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Longchain serum fatty acids and risk of thyroid cancer: a population-based case-control study in Norway

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Epidemiologic studies have shown an association between seafood consumption and risk of thyroid cancer. Fish meals increase the serum concentrations of the longchain fatty acids, eicosapentaenoic acid (20:5,*n*-3) (EPA) and docosahexaenoic acid (22:6,*n*-3) (DHA), for days. The hypothesis that serum concentrations of fatty acids may be associated with thyroid cancer risk therefore was tested in a population-based case-control study with 74 cases and 221 matched controls. Seventy-three cases with sera in the Norwegian serum bank (JANUS) were identified in the Norwegian Cancer Registry and matched with three controls, also in JANUS, on age, gender, place of residence, and time of blood sampling. Each case was matched with two controls. Serum concentrations of 11 longchain fatty acids were determined blindly by gas chromatography for all subjects. Controls were divided into three groups with increasing serum fatty acid concentrations, and odds ratios between cases and controls were estimated relative to the group with lowest serum level by univariate and multivariate analyses. The main finding was a significant inverse relation between the sum of arachidonic acid (20:4,*n*-6) (AA) and DHA serum concentrations and thyroid cancer risk. The significance of this association was weakened when the analyses were restricted to the papillary type of thyroid carcinoma. It was of the same order of magnitude whether the period between blood sampling and diagnosis was greater than eight years, or eight or less years. High EPA/AA ratio, indicating consumption of fish fat, was not associated significantly with increased thyroid-cancer risk. These data indicate that the association between seafood ingestion and increased thyroid-cancer risk may not be caused by the marine fatty acids. *Cancer Causes and Control* 1994, **5**, 433 - 439

Key words: Arachidonic acid, docosahexaenoic acid, case-control study, Norway, polyunsaturated fatty acids, risk reduction, thyroid cancer.

Introduction

The incidence rate of thyroid cancer shows considerable differences among countries.[1] Rates, especially of papillary carcinoma, are high, for instance, in Iceland, Hawaii (United States), and parts of Scandinavia, including fishing communities and certain high-risk coastal areas in Norway.[2] In inland regions where endemic goiter is prevalent, incidence rates of follicular carcinoma tend to be high. After the introduction of

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iodinized salt in Switzerland in the first half of this century, increasing incidence of papillary, compared with follicular, carcinoma has been observed.[3]

It is generally agreed that thyroid carcinogenesis includes dietary factors. Several epidemiologic studies have investigated different food items, including seafood, as possible risk factors for thyroid cancer. Despite significant research efforts, however, the results are conflicting—not the least concerning seafood and iodine.[4-7] In Norway, the intake of iodine shows little variation from high-risk coastal areas to low-risk inland regions, mainly due to the high iodine content in dairy products. Other putative risk factors associated with seafood consumption, therefore, should be evaluated.

Serum concentrations of longchain polyunsaturated fatty-acids of typical marine origin, as eicosapentaenoic acid (20:5,*n*-3) (EPA) and docosahexaenoic acid (22:6,*n*-3) (DHA), are correlated with fish consumption.[8] However EPA and DHA also may be synthesized endogenously from linolenic acid (18:3,*n*-3) (LNA). Linoleic acid (18:2,*n*-6) (LA) of plant origin is an important precursor of polyunsaturated fatty acids (PUFA) of the *n*-6 series, for instance, arachidonic acid (20:4,*n*-6) (AA).

In this study, we have measured the total concentrations of longchain fatty acids in sera from persons who subsequently developed thyroid cancer, and from matched controls to elucidate a possible association between serum levels of these fatty acids and future thyroid cancers.

Materials and methods

Subjects

The Norwegian serum bank, JANUS, was established in 1973.[9,10] By early 1993, the bank comprised nearly 150000 samples consolidated from 102000 healthy donors. In 1991, JANUS blood-donors who subsequently developed cancer were identified in the Cancer Registry of Norway using each subject's unique identification number. Nearly 6,000 persons were identified, including 74 cases with thyroid cancer.

For 73 of the 74 thyroid cancer cases, three donors matched on age (± 1 year), gender, place of residence, and time of blood sampling, were selected randomly as controls if they were free from malignancy at the time of diagnosis of the case. Each case was matched with two controls. Fifty-three of the 74 cases had papillary carcinoma as a morphologic diagnosis. The rest were mainly follicular carcinomas. Medullary carcinomas were not included.

Time between blood sampling and diagnosis varied between 18.8 and 0.8 years with a mean of 8.6 years. Thus, for 38 cases, the time lag was greater than eight years; for the remaining 36 cases, the time lag was eight years or less.

Determination of serum fatty acid concentrations

JANUS sera have been stored at about − 25°C since the bank was started. In a recent investigation, it was shown that serum fatty acids remain fairly stable during the storage period.[11]

Lipid extraction was carried out with methanol/chloroform.[12] An internal standard (non-adecanoic acid, C19:0) was added to serum prior to extraction. Fatty-acid methyl esters were formed by adding a BF_3-methanol reagent.[13] The fatty-acid methyl esters were extracted in heptane. The antioxidant BHT (butulated hydroxytoluene, 50 mg/l) was added to methanol, chloroform, and heptane before using these solvents. The serum specimen was 140-180 μl.

Gas chromatographic separation of fatty acids was performed on a Carlo Erba gas chromatograph (Milan, Italy) equipped with a flame ionization detector, and an attached LDC/Milton Roy integrator (Clare, Ireland). A 30 m × 0.32 mm I.D. Supel-cowax 10 column (SUPELCO, Bellafonte, PA, USA) was used. The program was: 170°C for four minutes, then the temperature was increased by 4°C/min to 225°C which was kept for 13 minutes. Flow of the carrier gas was 40 ml/min. Identities of the peaks were established by comparison with commercial standards (Sigma, St Louis, MO, USA).

Calculation was based on peak areas of the individ-

Table 1. Cases and controls by age, gender, residence, type of cancer, and time between blood-sampling and diagnosis, Norway

	Cases	Controls
Age (at diagnosis)		
< 40	11	31
40-49	27	78
50-59	28	89
60+	8	23
Gender		
Male	30	90
Female	44	131
Residence		
Oslo	23	69
Finnmark	16	47
Sogn og Fjordane	18	54
Oppland	17	51
Type		
Papillary	53	159
Other	21	62
Time between blood sampling and diagnosis		
≤ 8 yrs	36	108
> 8 yrs	38	113

ual fatty acids, as related to peak area of the internal standard. Results are given as mmol/l or as mol% of the fatty acids presented.

Statistical analysis

Odds ratio estimates and 95 percent confidence intervals were computed by logistic regression models for cases *cf* controls, in three groups corresponding to the first quartile, second plus third quartiles, and fourth quartile of the serum levels of the controls, respectively. This was to provide more extreme groups for comparison due to the small number of cases. The variation in the number of controls found in the three groups in the univariate analyses is caused by control sera containing identical amounts of the same fatty acid. The estimation method was conditional maximum likelihood performed by the EPICURE package.[14] Trend was tested by scoring the three groups. Effects were tested by log likelihood ratio tests.

Results

Cases were matched with control sera. Table 1 presents the distribution of cases and controls by age, gender, place of residence, morphologic type of thyroid cancer, and time between blood sampling and diagnosis.

Table 2 presents univariate, odds ratio estimates by type of longchain fatty acid and group of increasing serum level of the fatty acid. The estimated odds ratios for the intermediary and upper groups were not significantly different from 1.00 for any of the fatty acids presented in the table. The lowest *P* value for trend was obtained for AA and DHA.

When the serum concentrations of AA and DHA were combined, a significant inverse association with the risk of subsequently developing thyroid cancer was detected. This also was shown when prediagnostic serum levels of another marine fatty acid, EPA, was combined with AA and DHA (Table 3). Increased ratio between EPA and AA serum concentrations (EPA/AA) frequently is observed when the diet is supplemented with fish oils.[15-17] As seen in Table 3, high levels of EPA/AA may indicate an increased thyroid-cancer risk, but this was not statistically significant.

Table 4 presents the univariate analyses for the combination of DHA and AA or DHA, EPA, and AA serum concentrations as in Table 3, but restricted to the 53 cases with papillary carcinoma and their controls. The inverse association of high serum concentrations of these fatty acids diminished when restricted to the risk of developing papillary thyroid carcinoma compared with all thyroid malignancies. Nevertheless, the trend for the combination of AA and DHA remained statistically significant.

Table 2. Odds ratio estimates and 95% confidence intervals (in parentheses) by type of serum fatty acid and group of increasing serum concentrations; *P*-values for test and trend, Norway

Fatty acid	Univariate analyses				Trend
	Group			*P*	*P*
	Lower	Intermediary	Upper		
Palmitic	1.00	0.74 (0.40-1.38)	0.64 (0.31-1.35)	0.47	0.22
Cases/controls	24/56	35/110	15/55		
Palmitoleic	1.00	1.26 (0.65-2.45)	0.89 (0.38-2.08)	0.53	0.78
Cases/controls	18/59	43/112	13/50		
Stearic	1.00	0.81 (0.45-1.46)	0.52 (0.24-1.15)	0.25	0.10
Cases/controls	25/59	37/108	12/54		
Oleic	1.00	0.79 (0.43-1.47)	0.78 (0.37-1.62)	0.72	0.48
Cases/controls	23/58	34/108	17/55		
Linoleic	1.00	1.07 (0.56-2.06)	1.11 (0.53-2.31)	0.96	0.77
Cases/controls	18/57	37/110	19/54		
Linolenic	1.00	1.03 (0.54-1.96)	0.90 (0.39-2.05)	0.93	0.82
Cases/controls	21/62	39/113	14/46		
Eicosaenoic	1.00	0.80 (0.42-1.53)	1.04 (0.48-2.25)	0.67	0.96
Cases/controls	22/60	32/108	20/53		
Arachidonic	1.00	0.79 (0.43-1.47)	0.47 (0.20-1.06)	0.16	0.07
Cases/controls	25/59	38/107	11/55		
Eicosapentaenoic	1.00	0.73 (0.38-1.37)	0.85 (0.37-1.93)	0.63	0.59
Cases/controls	24/60	32/108	18/53		
Erucic	1.00	1.09 (0.41-2.93)	1.33 (0.49-3.55)	0.80	0.51
Cases/controls	26/81	27/85	21/55		
Docosahexaenoic	1.00	0.61 (0.32-1.14)	0.49 (0.21-1.13)	0.16	0.07
Cases/controls	32/71	30/102	12/48		

Table 3. Odds ratio estimates and 95% confidence intervals (in parentheses) by type of combinations of serum fatty acids and group of increasing serum levels or ratios; *P*-values for test and trend; Norway

Fatty acid[a]	Univariate analyses				Trend
	Group			*P*	*P*
	Lower	Intermediary	Upper		
AA + DHA	1.00	0.58 (0.32-1.06)	0.27 (0.11-0.66)	0.008	0.002
Cases/controls	30/56	34/107	10/58		
AA + EPA + DHA	1.00	0.57 (0.30-1.07)	0.38 (0.16-0.86)	0.05	0.01
Cases/controls	29/57	32/105	13/59		
EPA/AA	1.00	1.66 (0.80-3.43)	1.58 (0.64-3.89)	0.37	0.31
Cases/controls	13/55	42/111	19/55		

[a] AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

Table 4. Odds ratio estimates and 95% confidence intervals (in parentheses) by type of combinations of fatty acids and group of increasing serum concentrations; *P*-values for test and trend; papillary carcinoma cases; Norway

Fatty acid[a]	Univariate analyses				Trend
	Group			*P*	*P*
	Lower	Intermediary	Upper		
AA + DHA	1.00	0.71 (0.35-1.46)	0.37 (0.14-0.96)	0.11	0.04
Cases/controls	18/37	27/79	8/43		
AA + EPA + DHA	1.00	0.72 (0.34-1.53)	0.50 (0.19-1.28)	0.34	0.12
Cases/controls	17/38	26/79	10/42		

[a] AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

Table 5. Odds ratio estimates and 95% confidence intervals (in parentheses) by time lag, combinations of serum fatty acids, and group of increasing serum concentrations; *P*-values for test and trend; Norway

Fatty acid[a]	Univariate analyses				Trend
	Group			*P*	*P*
	Lower	Intermediary	Upper		
Time lag ≤ 8 yrs					
AA + DHA	1.00	0.50 (0.20-1.24)	0.26 (0.07-0.93)	0.08	0.02
Cases/controls	15/27	16/53	5/28		
AA + EPA + DHA	1.00	0.52 (0.20-1.31)	0.35 (0.11-1.16)	0.17	0.06
Cases/controls	15/29	15/51	6/28		
Time lag > 8 yrs					
AA + DHA	1.00	0.65 (0.29-1.46)	0.29 (0.09-0.95)	0.10	0.04
Cases/controls	15/29	18/54	5/30		
AA + EPA + DHA	1.00	0.62 (0.26-1.45)	0.40 (0.13-1.25)	0.27	0.10
Cases/controls	14/28	17/54	7/31		

[a] AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

In Table 5, the influence of the lag time from blood sampling to diagnosis on the association between the combination of AA and DHA serum levels and subsequent development of thyroid cancer was studied. The 74 sets of cases and controls were divided into one group with lag time from blood sampling to diagnosis equal to or less than eight years and one group with lag time greater than eight years. The inverse association associated with increasing serum levels of the fatty acids was of the same order of magnitude whether the lag time was greater than eight years or eight years or less.

Multivariate analyses of the combination of AA and DHA serum concentrations are presented in Table 6 and indicate, as the univariate analyses, an inverse association with the risk of developing thyroid cancer.

Serum concentrations of the precursors of AA and DHA, LA, and LNA, respectively, were not associated significantly with increased thyroid-cancer risk in the multivariate analysis.

Discussion

Results have been presented showing a negative association between combinations of AA, EPA, and DHA serum levels and the risk of subsequently developing thyroid cancer. The apparent protective effect was strongest for high serum levels of the sum of AA and DHA, but was weakened when restricted to the risk of developing papillary thyroid carcinoma compared with all thyroid neoplasms. The odds ratio estimates indicated that the protective effect of high AA and DHA serum levels was not specific for the papillary subtype of thyroid cancer. These data could suggest that the protection induced by these fatty acids is strongest for the follicular thyroid cancer. However, the number of follicular cases was too small to allow statistical analyses of this subtype alone.

The protective effect was confirmed in multivariate analyses. The protection could be seen both when the lag time between blood sampling and diagnosis was more than eight years, as well as when it was eight years or less. Any influence of AA and DHA on thyroid carcinogenesis detectable more than eight years before diagnosis is in accordance with the notion that well-differentiated thyroid cancers grow slowly and probably remain subclinical for a long time. The individual variation in serum fatty acid concentrations over time is not known. A protective effect of AA and DHA observed less than eight years before diagnosis may reflect that these fatty acid concentrations were high and inhibited thyroid carcinogenesis at an even earlier stage.

Table 6. Odds ratio estimates by type of fatty acid(s), group of increasing serum concentrations, and fatty acid variables included in two multivariate analyses; *P*-values[a] of test are given with AA and DHA in the model, Norway

Fatty acids[b]	Multivariate analyses		
	Model AA + DHA, LA + LNA		Model AA + DHA, LA, LNA	
AA + DHA				
Lower	1.00		1.00	
Intermediary	0.52		0.51	
Upper	0.22		0.22	
LA + LNA				
Lower	1.00		—	
Intermediary	1.11	$P = 0.30$	—	
Upper	1.77		—	
LA				
Lower	—		1.00	
Intermediary	—		1.10	
Upper	—		1.60	
LNA				$P = 0.74$
Lower	—		1.00	
Intermediary	—		1.16	
Upper	—		1.10	

[a] The *P*-values follow from the log likelihood ratio test with AA + DHA in the model.

[b] AA, arachidonic acid; DHA, docosahexaenoic acid; LA, linoleic acid; LNA, linolenic acid.

In epidemiologic studies, data have been presented suggesting that increased consumption of seafood may increase the risk of thyroid cancer.[4-6] However, no significant increase in thyroid cancer risk was associated with an increased EPA/AA, which is observed when the diet is supplemented with marine oils.[15-17] When compared with the thyroid-cancer risk reduction induced by the combination of AA, EPA, and DHA, the protective effect of AA seems to be greater than EPA. It is worthwhile noticing that the average serum level of AA was more than twice that of DHA and EPA. It was especially high in serum donors from inland communities, and may contribute to the lower thyroid-cancer risk in the inland regions of Norway compared with the coastal areas.[18]

High serum concentrations of LA and LNA, precursors of AA and DHA, respectively, seemed to increase the thyroid cancer risk. This association, however, was not statistically significant. The ratio between endogenously formed and exogenously supplied AA or DHA may vary according to the fatty acid content of the diet. Dietary sources rich in AA and DHA are peanut oil and fish oil, respectively.

It was presented recently that thyroid cancer risk in females increases with parity.[19] The fetus accumulates AA and DHA during pregnancy, strongest in the last trimester.[20] The pregnant woman, therefore, may experience a relative lack of these PUFAs. Suboptimal serum concentrations of AA and DHA subsequently may reduce an apparent protective effect against developing thyroid cancer.

We can only speculate if changes in serum fatty-acid levels alter the fatty acid contents of thyroid cells. DHA and AA plasma-phospholipid concentrations in preterm infants correlated significantly with DHA and AA phospholipid concentrations in erythrocytes.[21] In porcine thyroid-cell cultures, Dugrillon and Gärtner[22] showed that essential fatty acids were taken up rapidly by thyroid cells in culture. Pretreating the cells with DHA increased the growth inhibitory effect of iodide, which is an important physiologic inhibitor of thyroid cell proliferation.[23] This was not observed when the cells were treated with AA. However, AA, as well as

EPA and DHA, can be converted to iodolactones by peroxidases.[24] Iodolactone formed by iodination of AA in thyroid cells can mimic the cell-growth inhibitory effects of iodine.[25] Iodinated AA derivatives may play a specific role as mediators of some effects of iodine in thyroid cells. It is not known if increased serum-AA concentrations will render thyroid cells more susceptible to the inhibitory effects of iodine *in vivo*.

Interestingly, the fatty acids most prone to peroxidation (*i.e.*, AA, DHA, and EPA) were the most protective. Proliferation of human hepatoma cells in culture was inhibited by lipid peroxidation.[26] Fatty acids *n*-3 and *n*-6 selectively killed human breast, lung, and prostate cancer cells in coculture with normal human fibroblasts.[27] Further, proliferation of human breast-carcinoma cells implanted in athymic nude mice was suppressed by fish oil supplementation of the diet.[28] Increased peroxidation of AA and DHA and subsequent growth-inhibitory effects on cancerous thyroid cells is a possible explanation for the protective effect of high AA and DHA serum levels observed in this study.

Both AA- and DHA-activated protein kinase C (PKC) synergistically with diacylglycerol.[29] In addition, both fatty acids reduced the estrogen receptor content in MCF-7 breast cancer cells,[30] which is also observed after PKC stimulation of the cells.[31] The ratio between female and male incidence of thyroid cancer is high,[32] and Chaudhuri and Prinz[33] reported an increased estrogen-receptor binding capacity in thyroid adenomas and differentiated carcinomas compared with non-neoplastic tissues. AA and DHA possibly may prevent thyroid cancer by reducing the estrogen receptor contents in thyroid tissues.

Our results suggest a protective effect of high serum levels of AA and DHA on the risk of developing thyroid cancer. High EPA/AA levels, which are associated with consumption of fish fat and fish oils, did not alter thyroid cancer risk significantly. This suggests that the increase in thyroid cancer risk associated with fish consumption may not be related to the intake of marine fatty acids. Further studies are required to explain how these fatty acids inhibit thyroid carcinogenesis at the cellular level.

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