

ASSOCIATION BETWEEN BROILED FISH INTAKE AND CANCER
A COHORT STUDY
焼き魚摂取と発癌との関連に関するコホート調査

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In the continued interest of accurately defining the late effects of the atomic bombs, the qualitative and quantitative characteristics of the A-bomb radiation exposure doses are periodically refined. If warranted by future dose assessments, the data reported here will be reanalyzed and subsequently reported.

原爆の後影響を引き続いて正確に究明する目的をもって、原爆放射線被曝線量の質的・量的特質について定期的に改良を加えている。今後線量評価によって、その必要性が起これば、本報の資料を再解析の上、改めて報告する。

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SUMMARY

To examine the possible carcinogenic effects of frequent intake of mutagenic pyrolysates of proteins and amino acids, a cohort study was undertaken by following up for about 11 years 7,553 adult subjects whose personal characteristics together with dietary habits (including frequency of consumption of broiled fish and dried fish) had been examined at RERF. The stepwise multiple regression analysis revealed that frequent consumption of broiled fish was significantly positively associated with mortality from all cancer, as well as from cancer of the stomach. Among the 11 independent variables tested, consumption of broiled fish ranked high as a variable associated with mortality from all cancer and gastric cancer. Similar analyses by sex and city (Hiroshima and Nagasaki) showed that consumption of broiled fish was associated consistently and positively with mortality from all cancer in both sexes and cities but, with a few exceptions, this association was not statistically significant. The association of broiled fish consumption with mortality from gastric cancer was also consistently positive, but not statistically significant by sex and city. The relative risks of cancer mortality associated with frequent (twice or more weekly) consumption of broiled fish, as compared to less frequent consumption, were 1.3 ($p < 0.05$) for mortality from all cancer and 1.7 ($p < 0.05$) for mortality from gastric cancer. Contrary to

要約

蛋白質やアミノ酸の加熱による突然変異誘発性の変異物を常習的に摂取することが、発癌に何らかの影響を及ぼすかも知れない。このことを究明するためにコホート調査が行われた。対象集団は放射研が約11年間追跡調査した成人7,553名で、焼き魚、干し魚の摂取回数を含む食習慣など個人の特性について調査がされていたものである。段階的重回帰分析では、焼き魚の高頻度摂取が胃癌だけでなく全癌による死亡と有意に正の関連があることが示された。11個の独立変数を同時に検定したが、そのうち焼き魚の摂取は全癌死亡、胃癌死亡と関連のある変数でも上位にあった。同様の解析を性別、都市別(広島・長崎)にも行ったが、焼き魚の摂取頻度は、男女、両都市とも一貫して全癌死亡と正の関連を示した。しかし、1~2の例外を除いては統計的には有意でなかった。胃癌による死亡に対しても焼き魚の摂取は、性別、年齢別に正の関連を示したが、統計的には有意でなかった。焼き魚多食者(週に2回以上食べる)と、それ以下の焼き魚少食者に対する相対危険度は全癌死亡については1.3 ($p < 0.05$)、胃癌死亡については1.7 ($p < 0.05$)であった。焼き魚の

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broiled fish consumption, frequent consumption of dried fish was hardly associated with mortality from all cancers or from gastric cancer, but significantly positively associated with mortality from liver cancer.

INTRODUCTION

A strong mutagenicity of products of protein and amino acid pyrolysis has recently been demonstrated by several investigators.¹⁻⁶ Since such pyrolysates can be formed during cooking, their possible role in human carcinogenesis should be elucidated. This is particularly important to the Japanese who often eat broiled fish and are quite liable to gastric cancer.

According to the latest National Nutrition Survey conducted in 1979, broiled fish was served at supper in 22% of 16,195 randomly sampled households, while fish cooked with soy-sauce or sashimi (sliced raw fish) was served in 8% and 12% of them, respectively.⁷ Thus, broiling seems common among current fish cooking in Japan. A similar custom must have prevailed in the past too, because broiled fish is generally considered to be one of the traditional dishes of Japan, although no precise national figures are available to prove it. All of these facts indicate the necessity of epidemiologic studies to investigate the possible ill effects of frequent intake of fish prepared in this manner. More than 10 years ago, RERF investigated the dietary habits, including the intake of broiled and dried fish, of a group of persons. In the present study, their cancer mortality, particularly mortality from gastric cancer, was examined using the multiple regression analysis, for possible associations with such dietary habits and other related parameters.

MATERIALS AND METHODS

During 1968-70, 11,203 Adult Health Study subjects⁸ were interviewed for personal histories, including current dietary and various other habits, in Hiroshima and Nagasaki. The nurses participating in this study interviewed the subjects when they came for a biennial physical examination. In both cities, these nurses were instructed and trained beforehand to ensure uniformity of the method of inquiry. About three-quarters of the above population consisted of those exposed to ionizing radiation, while the remaining quarter formed a nonexposed group. For 7,553 of the 11,203 subjects,

摂取とは対照的に、干し魚の多食は全癌死亡、胃癌死亡ともにほとんど関連がなかったが、肝癌による死亡とは正の関連があり、統計的に有意であった。

緒言

蛋白質やアミノ酸の熱分解産物が高い突然変異原性を示すということが、最近数名の研究者によって証明された。¹⁻⁶ このような熱分解産物は調理中に形成されるので、これらがヒトの発癌に果たす役割を解明する必要がある。このことは、焼き魚を多く食し、しかも胃癌にもかかりやすい日本人にとっては特に重要である。

1979年に実施された最新の国民栄養調査によれば、無作為抽出された16,195世帯のうち、夕食で焼き魚を食べたのは22%、煮魚は8%、刺し身は12%であった。⁷ このように、日本では焼き魚は今日の魚料理の中では一般的なものである。全国的な正確な数値を挙げて証明することはできないが、一般に焼き魚は伝統的な日本料理の一つと考えられているので、似たような習慣が過去においても一般的であったに違いない。これらの事実により、疫学的調査を行い、焼き魚の多食が悪影響を及ぼすかどうかを研究することが必要であると示唆される。10年以上前に、放影研はある集団に対して、焼き魚や干し魚の摂取を含む食習慣を調査した。本研究では、その集団の癌死亡、特に胃癌死亡と、このような食習慣及びその他の関連要因との関係を重回帰分析を用いて研究した。

材料及び方法

1968～70年に、広島及び長崎において成人健康調査対象者⁸ 11,203名に対して面接を行い、食習慣やその他の種々な習慣を含む個人歴を調査した。面接は対象者が2年に1回の健康診断で来所した際に、看護婦によって行われた。両都市とも、質問方法を確実に統一するため、看護婦は前もって指示及び訓練を受けた。対象集団のうち約3/4は電離放射線に被曝した者で、残りの約1/4は非被曝者である。11,203名の対象者のうち7,553名については、選ば

complete records were available for the 11 independent variables and one dependent variable prescribed. The independent variables include: age at interview, sex, radiation dose, school career, smoking habit, and frequency of consumption of broiled fish, dried fish, milk, salted pickle, fruit, and rice, all of which were used for the present analysis. The number of subjects by sex, city, and average age at interview are shown in Table 1.

れた11個の独立変数と一つの従属変数について完全な記録が得られた。独立変数は、面接時年齢、性別、放射線量、学歴、喫煙習慣、及び焼き魚、干し魚、牛乳、漬け物、果物、米の摂取頻度であり、すべて今回の解析に供された。性別、都市別、面接時平均年齢別の対象者数を表1に示す。

TABLE 1 SUBJECTS BY SEX AND CITY, AND AVERAGE AGE AT INTERVIEW

表1 性別、都市別対象者数と面接時平均年齢

City	Sex	Subjects	Age in years
			Average \pm SD
Hiroshima	Male	1781	51.1 \pm 14.4
	Female	3341	51.6 \pm 13.1
Nagasaki	Male	965	48.4 \pm 13.7
	Female	1466	46.2 \pm 11.6
Total	Male + Female	7553	50.1 \pm 13.4

Deaths seen among the cohort from January 1968 to December 1978 were pursued by a periodic family registration (koseki) check with practically no follow-up loss. Moreover, 30%-40% of the deceased were autopsied. Cause of death was obtained through the vital statistics death schedules kept in health centers throughout Japan.

1968年1月から1978年12月の間のこのコホート内での死亡は戸籍を定期的に照合して把握し、追跡洩れはほとんどなかった。また、死亡者の30%~40%は剖検された。死因は、全国の保健所が保管している人口動態死亡票から入手した。

Mortality rates during the observation period for all cancer, cancer of stomach, and cancer of liver (ICD 140-208, 151, and 155.0, respectively, classified according to the International Classification of Diseases, 8th Revision) were calculated for males and females from both cities combined by age and frequency of broiled fish intake (once or less, or twice or more per week) and compared. The mortality rates were then examined by stepwise linear multiple regression analysis, using the following linear model without considering interaction effects of the variables tested.⁹

調査期間中の全癌、胃癌、肝癌の死亡率(第8回修正の国際疾病傷害及び死因統計分類に従えば、それぞれ ICD 140-208, 151, 155.0)を両都市合計の男女について、年齢別、焼き魚の摂取頻度(週に1回以下、2回以上)別に計算し、比較した。また、死亡率については、用いた変数の交互作用を考慮しない次に示す線形モデルを用いた段階的線形重回帰分析⁹を行った。

Expected mortality rate = $a_0 + a_1x_1 + \dots + a_nx_n$, where a_0 is constant, a_1, \dots, a_n are regression coefficients, and x_1, \dots, x_n are independent variables. Table 2 shows the values given to the independent and dependent variables.

期待死亡率 = $a_0 + a_1x_1 + \dots + a_nx_n$, ただし a_0 は定数, a_1, \dots, a_n は回帰係数, x_1, \dots, x_n は独立変数である。独立及び従属変数に与えられる値を表2に示す。焼き魚の摂取による影響を回帰分析で解析

Dried fish, often eaten after broiling, was not included in the independent variables when the possible effect of broiled fish intake was to be examined by the regression analysis. Similar regression analysis was made also for consumption of dried fish by sex and city. When dried fish was analyzed, broiled fish was excluded from the independent variables, for the same reason as mentioned above.

する場合は、干し魚はしばしば焼魚として食されるので独立変数から除外し、干し魚の摂取については別に、性別、都市別に同様の回帰分析を行った。上と同じ理由から、干し魚を解析する場合は焼き魚は独立変数から除外した。

TABLE 2 VARIABLES TESTED AND GIVEN VALUES

表2 解析に供された変数と、それに付与された値

Variable	Value for variables
1. Frequency of broiled fish consumption*	1: once or less 2: 2-4 times 3: 5 times or more per week
2. Frequency of dried fish consumption*	
3. Frequency of milk consumption	
4. Frequency of salted pickle consumption	
5. Frequency of fruit consumption	
6. Amount of rice consumption	1: less than 285 g daily 2: 285 g or more, daily
7. School career	0: no formal education 1: primary or junior high school 2: senior high school 3: junior college 4: college or university
8. Smoking	1: no smoking; 2: 1-19 cigarettes; 3: 20 or more cigarettes, daily
9. Radiation dose	estimated dose in rad but 600 rad is given for those exposed to 600 rad or more
10. Age	age at interview
11. Sex	0: female; 1: male
12. Vital status (dependent variable)	0: alive; 1: dead

*When the effect of frequency of broiled fish consumption was to be examined by the multiple regression analysis, frequency of dried fish consumption was excluded from the independent variables and vice versa. 焼き魚の摂取頻度の効果を重回帰分析で解析する場合は、干し魚の摂取頻度は独立変数から除外し、その逆の場合も同様とした。

Relative risks were calculated as ratios of the cancer death rate of subjects who eat broiled fish twice or more weekly to the corresponding rate of those with less intake. This was accomplished by using the Mantel-Haenszel method¹⁰ and the above-mentioned regression equation, assuming that the variables other than broiled fish consumption take their respective mean values.

相対危険度を、週に2回以上焼き魚を摂取する者の癌死亡率と、週1回以下の者の癌死亡率の比として計算した。これには Mantel-Haenszel 法¹⁰を用い、更に焼き魚の摂取以外の変数はそれぞれ平均値をとるものとして、上述の回帰式を用いて計算した。

RESULTS

Dried Fish. It was revealed that dried fish was considerably less than broiled fish consumption among both sexes, because the proportions of subjects who reported dried fish intake twice or more weekly were 23% for males and 18% for females, while the corresponding proportions for broiled fish were 41% and 34%, respectively. It was also shown that the frequency of dried fish consumption was hardly associated with deaths from all cancer and gastric cancer; relative risks calculated by the Mantel-Haenszel method being 0.92 ($\chi^2=0.19$) and 0.95 ($\chi^2=0.00$), respectively, as shown in Table 3. The multiple regression analysis also yielded practically the same results. However, frequent consumption of dried fish was shown to be significantly, positively associated with mortality from cancer of the liver, with a relative risk of 2.75 ($\chi^2=5.12$). However, no further multiple regression analysis was made, because the number of deaths from liver cancer was limited and no deaths were seen in some age-classes.

結果

干し魚. 焼き魚を週に2回以上食べると答えた者は男性41%, 女性34%であったのに対して, 干し魚を週に2回以上食べると答えた者は男性23%, 女性18%であることより, 男女とも, 干し魚の摂取頻度は焼き魚と比べてかなり低いことが明らかになった. また, 干し魚の摂取頻度は全癌及び胃癌死亡とほとんど関連がないことも示された. 表3に示すように, Mantel-Haenszel法で算出された相対危険度は, 全癌0.92 ($\chi^2=0.19$), 胃癌0.95 ($\chi^2=0.00$)である. 重回帰分析の結果もほとんど同じであった. しかしながら, 干し魚の多食は相対危険度2.75 ($\chi^2=5.12$)で, 肝癌死亡と有意に正の関連があることが示された. しかしながら, 肝癌死亡数は少ない上に, 死亡が見られない年齢階級群もあるので, あえて重回帰分析を行うことはしなかった.

TABLE 3 CANCER DEATHS AND DEATH RATES(%)BY DRIED FISH CONSUMPTION
表3 干し魚の摂取頻度別癌死亡及び死亡率(%)

Age	Subjects		Deaths											
			All cancer		Stomach cancer				Liver cancer					
			Less freq.*	Freq.**	Less freq.*	Freq.**	Less freq.*	Freq.**	Less freq.*	Freq.**				
		No.	rate	No.	rate	No.	rate	No.	rate	No.	rate			
Male														
0-39	587	207	8	13.6	2	9.7	4	6.8	0	-	0	-	1	4.8
40-49	400	143	6	15.0	1	7.0	2	5.0	1	7.0	0	-	0	-
50-59	402	133	23	57.2	6	45.1	9	22.4	1	7.5	4	10.0	1	7.5
60-69	463	105	39	84.2	11	104.8	14	30.2	5	47.6	3	6.5	3	28.6
70-79	239	45	32	133.9	4	88.9	11	46.0	1	22.2	3	12.6	1	22.2
80-99	18	4	0	-	0	-	0	-	0	-	0	-	0	-
Total	2109	637	108	51.2	24	37.7	40	19.0	8	12.6	10	4.7	6	9.4
Female														
0-39	848	261	9	10.6	3	11.5	0	-	2	7.7	0	-	0	-
40-49	1180	329	19	16.1	5	15.2	4	3.4	1	3.0	1	0.8	0	0
50-59	754	156	23	30.5	1	6.4	8	10.6	0	-	0	-	0	0
60-69	767	116	27	35.2	8	69.0	7	9.1	3	25.9	3	3.9	2	17.2
70-79	327	34	15	45.9	1	29.4	5	152.9	0	-	1	3.1	1	29.4
80-99	32	3	1	31.3	0	-	1	31.3	0	-	0	-	0	-
Total	3908	899	94	24.1	18	20.0	25	6.4	6	6.7	5	1.3	3	3.3
Male+Female			RR† = 0.92, $\chi^2=0.19$				RR = 0.95, $\chi^2=0.00$				RR = 2.75, $\chi^2=5.12$			

*Less freq. : Dried fish consumed less than twice weekly. 低頻度: 干し魚を週に2回未満摂取する.

**Freq. : Dried fish consumed twice or more weekly. 高頻度: 干し魚を週に2回以上摂取する.

†RR: Relative risk. RR 相対危険度.

Broiled Fish. Table 4 shows the number of cancer deaths and cancer death rates by consumption of broiled fish, age, and sex. The number of deaths seen at most ages was relatively small and no highly consistent difference could be seen in mortality rates between the groups. However, mortality rates of all cancer and stomach cancer for all ages were higher among the frequent consumers of broiled fish than the less frequent consumers, in both sexes. Relative risks were slightly but significantly elevated over unity for these cancers. A slightly elevated relative risk was also seen for liver cancer, but without statistical significance. No further analysis was made as mentioned previously.

焼き魚。焼き魚の摂取頻度別、年齢別、性別の癌死亡数、癌死亡率を表4に示す。ほとんどの年齢において死亡数は比較的少なく、グループ間では、高度に一貫性のある死亡率の差異は認められなかった。しかし、男女ともすべての年代において全癌及び胃癌死亡率は焼き魚多食の方が焼き魚少食者よりも高かった。これらの癌の相対危険度は、わずかではあるが1より有意に大きかった。肝癌の相対危険度もわずかに1より大きかったが、統計的に有意ではなかった。既に述べたように、更に詳しく解析を行うことはしなかった。

TABLE 4 CANCER DEATHS AND DEATH RATES(%)BY BROILED FISH CONSUMPTION

表4 焼き魚の摂取頻度別癌死亡及び死亡率(%)

Age	Subjects		Deaths											
			All cancer				Stomach cancer				Liver cancer			
	Less* freq.	Freq.**	Less freq.*		Freq.**		Less freq.*		Freq.**		Less freq.*		Freq.**	
No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	
Male														
0-39	511	283	6	11.7	4	14.1	3	5.9	1	3.5	0	-	1	3.5
40-49	308	235	6	19.5	1	4.3	2	6.5	1	4.3	0	-	0	-
50-59	304	231	11	36.2	18	77.9	4	13.2	6	26.0	3	9.9	2	8.7
60-69	304	264	19	62.5	31	117.4	5	16.4	14	53.0	3	9.9	3	11.4
70-79	172	112	21	122.1	15	113.9	7	40.7	5	44.6	4	23.3	0	-
80-99	9	13	0	-	0	-	0	-	0	-	0	-	0	-
Total	1608	1138	63	39.2	69	60.6	21	13.1	27	23.7	10	6.2	6	5.3
Female														
0-39	704	405	9	12.8	3	7.4	0	-	2	4.9	0	-	0	-
40-49	976	533	14	14.3	10	18.8	2	2.0	3	5.6	0	-	1	1.9
50-59	589	321	15	25.5	9	28.0	6	10.2	2	6.2	0	-	0	-
60-69	603	280	21	34.8	14	50.0	5	8.3	5	17.9	2	3.3	3	10.7
70-79	263	98	12	45.6	4	40.8	4	15.2	1	10.2	1	3.8	1	10.2
80-99	30	5	1	33.3	0	-	1	33.3	0	-	0	-	0	-
Total	3165	1642	72	22.7	40	24.4	18	5.7	13	7.9	3	0.9	5	3.0
Male+Female			RR [†] = 1.33, $\chi^2 = 4.22$				RR = 1.67, $\chi^2 = 4.39$				RR = 1.32, $\chi^2 = 0.23$			

*Less freq. : Broiled fish consumed less than twice weekly.

低頻度: 焼き魚を週に2回未満摂取する。

**Freq. : Broiled fish consumed twice or more weekly.

高頻度: 焼き魚を週に2回以上摂取する。

†RR : Relative risk.

RR 相対危険度。

As shown in Table 5, consumption of broiled fish showed the fourth largest contribution to death from all cancer, following the variables of age at interview, sex, and radiation dose. Table 6 also shows that this variable was significantly associated with death from all cancer.

表5に示されるように、焼き魚の摂取は面接時年齢、性、放射線量変数に次いで四番目に大きく全癌死亡に寄与している。表6も、この変数が全癌死亡と有意に関連があることを示すものである。

TABLE 5 STEPWISE REGRESSION ANALYSIS FOR 7,553 PERSONS

表5 7,553名を対象に行った段階的回帰分析

Order	All cancer		Stomach cancer	
	Variable	F-value	Variable	F-value
1	Age	126.93**	Age	44.85**
2	Sex	80.22**	Sex	32.37**
3	Radiation	56.87**	Broiled fish	23.22**
4	Broiled fish	44.20**	Milk	18.21**
5	Smoking	36.25**	Fruit	14.82**
6	Salted pickle	30.70**	Radiation	12.45**
7	Rice	26.54**	Salted pickle	10.71**
8	School career	23.30**	School career	9.38**
9	Fruit	20.72**	Smoking	8.34**
10	Milk	18.65**	Rice	7.51**

**p<0.01

TABLE 6 MULTIPLE REGRESSION ANALYSIS OF DEATHS FROM ALL CANCER

表6 全癌死亡の重回帰分析

Variable	Regression coefficient $\times 10^4$ (Standard error $\times 10^4$)								
	Total	Male				Female			
		Hiroshima	Nagasaki	Hiroshima	Nagasaki				
Broiled fish	97* (38)	214* (92)	92 (117)	15 (51)	54 (70)				
Milk	5 (23)	42 (57)	-82 (79)	-21 (30)	58 (45)				
Salted pickle	-47 (31)	-36 (75)	-40 (91)	-20 (42)	-120* (61)				
Fruit	-12 (30)	-84 (68)	38 (91)	7 (43)	-13 (57)				
Rice	-56 (42)	-131 (108)	7 (142)	-50 (55)	42 (75)				
School career	-23 (31)	5 (62)	-77 (83)	-23 (50)	-65 (67)				
Smoking	73* (36)	19 (67)	124 (87)	138* (65)	195 (105)				
Radiation dose	0.48** (0.16)	0.06 (0.39)	0.10 (0.46)	0.84** (0.23)	0.04 (0.26)				
Age at interview	16** (2)	25** (4)	27** (5)	9** (2)	8* (3)				
Sex	161** (55)	-	-	-	-				
Constant	-576	-791	-985	-279	-199				
R ² (%)	2.41	3.48	4.26	1.31	1.51				
Subjects	7553	1781	965	3341	1446				
Deaths	244	90	42	83	29				

R: Multiple correlation coefficient.

重相関係数.

*P<0.05 **P<0.01

When the subjects were divided by sex and city, broiled fish consumption still showed a consistent positive association with death from all cancer, but the association was not statistically significant except for males in Hiroshima. The age-at-interview variable showed a significantly positive association in both sexes and cities. Radiation dose and smoking also showed a consistent positive association with such deaths, but without statistical significance except for females in Hiroshima. In contrast with the above variables, consumption of salted pickles showed a consistent negative association with death from all cancer which was statistically significant for females in Nagasaki. For other variables, neither consistent nor significant associations were seen.

As shown in Table 5, consumption of broiled fish showed the third largest contribution to death from stomach cancer, surpassed only by age and sex. Table 7 also shows that this variable is significantly, positively associated with death from stomach cancer. Other variables such as age, sex, and milk consumption as well, were shown to be positively associated with this cancer.

対象者を性別、都市別に区別した場合でも、焼き魚の摂取は一貫して全癌死亡と正の関連を示したが、広島を男性を除いては統計的に有意ではなかった。面接時年齢は男女ともいずれの都市においても有意な正の関連を示した。放射線量及び喫煙も一貫してこれらの癌と正の関連が見られたが、広島を女性を除いては統計的に有意ではなかった。上述の変数とは対照的に、漬け物の摂取は一貫して全癌死亡と負の関連を示し、長崎の女性においては統計的に有意であった。他の変数に関しては、一貫した関連も有意な関連も見られなかった。

表5に示すように、焼き魚の摂取は年齢と性に次いで三番目に大きく胃癌死亡に寄与している。表7も、この変数が胃癌死亡と有意な正の関連をもつことを示すものである。年齢、性及び牛乳の摂取など他の要因も胃癌と正の関連が見られた。

TABLE 7 MULTIPLE REGRESSION ANALYSIS OF DEATHS FROM STOMACH CANCER

表7 胃癌死亡の重回帰分析

Variable	Regression coefficient $\times 10^4$ (Standard error $\times 10^4$)									
	Total		Male				Female			
			Hiroshima		Nagasaki		Hiroshima		Nagasaki	
Broiled fish	47*	(22)	105	(60)	2	(62)	13	(26)	52	(42)
Milk	27*	(13)	68	(38)	47	(42)	-5	(15)	34	(26)
Salted pickle	9	(18)	28	(49)	-7	(48)	7	(21)	-2	(36)
Fruit	-19	(17)	-46	(45)	1	(48)	-18	(22)	-22	(34)
Rice	3	(24)	44	(71)	58	(75)	-37	(28)	32	(44)
School career	-5	(18)	15	(41)	-59	(44)	-14	(25)	8	(40)
Smoking	4	(21)	-40	(44)	73	(46)	47	(33)	-25	(63)
Radiation dose	0.07	(0.09)	0.26	(0.26)	-0.20	(0.24)	-0.09	(0.12)	0.26	(0.15)
Age at interview	6**	(1)	11**	(3)	5	(3)	4**	(1)	3	(2)
Sex	92**	(32)	-		-		-		-	
Constant	-329		-662		-308		-80		-210	
R ² (%)	0.99		1.68		1.05		0.67		0.61	
Subjects	7553		1781		965		3341		1446	
Deaths	79		37		11		21		10	

R: Multiple correlation coefficient.

重相関係数.

*P<0.05 **P<0.01

When the analysis was made by sex and city, age at interview still showed a significantly positive association in Hiroshima. Consumption of broiled fish gave a consistent positive association for both sexes and cities, but without statistical significance. None of the other variables tested showed any consistent or statistically significant associations at all.

Relative Risk for Consumption of Broiled Fish. Relative risks calculated by the multiple regression equations were slightly higher than unity with a statistical significance, specifically, 1.3 ($p < 0.05$) for all cancer and 1.7 ($p < 0.05$) for stomach cancer. It is notable that these figures are very close to the relative risks as calculated by the Mantel-Haenszel method as shown in Table 4.

Person-months. Both those who consumed broiled fish frequently and those with less frequent intake were much alike in regard to average person-months of observation as calculated by sex, age, and radiation dose. Thus, it does not seem probable that the observed differences in mortality between these groups were due to any difference in length of observation.

DISCUSSION

Epidemiologic pursuit of possible cancer risks caused by frequent intake of mutagenic pyrolysates in food is of course very important, but determining the actual risks of pyrolysate intake seems to be quite difficult, because the heating of foods is a universal practice of mankind, rendering it difficult to find good control subjects who are free from such pyrolysates. Even if the pyrolysates happen to be highly carcinogenic in man, epidemiologic demonstration of such potency will not be easy unless appropriate negative or positive controls are available. Without such good control subjects it is likely that the relative risks of cancer attributable to the intake of such pyrolysates, if any, would become quite small. Furthermore, the acquisition of accurate information on individual dietary habits over a period of years, which is essential to elucidate any possible diet-cancer association, is also difficult to determine, as is well known.^{11,12}

In view of these inevitable difficulties, a cohort study, rather than a case-control study, was undertaken since the former is less prone to

性別、都市別に解析を行った場合でも、広島では面接時年齢は有意に高い関連を示した。焼き魚の摂取は、男女ともいずれの都市においても一貫して正の関連を示したが、統計的に有意ではなかった。解析された他の変数はいずれも一貫した関連も、統計的に有意な関連も全く示さなかった。

焼き魚の摂取についての相対危険度。重回帰式を用いて計算した相対危険度は全癌については1.3 ($p < 0.05$)、胃癌については1.7 ($p < 0.05$)で、わずかではあるが1より有意に大きかった。これらの値は、表4に示されるMantel-Haenszel法で計算した相対危険度と非常に近似していることは注目すべきである。

人月数。観察された平均人月数を性別、年齢別、放射線量別に計算した場合、焼き魚の多食者と少食者でよく似ていた。このことから、これらのグループ間で見られる死亡の差異は観察期間の長短によるものとは思われない。

考 察

食物中の、突然変異原性をもつ熱分解産物を常習的に摂取することによって引き起こされる癌のリスクを疫学的に追求することは言うまでもなく非常に重要である。しかし、食物を加熱するということは人類に普遍の慣習であり、加熱物を摂取していない適当な対照群を見つけることは困難であるので、熱分解産物摂取の実際のリスク究明となると非常に困難である。たとえ、熱分解産物がヒトに対して高い発癌性があるとしても、適当な正又は負の対照群が得られないかぎり、そのような潜在的効果を疫学的に証明することは容易ではない。そのような適当な対照群がないかぎり、熱分解産物の摂取に起因する癌についての相対危険度は、たとえあるとしても非常に小さいであろう。更に、何年にもわたって個人の食習慣について正確な情報を得ることも、食物と癌の関連を解明するのに必要欠くべからざることではあるが、よく知られているように^{11,12}その収集は困難である。

このような避け得ない問題を考慮して、症例-対照研究を行う代わりに、対象選択の偏りや情報収集の

selection and information biases. Also multiple regression analysis was used rather than the conventional mono-variate analysis often used in cohort studies, because the former facilitates the full use of the information collected and is considered to be more sensitive for detecting excess risks. These considerations seem to have been appropriate since a slight but statistically significant excess mortality for all cancer and stomach cancer was demonstrated to be associated with frequent intake of broiled fish. It was also notable that both the multiple regression analysis and Mantel-Haenszel method yielded practically the same magnitude for relative risks. These relative risks derived from the multiple regression equations cannot be explained by reference to any of the independent variables other than broiled fish which are listed in Table 2, since those variables are controlled in the analysis. Thus, the observed association between mortality from all cancer as well as stomach cancer, and intake of broiled fish seems to be a real one.

Any conclusive remarks, however, cannot readily be made, because 1) the possibility cannot be denied absolutely that some yet unknown confounding variable or variables other than those tested in this study might exist or that the observed association might be simply a chance association, 2) the observed significant positive association became statistically non-significant when the analysis was made by sex and city, 3) two case-control studies^{11,13} so far reported have failed to demonstrate any association between consumption of charcoal-broiled fish or foods prepared by other methods and stomach cancer. The unreliability of personal information about past dietary habits also justifies the conservative attitude taken in interpreting the present results. Much more evidence gathered and analyzed by similar or perhaps different epidemiologic approaches will be needed to reach any convincing conclusions.

Although no detailed analysis of liver cancer was made in this study, such analysis is highly desirable when the number of deaths becomes adequately large, because the relative risk obtained for liver cancer was significantly elevated among frequent consumers of dried fish and also elevated, but not significantly so, among frequent consumers of broiled fish, and because the highly mutagenic pyrolytic

偏りがそれほど生じないコホート研究を実施した。また、コホート研究によく用いられる従来の単独変数解析ではなく、重回帰分析を用いた。これは、重回帰分析では、収集された情報をより有効に利用でき、また、過剰リスクを発見する上でより鋭敏であると考えられているからである。全癌及び胃癌のわずかながら統計的に有意な過剰死亡が、焼き魚の多食と関連があることが証明されたことを考えれば、上述の考慮は適当であつたと思われる。重回帰分析によつても、Mantel-Haenszel法によつてもほとんど同じ程度の相対危険度が得られたことも注目し得る。表2に示す焼き魚以外のどの変数も解析の際にコントロールされているので、重回帰式から得られたこれらの相対危険度は、焼き魚以外のどの独立変数からも説明できない。胃癌だけでなく、全癌死亡と焼き魚の摂取との間に関連が認められるが、以上のことからすれば、実際に両者間に関連があるとと思われる。

しかしながら、以下に述べる理由から、たやすく結論を出すことはできない。1) 未知の交絡変数又はこの研究で用いられた変数以外の変数が存在する可能性や、認められた関連が単なる偶然による可能性が完全に否定できない。2) 有意な正の関連が認められていても、性別、都市別に解析すると統計的に有意ではなくなった。3) これまでに報告されている二つの症例-対照研究^{11,13}では炭火で焼いた魚やその他の方法で調理された食物と胃癌とのいかなる関連も証明されていない。個人の過去の食習慣に関する情報は信頼しにくいということも、本研究の結果の解釈を控え目にしている理由の一つである。納得のいく結論を得るには、更に多くの信頼できる資料を収集し、同様の、又は異なる統計的方法によつて解析する必要がある。

この研究では肝癌の詳しい解析は行われなかったが、このような解析は十分な死亡数がある場合は大変望ましい。なぜならば、得られた肝癌についての相対危険度は干し魚の多食者に有意に高く、焼き魚の多食者には有意ではないが高く、突然変異原性の高い tryptophan などの熱分解産物は動物に肝腫瘍を

products of tryptophan are known to induce hepatoma in animals.^{1,3,4}

Dried fish has been reported to be a risk factor for stomach cancer among Hawaiian Japanese by Haenszel et al.¹⁴ Yet, their similar case-control study, undertaken in Hiroshima, failed to reconfirm such an association for Japanese subjects.¹⁵ In view of their findings, our negative result does not seem to be unusual. Even so, a positive association might be expected because dried fish is often eaten after broiling. Though, with no certainty, the fact that dried fish, particularly well-dried varieties, are usually broiled only slightly as compared with the way raw fish is broiled, might be used to explain our negative result.

Our study indicated that frequent milk consumption is a risk factor with regard to stomach cancer, but this is quite contrary to the observations of Hirayama.^{16,17} Haenszel et al.¹⁴ also observed an association of decreased risk of stomach cancer and milk consumption only in Japanese "Issei", but not in "Nisei". Again, no reasonable explanation is available for this discrepancy, but the following possibilities seem to be conceivable: 1) our observation might be simply a chance association, 2) we used the multiple regression method for analysis while they did not, 3) in our cohort, people with chronic stomach trouble might have been particularly concerned about drinking milk, and 4) either our study or their studies might be biased in some currently unrecognized manner. The actual cause for the discrepancy cannot be decided at present. The drinking of milk cannot be concluded as an altogether effective preventative for stomach cancer, since some authors have failed to observe such beneficial effects of milk.¹⁸⁻²⁰

誘発することが知られているからである。^{1,3,4}

Haenszel ら¹⁴によって、干し魚は日系ハワイ人の間では胃癌の危険因子であると報告されている。しかし、彼らが広島で行った同様の症例-対照研究では、日本人対象者に対してそのような関連を再確認することはできなかった。¹⁵ 彼らの所見を考えると、我々の所見が否定的であったのも異例ではない。それにしても、干し魚はしばしば焼いて摂取されるので、正の関連が期待される。しかし、確実ではないが、我々の結果が否定的であったのは、通常干し魚、特に固干しのものは生の魚を焼く場合に比べて少ししか火を通さないからだとも考えられる。

我々の研究では牛乳の多飲は胃癌の危険因子であると示唆されたが、これは平山の所見^{16,17}とは全く相入れない。Haenszel ら¹⁴も胃癌のリスクが低いことと牛乳の摂取との関連を日系一世には認めたが、二世には認めなかった。この食い違いを論理的に説明するてだてはないが、以下に述べる可能性が考えられる: 1) 我々の所見は単なる偶然であった。2) 我々は解析に重回帰法を用いたが、彼らはこれを用いなかった。3) 我々のコホートでは慢性的に胃を患っている人が特に牛乳を摂取した。4) 我々の研究又は彼らの研究いずれにか、現在のところ知られていない点で偏りがある。現時点では、この食い違いの本当の原因を決定することはできない。幾つかの研究では、牛乳に胃癌予防上有益な効果があることができなかったのもので、¹⁸⁻²⁰ 牛乳にそのような効果があると結論付けることはできない。

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