels and risk of non-melanoma skin cancer among the general population in the US [37]. A prospective study found that increased toenail mercury concentrations were associated with increased risk of skin cancer, including non-melanoma skin cancer and melanoma. [38].

However, our findings are not consistent with a few smaller-scale case–control studies, which indicated a protective role or no effect of fish intake on risk of melanoma [13–16]. The inconsistent results could be partly due to sample size, selection bias, recall bias, or confounder adjustments. Compared with previous studies, our study adjusted for more variables in the multivariate analyses, including socio-demographic factors, family history of cancer, and UVR exposure [13–16]. The multivariable-adjusted models yielded similar effect sizes compared to the age and sex-adjusted models for each type of fish intake and risk of melanoma.

Table 3 Association of types of fish intake with malignant melanoma and melanoma in situ in the NIH-AARP Diet and Health Study ($n = 491{,}367$)

	Median (g/day)	Malignant melanoma		Melanoma in situ	
		Age & sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[b]	Age & sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[a]
Tuna intake					
Q1	0.29	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2	1.59	1.04 (0.95–1.14)	1.01 (0.92–1.11)	1.04 (0.92–1.17)	1.01 (0.90–1.14)
Q3	2.45	1.07 (0.98–1.17)	1.02 (0.93–1.11)	1.17 (1.05–1.30)	1.11 (0.99–1.26)
Q4	5.29	1.19 (1.09–1.29)	1.11 (1.02–1.21)	1.23 (1.10–1.37)	1.14 (1.02–1.27)
Q5	14.2	1.26 (1.16–1.38)	1.20 (1.09–1.31)	1.25 (1.12–1.39)	1.17 (1.05–1.31)
p trend		< 0.001	< 0.001	< 0.001	0.005
Fried fish intake					
Q1	0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2	0.94	0.91 (0.81–1.02)	0.92 (0.82–1.03)	0.93 (0.81–1.07)	0.95 (0.83–1.09)
Q3	0.96	0.90 (0.82–0.97)	0.92 (0.85–1.00)	0.96 (0.87–1.06)	1.01 (0.91–1.12)
Q4	3.31	0.92 (0.85–0.99)	0.98 (0.90–1.06)	0.93 (0.84–1.02)	1.02 (0.93–1.13)
Q5	9.48	0.80 (0.74–0.87)	0.90 (0.83–0.98)	0.80 (0.72–0.89)	0.96 (0.86–1.07)
p trend		< 0.001	0.06	< 0.001	0.36
Non-fried fish intake					
Q1	0.31	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q2	2.82	1.11 (0.99–1.23)	1.07 (0.96–1.19)	1.05 (0.92–1.21)	1.01 (0.88–1.16)
Q3	3.5	1.17 (1.05–1.29)	1.10 (0.99–1.21)	1.23 (1.09–1.40)	1.15 (1.01–1.30)
Q4	7.67	1.33 (1.21–1.47)	1.21 (1.10–1.34)	1.37 (1.21–1.55)	1.22 (1.08–1.38)
Q5	17.76	1.31 (1.19–1.44)	1.18 (1.07–1.30)	1.43 (1.27–1.61)	1.25 (1.11–1.42)
p trend		< 0.001	0.003	< 0.001	< 0.001

CI confidence interval

[a]Adjusted for age (continuous), sex (male, female), education (≤ 11 years, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race (non-Hispanic white, non-Hispanic black, Hispanic, others), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 min or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, ≥ 5 times per week), July erythemal UVR (≤ 180, > 180–188, > 188–236, and > 236 J/m^2), alcohol intake (defined as average daily alcohol intake over the last 12 months from drinks of alcohol including beer, wine, and liquid; continuous), caffeinated coffee intake (continuous), smoking history (never, former, or current smoker), and daily energy intake (continuous)

There were several major strengths of our study. First, the large sample size and relatively long follow-up period provided sufficient statistical power to detect an association between fish intake and melanoma [17]. Second, our study used a prospective study design, in which dietary assessment was measured prior to melanoma diagnoses, which reduced the possibility of recall bias and selection bias. In addition, the detailed information on dietary and nondietary factors contained in this dataset allowed us to adjust for an extensive number of potential confounders. Lastly, our study examined different types of fish intake, which allowed for a more comprehensive understanding of intake and preparation of fish and melanoma risk.

There were also several limitations in our study. First, the associations we detected in our cohort study may not imply causality because this was not an intervention study. However, it would not be practical to conduct a clinical trial to evaluate adverse effect of fish intake. A prospective study design would be the best choice in this case, which we adopted. Also, the consistent and linear dose–response relationship between fish intake and melanoma risk support a potential causal relationship between fish intake and melanoma risk. Second, our study used a FFQ, a self-reported measure of dietary intake, to measure fish intake in the past 12 months before the beginning of follow-up. Despite the fact that the FFQ has been validated and used as a common tool to assess dietary intake, measurement error may have attenuated the findings [39, 40].

In addition, since dietary intake was measured at baseline only, we were not able to assess possible changes in diet over the follow-up period. We assumed that the baseline FFQ assessment did not change over time, reflected the cumulative exposure, and was captured during the etiologically relevant window. However, misclassification of exposure,

which was likely non-differential, could occur if participants changed their dietary intake during follow-up, and may further contribute to attenuating the associations we found. Thus, the true association between fish intake and skin cancer may even be stronger. Third, the UVR exposure was calculated for each participant based on their residence at baseline, instead of individual sun-related behaviors. Another potential limitation is the misclassification of cause of death in using the National Death Index to ascertain vital status. Finally, the cohort study lacked information on some risk factors of melanoma such as mole count, hair color, and history of severe sun burn.

Fish intake has been on the rise in the US and Europe in recent decades [41]. We observed positive associations between fish intake and malignant melanoma and melanoma in situ. The association was largely consistent by type of fish intake and by different population characteristics. Further studies are needed to replicate our findings and identify the components of fish which are responsible for the association and related biological mechanisms.

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Declarations

Conflict of interest The authors have not disclosed any competing interests.

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