厚生労働科学研究費補助金

子ども家庭総合研究事業

生涯を通じた健康の管理・保持増進のための健康教育・相談支援等の充実に関する研究

平成14～16年度　総合研究報告書

主任研究者　稲葉 裕

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Ⅰ.総合研究報告書

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主任研究者　稲葉　裕　順天堂大学医学部衛生学教授

分担研究者
平井愛山　千葉県立東金病院院長
三上春夫　千葉県がんセンター研究局・疫学研究部部長
松村康弘　国立健康・栄養研究所健康栄養情報・教育研究部部長
永田知里　岐阜大学医学部医学科総合病態・予防医学講座疫学予防医学分野助教授
水嶋春朔　国立保健医療科学院人材育成部部長

１．研究目的

種々の疾患で性差のあることは古くから知られているが、その理由の解明や対策が注目され始めたのはつい最近10年ぐらいのことである。

生涯を通じた女性の健康づくりの観点から、現在のわが国における女性の健康障害の実状を明らかにすること、またその健康管理や相談支援の体制についての提案するための基礎的な資料づくりをすることがこの研究の目的である。

具体的には以下の4課題を中心に研究を進めてきた。

(1) 千葉県下の女性専門外来および保健所の女性健康相談のデータを基に、今後必要とされる女性医療サービス並びのその担い手の育成システムに求められるものを明らかにする。

(2) 日本の既存コホート調査に蓄積されているデータを性差や年齢差という観点で再分析し、疾病の罹患や死因に対する性や年齢の影響及びその内容を明らかにする。

(3) 千葉県安房地区の市町村検診受診者とその家族を対象にコホート調査を行う。

(4) 人口動態統計、患者調査、国民栄養調査など既存資料を利用して、女性の死因、疾病、食品摂取状況について生態学的な分析を試みる。

２．研究方法

(1) 千葉県で女性外来と保健所女性相談来所者を対象とした質問票調査をH14～16年に実施した。女性外来受診者や保健所相談来所者の実態を明らかにし、その背景にある女性医療に関する医学的・社会的ニーズを解析した。

(2) 約3万人の高山コホートの結果を用いて女性の栄養摂取量、特にカルシウム、イソフラボン摂取量を分析し、食物摂取頻度調査票の妥当性を確認した。また、生活習慣と死亡との関連性を性差に注目して評価した。さらに、食事の変化による短期のイソフラボン代謝への影響を一般健康人を対象に食事記録、尿・血液のイソフラボン代謝物測定を行い、イソフラボン代謝物測定値とエストロゲン、カドミウム、ヨード等の測定値との関連も評価した。

文部科学省研究費助成による大規模コホートについては女性に関連する要因の解析を行った。11万人を約10年間追跡した大規模コホート調査において年齢・喫煙・飲酒の影響を考慮し、性差が部位別癌の死亡にどれぐらい影響を与えるのかを検討した。

栗源町コホートは平成元年に追跡開始した2,160名の約6割の予後について、女性のがん罹患と県との比較、循環器疾患と生命予後との関連、受療態度や医療の供給と重症化の関連を分析した。H15年度より追跡調査を実施し女性の全死亡のリスクと生殖歴との関連を分析した。

(3) 安房及び印旛山武医療圏住民、住民検診受診者、女性外来受診者及び保健所女性相談来所者を対象とし、ベースライン調査として、ライフスタイル、食生活状況、パーソナリティー、健康管理態度、健康状況と日常生活能力、血清、検診受診歴、受療動向・満足度・医療費の情報

を得て、コホート研究のベースラインデータの集計解析をすすめ、詳細な評価検討した。疾病発生、介護状況の変化、死亡等を把握する追跡システムを構築し、総務省へ死亡小票の閲覧のための目的外使用の申請を行っている。千葉県における調査企画委員会、専門部会、庁内組織として調査サポート班、保健所チーム、がんセンター疫学部、衛生研究所感染症疫学室及び東京大学が共同で安房医療圏の調査を実施運営してきた。

(4) 人口動態統計のデータを用いて性・年齢・死因別に比較し、性差の大きい死因等を明らかにした。1990年以降の死因データ、1993年の患者調査の分析をした。国民栄養調査の目的外使用の許可を受け、栄養素等摂取量、食品摂取量、栄養素摂取源食品の状況を性・年齢・地域別に調べた。さらに、死亡統計・患者調査より地域別に主な死因別死亡率・疾患別受療率と栄養・食品摂取量、生活習慣関連項目を生態学的手法で検討した。

3．研究成果及び考察

(1) 千葉県で女性外来と保健所女性相談来所者を対象とした質問票調査を実施し、2,934名の問診票解析を行った。来所者の主な受診理由は①からだの不調、②更年期(閉経)関連事項、③心の問題、④セカンドオピニオン等であった。保健所と医療施設では受診目的の割合がやや異なり、医療施設受診者は保健所来所者よりからだの不調や更年期関連の相談割合が高く、保健所来所者にはセカンドオピニオン関連の相談割合が高かった。今まで明らかにされなかった実態が見えてきた。

(2) 高山コホートでは女性の栄養摂取量、カルシウム、イソフラボン摂取量を分析し、食物摂取頻度調査票による大豆イソフラボン摂取推定の妥当性が良好であることを確認した。配偶者の死亡や別離と本人の死亡率に性差が認められるか評価し、男性では配偶者の死亡による影響は認められなかったが女性では配偶者の死亡後3年以上で死亡率は低かった。塩分摂取と脳卒中死亡に関する分析では男性においてナトリウム摂取と脳内出血、脳梗塞死亡に統計的に有意な正の関連性が示された。女性では統計的に有意でないもののナトリウム摂取と脳卒中全体、脳梗塞による死亡に正の関連性が認められた。大豆に多く含まれるイソフラボンにはエストロゲン代謝やプロスタグランディン産生に影響を及ぼす可能性があるが、若年女性を対象にこれらの機序が関与すると考えられる月経痛、月経前症状と大豆摂取との関連性を調べたが、有意な関連性は認められなかった。

大規模コホートの分析結果では甲状腺、胆のう癌を除く殆どの部位別がん死亡で男性の死亡リスクが高かった。喫煙や飲酒で調整しても男性の死亡リスクが高い癌は食道、胃、直腸、肝、肺、腎で、本質的に男性の死亡リスクが高いことが示唆された。しかし結腸、膀胱、喉頭、その他及び部位不明の胆道癌死亡では喫煙を調整すると性差は認められず、喫煙の影響が大きいことがわかった。

栗源町コホートでは女性のがん罹患が県平均より少なく、循環器疾患が生命予後に大きく関与すること、また重症化の傾向が認められることから受療態度や医療の供給に問題のあることが推測された。生殖歴と死亡については妊娠回数1〜3回の女性は妊娠歴のないものに対し全死亡のリスク低下があることを認め、初産年齢が21〜29歳より若年または高齢でリスクの増加傾向、閉経年齢が遅いものにリスクの低下傾向があることがわかった。生殖歴の全死亡に対するリスクの傾向を総括すると、1)初潮年齢の低下と閉経年齢の上昇は女性の寿命を延長させ、2)初産は20歳代が望ましく、3)妊娠回数は女性の寿命を規定する重要な因子で、1〜2子が望ましいことが示された。1980年代以降、初産年齢の上昇、少子化の進行はホルモン感受性がんの増加等の疾病構造の変化に結びついている可能性がある。女性のライフステージの変化により生物学的に望ましい生殖時期からのずれが生じてきている可能性がある。保健サービスや医療の問題を越えて、社会全体で女性のライフステージ毎に適切なサポートが提供される必要がある。

(3) 安房地域コホートでは、住民からインフォー

ムドコンセントを受けて参加していただくために、30 分間のビデオを製作し千葉ＴＶにて放映し、参加行動への影響を評価した。また、ベースライン調査として、生活習慣や予防保健サービス利用状況と健康状態、ＱＯＬ等に関する調査を自記式郵送法により実施した。回収率 46.5%（10,740/23,073）で有効回答数は 10,127 人であった。過去 5 年間に 1 回も健康診断を受けていない者の割合は 14%、3～4 回以上受診している者は 65.2%であった。これまでの健康診断で、高血圧を指摘された者は男性 33%、女性 27%、生活習慣の指導を受けていない者は、男性 30%、女性 26%であった。70 代以上では 3 割以上が高血圧の治療を受けていた。今後、コホート集団として追跡を継続する予定である。

(4) 人口動態統計死亡票の公表データを用いて性・年齢・死因別に比較し、75 才以上のくも膜下出血による死亡で性差が著しいことがわかった。1995～2000 年の人口動態死亡統計・患者調査を利用し女性の死因別・年齢別・地域別死亡率と性比を算出し、年齢階級別の患者数、受療率を算出した。死因別死亡率では県別分布に性差はあまり大きくないが、疾患別受療率では男女で異なる分布を示すものが多かった。

国民栄養調査に関しては目的外使用の許可を受け、性・年齢階級別栄養摂取量と食品摂取量、及び食品群別カルシウム・マグネシウムの摂取比率を調べた。千葉県においては 15～20 才代の女性のカルシウム摂取量が 450mg/日で厚労省の目標値 600mg/日を下回っていることがわかった。

また 2002 年の死因別年齢調整死亡率、疾患別年齢調整受療率を算出し、性別に 1996 年の国民栄養調査の生活習慣・食品摂取量のデータとの都道府県別相関を比較検討した。個人のリスク因子とは異なる因子がいくつか浮かび上がっており今後の検討課題であろう。

4．評価

1）達成度について

(1)についてはほぼ 80%、(2)は 90%、(3)は 50%、(4)は 80%と考えている。全体としては 75%程度である。

2）研究成果の学術的・社会的意義について

生涯にわたる女性の健康支援策の策定の一助として、女性外来および保健所が実施する女性の健康相談の受診者の実態調査を行い、女性外来の受療者の需要について調査研究をおこない、女性外来で提供する医療サービスの質的向上および女性外来の診療を担う医師の育成プログラムの確立も目指した研究で、ある程度実態を把握できた。

女性の健康に焦点を当てた研究は最近急速に増加している。しかし、国内にあってはまだ数少ないのが現状である。その理由として通常の地域コホートでは死亡、死因を end point とするため、女性の場合は男性より寿命が長いので結果が遅れて出る傾向があること、死因別では対象数が少なく有意差が出にくいこと等があげられる。今回の研究では既に実施されている日本の代表的コホートを対象に女性に対するリスクを集中的に分析することができた。その結果の一つとして、女性のライフステージの変化により生物学的に望ましい生殖時期からのずれが生じてきている可能性があることを指摘した。社会全体で女性のライフステージ毎に適切なサポートの提供が必要であると考える。

3）今後の展望について

今後展開されるであろう新たな女性医療サービスの基礎が確実なものになっており、さらに継続中のコホート研究の成果と相まって、女性の生涯を通じた健康支援事業の発展に貢献することが期待される。

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健康危険情報

特になし

知的財産権の出願・登録状況 (予定を含む)

特許取得	特になし
実用新案登録	特になし
その他	特になし

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Lin Y, Tamakoshi A, Kawamura Y, Inaba Y, et al.	Risk of Pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk.	Int. J.Cancer	99	742-746	2002
Lin Y, Tamakoshi A, Kawamura Y, Inaba Y, et al.	A prospective cohort study of cigarette-smoking and pancreatic cancer in Japan.	Cancer Causes Control	13(3)	249-254	2002
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Ⅲ. 研究成果の刊行物・別刷

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RISK OF PANCREATIC CANCER IN RELATION TO ALCOHOL DRINKING, COFFEE CONSUMPTION AND MEDICAL HISTORY: FINDINGS FROM THE JAPAN COLLABORATIVE COHORT STUDY FOR EVALUATION OF CANCER RISK

Yingsong LIN[1,2], Akiko TAMAKOSHI[2]*, Takashi KAWAMURA[3], Yutaka INABA[4], Shogo KIKUCHI[1], Yutaka MOTOHASHI[5], Michiko KUROSAWA[4] and Yoshiyuki OHNO[2] for the JACC Study Group

[1]*Department of Public Health, Aichi Medical University School of Medicine, Aichi, Japan*
[2]*Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[3]*Kyoto University Center for Student Health, Kyoto, Japan*
[4]*Department of Epidemiology and Environmental Health, Juntendo University School of Medicine, Tokyo, Japan*
[5]*Department of Public Health, Akita University School of Medicine, Akita, Japan*

We evaluated the associations of such lifestyle factors as alcohol drinking, coffee consumption and medical history with risk of death from pancreatic cancer in a large-scale prospective cohort study [the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study)] in Japan. Subjects were 110,792 (46,465 men and 64,327 women) inhabitants who were enrolled from 45 areas throughout Japan. At baseline, a self-administered questionnaire was used to obtain information on lifestyle factors and medical history. Cox proportional hazard models were used to calculate relative risks. During the follow-up period (mean ± SD 8.1 ± 1.8 years), 225 deaths due to pancreatic cancer were identified. Overall, neither alcohol nor coffee intake was associated with risk of death from pancreatic cancer. Heavy coffee consumption (≥4 cups/day), however, may increase the risk. Men who reported a history of diabetes mellitus and women who reported a history of gallstone/cholecystitis were at significantly (2-fold) increased risk of death from pancreatic cancer.

Key words: *pancreatic cancer; alcohol; coffee; medical history; prospective cohort study; Japan*

Pancreatic cancer is the fifth leading cause of cancer death and has markedly increased in both incidence and mortality over the past 4 decades in Japan.[1] Nevertheless, few epidemiologic studies have been conducted to identify environmental/genetic risk factors that contribute to pancreatic cancer development, and the etiology remains unknown.

Based on findings from epidemiologic studies, cigarette smoking has been firmly established as a risk factor for pancreatic cancer.[2–5] The relative risk (RR) for current smokers ranged from 1.5–3.9 compared to nonsmokers. Other possible risk factors are a long-term history of diabetes mellitus[6] and familial chronic pancreatitis.[7] Some studies have also indicated that heavy alcohol and coffee consumption may increase the risk of pancreatic cancer,[3,8–10] but the results have been inconclusive.

In a large-scale prospective cohort study, we found that current smokers had a 1.6-fold increased risk of pancreatic cancer compared with nonsmokers.[11] The same data set allowed us to investigate the association of other lifestyle factors, such as alcohol drinking, coffee consumption and medical history, with the risk of death from pancreatic cancer.

MATERIAL AND METHODS

Study cohort

The data set for the present analysis was obtained from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (the JACC Study). The details of the JACC Study have been described elsewhere.[12] In brief, it was initiated in 1988–1990 when 127,500 apparently healthy inhabitants who underwent a general health checkup were enrolled as a basic cohort population from 45 areas throughout Japan. The response rate was >90%, and the study areas covered almost all of Japan, including 6 cities (35% of the cohort population), 34 towns and 5 villages (65%). Among the cohort population, 46,465 men and 64,327 women (110,792 total), aged 40–79 years, were followed up for mortality to the end of 1997. Subjects provided informed consent by signing the cover of the questionnaire in the majority of areas. We excluded subjects with a history of any cancers at baseline and those with unknown smoking status. This left 99,527 subjects (44,646 men and 54,881 women) eligible for the present analysis. The mean age ± SD of the subjects was 57.3 ± 10.1 years at baseline.

Data collection

At baseline, we used a self-administered questionnaire to collect data on demographic characteristics, medical history of selected diseases such as diabetes mellitus and gallstone/cholecystitis, tobacco and alcohol use, coffee consumption, physical activity, female reproductive characteristics and dietary habits. For alcohol drinking, subjects were asked to describe their drinking status (never, former or current), age at starting drinking, frequency of consumption, type of beverages (Japanese sake, *shochu*, beer, whiskey and wine) and average amount converted to *go* (1 *go* includes ethanol content of 29 g). The frequency of alcohol consumption was divided into 4 categories: almost every day, 3–4 times/week, 1–2 times/week and <1/week. As for coffee consumption, the frequency was classified into 6 categories: >4 cups/day, 2–3 cups/day, 1 cup/day, 1–4 cups/week, 1–2 cups/month and seldom or never. In the section of medical history, subjects were asked whether they had ever suffered from the following diseases: stroke, hypertension, myocardial infarction,

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The members of the JACC Study Group are listed in Appendix I.

*Correspondence to: Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8550, Japan. Fax: +81-52-744-2971. E-mail: tamaa@med.nagoya-u.ac.jp

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renal diseases, hepatic diseases, gallstone/cholecystitis, diabetes mellitus, gastric/duodenal ulcer and tuberculosis.

Follow-up and identification of pancreatic cancer cases

During the follow-up period, the vital status of subjects was checked annually in each study area by reviewing their population-register sheets from the Ministry of Public Management, Home Affairs, Post and Telecommunications. For the deceased, causes of death were determined by death certificates, available from the Ministry of Health, Labor and Welfare. Verification of vital status was believed to be accurate because of the firmly established population registration system in Japan. The end point in this cohort study was death from pancreatic cancer (ICD-10[13]). We could not obtain further data on the proportion of histologically confirmed and deceased subjects who underwent autopsy. Neither did we have information on whether cases were detected incidentally at autopsy. Person-time of follow-up for each subject was computed from enrollment to the day of death from pancreatic cancer or any other cause, the time of moving out of the study area or the end of 1997, whichever occurred first. Move-outs were annually verified by the investigator with administrative assistance from public health nurses in each area by reviewing population-register sheets of the cohort member. As of the end of 1997, a total of 1,264 men (2.7% of the cohort population) and 1,978 women (3.9%) had moved out of the study region. Subjects who moved out of the study area or died from causes other than pancreatic cancer were treated as censored cases (n = 10,662). This investigation was approved by the Ethical Board of the Nagoya University Graduate School of Medicine.

Statistical analysis

All data were analyzed using SAS software.[14] The strength of associations was examined using RRs derived from the Cox proportional hazards model.[15] All RRs were adjusted for such potentially confounding factors as age and smoking in pack-years (never, 0–19, 20–39, ≥40 pack-years). Tests for trend were performed using continuous variables, and the Wald χ^2 was used to calculate p values for tests for trend. Ethanol intake (g/day) was calculated by multiplying the average amount consumed with the frequency of alcohol intake. All p values were based on 2-sided tests, and $p < 0.05$ was considered statistically significant.

RESULTS

We identified 225 deaths from pancreatic cancer during the follow-up of 775,697 person-years. The mean follow-up period (±SD) was 8.1 (±1.8) years. Table I shows the RRs of death from pancreatic cancer in relation to alcohol drinking. Daily amount, years of drinking and cumulative amount were not associated with increased risk of death from pancreatic cancer in either men or women. Similarly, we found no overall significant association between coffee intake and the risk of death from pancreatic cancer (Table II). However, the RR significantly increased to 3.19 [95% confidence interval (CI) 1.22–8.35] for men who consumed ≥4 cups of coffee/day.

Table III shows the risk of death from pancreatic cancer in relation to history of diabetes mellitus and gallstone/cholecystitis. A history of diabetes mellitus significantly increased the risk of pancreatic cancer in men. Compared to men having no history of diabetes mellitus, the RR for those having a history of diabetes mellitus was 2.12 (95% CI 1.19–3.77). A history of gallstone/cholecystitis was significantly associated with an increased risk of death from pancreatic cancer in women (RR = 2.51, 95% CI 1.41–4.46).

DISCUSSION

We found no significant association between alcohol drinking and risk of death from pancreatic cancer in this prospective cohort study. Given the possibility that the association between alcohol drinking and pancreatic cancer might be confounded by cigarette smoking, we examined alcohol intake stratified by smoking status (nonsmokers, current smokers smoking 1–19 and ≥20 cigarettes/day) and found that smoking did not change the association (data not shown). This analysis may have been limited by poor power. Specifically, after adjustment for other risk factors within each strata of smoking status, there was likely little power to discriminate between risk estimates. Nevertheless, the lack of an association found in our study was in agreement with most of the recent epidemiologic data.[16–22] After critically reviewing the available studies, the IARC concluded that there was little evidence to support a causal relation between alcohol and risk of pancreatic cancer.[23]

TABLE I – RR FOR PANCREATIC CANCER IN RELATION TO ALCOHOL DRINKING IN THE JACC STUDY[1]

	Males				Females			
	Person-years	Deaths	RR	95% CI	Person-years	Deaths	RR	95% CI
Daily amount (g)								
Nondrinkers	65,404	26	1.00		323,989	82	1.00	
Ex-drinkers	20,532	6	0.74	0.30–1.82	6,923	3	1.59	0.49–5.13
Current drinkers								
0–29	100,596	35	1.16	0.66–2.04	55,562	12	1.01	0.53–1.91
30–59	71,569	20	1.07	0.56–2.06	2,578	0	0.00	
≥60	34,408	7	0.98	0.39–2.46	3,453	0	0.00	
P_{trend}				0.76				0.66
Years of drinking								
Nondrinkers	65,404	26	1.00		323,989	82	1.00	
Current drinkers								
0–19	53,267	9	0.93	0.40–2.14	32,780	7	1.02	0.44–2.36
20–39	113,789	28	1.09	0.60–1.99	17,346	3	0.77	0.24–2.48
≥40	34,311	23	0.97	0.52–1.83	2,644	2	1.45	0.35–5.96
P_{trend}				0.66				0.79
Cumulative amount (g)								
Nondrinkers	65,404	26	1.00		323,989	82	1.00	
Current drinkers								
0–999	88,968	19	0.8	0.41–1.57	39,963	9	1.04	0.50–2.19
1,000–1,999	56,442	23	1.55	0.84–2.86	2,012	1	1.81	0.25–13.27
≥2,000	36,781	8	0.61	0.26–1.44	1,054	0		
P_{trend}				0.89				0.94

[1]Risk factor data were collected at baseline. Adjusted for age and cigarette smoking in pack-years.

TABLE II - RR FOR PANCREATIC CANCER IN RELATION TO COFFFEE CONSUMPTION IN THE JACC STUDY[1]

	Males				Females			
	Person-years	Deaths	RR	95% CI	Person-years	Deaths	RR	95% CI
Nondrinkers	72,420	35	1.00		100,688	27	1.00	
1–2 cups/month	38,022	12	0.74	0.37–1.49	48,114	12	1.27	0.64–2.54
1–4 cups/week	71,036	19	0.58	0.32–1.08	82,518	11	0.74	0.36–1.50
1 cup/day	33,706	8	0.59	0.26–1.33	52,975	9	0.94	0.44–2.01
2–3 cups/day	45,365	11	0.75	0.36–1.59	48,072	2	0.31	0.07–1.33
≥4 cups/day	8,054	5	3.19	1.22–8.35	5,204	1	1.80	0.24–13.66
P_{trend}				0.79				0.21

[1]Risk factor data were collected at baseline. Adjusted for age and cigarette smoking in pack-years.

TABLE III - RISK OF PANCREATIC CANCER IN RELATION TO HISTORY OF DIABETES MELLITUS AND GALLSTONE/CHOLECYSTITIS IN THE JACC STUDY[1]

	Males				Females			
	Person-years	Deaths	RR	95% CI	Person-years	Deaths	RR	95% CI
History of diabetes mellitus								
No	295,718	82	1.00		389,650	88	1.00	
Yes	20,859	17	2.12	1.19–3.77	15,389	9	1.50	0.73–3.12
History of gallstone/cholecystitis								
No	262,535	75	1.00		339,570	76	1.00	
Yes	11,304	7	1.93	0.88–4.22	19,382	14	2.51	1.41–4.46

[1]Risk factor data were collected at baseline. Adjusted for age and cigarette smoking in pack-years.

Several epidemiologic studies, however, have suggested that heavy alcohol drinking may be associated with an increased risk of pancreatic cancer.[3,4,8,24–26] Among them, 2 cohort studies[3,4] showed a statistically significant increase in risk with higher total alcohol intake. A population-based case-control study[26] found that alcohol drinking at the levels typically consumed by the general population was probably not a risk factor for pancreatic cancer but that heavy alcohol drinking might be related to pancreatic cancer risk. In that study,[26] blacks and whites who drank at least 57 drinks/week had odds ratios of 2.2 (95% CI 0.9–5.6) and 1.4 (95% CI 0.6–3.2), respectively, compared to nondrinkers. The difference in findings could be due to the consumption of different types of alcohol, measurement of alcohol consumption (baseline *vs.* repeated measures) and different categorization of alcohol consumption. The role of heavy alcohol drinking in pancreatic cancer development should be clarified in future studies.

We found that drinking fewer than 4 cups of coffee/day was not associated with pancreatic cancer risk. Previous case-control and cohort studies addressing this issue have produced conflicting results.[3,4,8–10,17,19,21,22] Because of extremely poor survival, many case-control studies had to rely on interviews with surrogates, which may contribute to inconsistent results. However, a cohort study of 33,976 postmenopausal U.S. women[4] demonstrated a statistically significant 2-fold elevated risk among those who consumed >17.5 cups of coffee/week compared to those who consumed <7 cups/week, and the association was independent of age and smoking. In contrast, data from 2 prospective U.S. cohorts[19] did not support any overall association between coffee consumption and risk of pancreatic cancer. Since cigarette smoking might confound the effect of coffee consumption, we examined coffee consumption stratified by smoking status (nonsmokers, current smokers smoking 1–19 and ≥20 cigarettes/day). The association between coffee consumption and pancreatic cancer risk was similar for nonsmokers and current smokers (data not shown). However, we found a significant elevation in risk (RR = 3.19) for those who drank ≥4 cups of coffee/day, suggesting that heavy consumption increases pancreatic cancer risk. This should be confirmed in other cohort studies.

We found that men who reported a history of diabetes mellitus at baseline were at significantly increased risk of pancreatic cancer. Given the possibility that diabetes was just a complication of pancreatic cancer, we analyzed the data by excluding subjects who died from pancreatic cancer within 1 year from the baseline. The significantly increased risk remained among men who reported a history of diabetes mellitus (RR = 2.1, 95% CI 1.2–3.6). Most studies that have assessed the association between diabetes mellitus and pancreatic cancer risk have shown a positive relationship.[6,27–30] Silverman *et al.*[6] reported a significant 50% increased risk of pancreatic cancer in subjects diagnosed with diabetes at least 10 years prior to the diagnosis of cancer. Another study, from the American Cancer Society,[29] found a small but persistent increased risk of death from pancreatic cancer in diabetics and concluded that diabetes may be a true, but modest, risk factor for pancreatic cancer. A meta-analysis showed that diabetics diagnosed at least 5 years prior to the diagnosis of pancreatic cancer had a pooled RR of 2.2 (95% CI 1.2–3.2).[31] The mechanism by which longstanding diabetes causes pancreatic cancer remains uncertain, but one possibility is that exposure to insulin may promote growth in human pancreatic cell lines.[32]

Hyperinsulinaemia is characterized by both obesity and non-insulin-dependent diabetes mellitus and may play a role in pancreatic cancer carcinogenesis. It is likely, however, that diabetes could just be a consequence of pancreatic cancer. Pancreatic cancer can cause diabetes by destroying islet cells or by causing peripheral resistance to insulin, which may explain why diabetes can appear before the symptoms of the pancreatic tumor. The possibility of reverse causation should be examined in future studies.

Previous epidemiologic studies have suggested that pancreatic cancer risk may be elevated after cholecystectomy.[28,33] In a cohort study,[20] a 2-fold increased risk was observed among subjects who had a history of cholecystectomy. The proposed mechanism was that cholecystokinin, a peptide hormone produced by intestinal mucosa, may play a role in pancreatic cancer carcinogenesis.[34] However, a later cohort study in Sweden[35] did not show an increased risk of pancreatic cancer after cholecystectomy. Although the data on history of cholecystectomy were not available in our study, we found that a history of gallbladder/cholecystitis was associated with 2-fold increased risk for pancreatic cancer in women.

Strengths of our study include its prospective design and large size. Data on exposure were collected before diagnosis and death from pancreatic cancer, which could preclude recall bias. One limitation is that we could not update the exposure data during the follow-up period. There may have been changes in the risk factors

of subjects. For example, if current drinkers quit drinking during the follow-up period, the true association may be attenuated. The follow-up period of our study was relatively short (8.1 ± 1.8 years), and subjects would not easily change their lifestyle habits unless any diseases were detected; thus, the magnitude of this bias may not be that large. Michaud *et al.*[19] showed that neither alcohol nor coffee consumption was associated with pancreatic cancer risk, on the basis of 2 ongoing cohort studies, the Health Professionals Follow-Up (HPFs) Study and the Nurses' Health Study. In that study, the exposure data were updated every 2 years and removing women in the Nurses Health Study who reported having changed their coffee intake substantially did not change the findings for coffee intake. Another limitation is a poor definition of diabetes mellitus because we had to rely on self-reported information in the questionnaire. The lack of exact definition of diabetes mellitus may have led to exposure misclassification, which may have weakened the true association. Moreover, a nested case-control study,[36] using a 50 g oral glucose load as the diagnostic criterion, demonstrated a significant dose-response relationship between postload plasma level and subsequent risk of pancreatic cancer mortality.

In conclusion, alcohol drinking and coffee consumption were not associated with overall risk of pancreatic cancer in our cohort study, but heavy coffee consumption (≥4 cups/day) may increase the risk. A history of diabetes mellitus in men and gallstone/cholecystitis in women may increase the subsequent risk of pancreatic cancer.

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APPENDIX I–JACC STUDY GROUP MEMBERS

The present members of the JACC Study Group and their affiliations are as follows: Dr. Y. Ohno (chair), Nagoya University Graduate School of Medicine; Dr. M. Mori, Sapporo Medical University School of Medicine; Dr. Y. Motohashi, Akita University School of Medicine; Dr. S. Hisamichi, Tohoku University Graduate School of Medicine; Dr. Y. Nakamura, Jichi Medical School; Dr. T. Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. H. Mikami, Chiba Cancer Center; Dr. S. Hashimoto, School of Health Sciences and Nursing, University of Tokyo; Dr. Y. Inaba, Juntendo University School of Medicine; Dr. H. Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Y. Hoshiyama, Showa University School of Medicine; Dr. H. Suzuki, Niigata University School of Medicine; Dr. H. Shimizu, Gifu University School of Medicine; Dr. H. Toyoshima, Nagoya University Graduate School of Medicine; Dr. A. Tamakoshi, Nagoya University Graduate School of Medicine; Dr. S. Tokudome, Nagoya City University Medical School; Dr. Y. Ito, Fujita Health University School of Health Sciences; Dr. A. Koizumi, Graduate School of Medicine and Faculty of Medicine Kyoto University; Dr. T. Kawamura, Kyoto University Center for Student Health; Dr. Y. Watanabe, Kyoto Prefectural University of Medicine, Research Institute for Neurological Diseases and Geriatrics; Dr. M. Nakao, Kyoto Prefectural University of Medicine; Dr. T. Suzuki, Research Institute Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. T. Hashimoto, Wakayama Medical University; Dr. T. Nose, Tottori University Faculty of Medicine; Dr. N. Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. T. Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health; Dr. K. Fukuda, Kurume University School of Medicine; Dr. N. Okamoto, Kanagawa Cancer Center; Dr. T. Ishibashi, Asama General Hospital; Dr. H. Shio, Shiga Medical Center; Dr. T. Kitagawa, Cancer Institute of Japanese Foundation for Cancer Research; Dr. T. Kuroki, Institute of Molecular Oncology, Showa University; and Dr. K. Tajima, Aichi Cancer Center Research Institute. The past investigators of the study group are listed in Ohno *et al.*[12] except for the following (affiliations are those where they participated in the study): Dr. T. Shimamoto, Institute of Community Medicine, University of Tsukuba; and Dr. H. Tanaka, Medical Research Institute, Tokyo Medical and Dental University.

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A prospective cohort study of cigarette smoking and pancreatic cancer in Japan

Yingsong Lin[1,2], Akiko Tamakoshi[2,*], Takashi Kawamura[3], Yutaka Inaba[4], Shogo Kikuchi[1], Yutaka Motohashi[5], Michiko Kurosawa[4] & Yoshiyuki Ohno[2] for the JACC Study Group[6,†]

[1]*Department of Public Health, Aichi Medical University School of Medicine, Aichi Prefecture, Japan;* [2]*Department of Preventive Medicine/Biostatistics and Medical Decision making, Nagoya University Graduate School of Medicine, Nagoya, Japan;* [3]*Kyoto University Center for Student Health, Kyoto, Japan;* [4]*Department of Epidemiology and Environmental Health, Juentendo University School of Medicine, Tokyo, Japan;* [5]*Department of Public Health, Akita University School of Medicine, Akita, Japan;* [6]*Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho*

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Abstract

Objective: To examine the association of cigarette smoking with the risk of death from pancreatic cancer in a prospective cohort study.
Methods: A total of 110,792 inhabitants, aged 40–79 years (46,465 men and 64,327 women), were enrolled from 1988 to 1990 and followed up for mortality to the end of 1997. At baseline a self-administered questionnaire was used to obtain information on cigarette smoking and other lifestyle factors.
Results: During the follow-up period (mean ± SD: 8.1 ± 1.8 years), 225 deaths due to pancreatic cancer were identified. After adjustment for age, body mass index, history of diabetes mellitus, and gallbladder diseases, the relative risks (RRs) for current smokers were 1.6 (95% CI 0.95–2.6) in males, and 1.7 (95% CI: 0.84–3.3) in females. Men who smoked more than 40 cigarettes per day had a substantially higher risk of pancreatic cancer, with a RR of 3.3 (95% CI: 1.4–8.1). A significantly decreasing trend in risk with increasing years after smoking cessation was observed (trend $p = 0.04$) among male ex-smokers. The RRs were 0.85 (95% CI 0.36–2.0) and 0.85 (0.36–2.0) for those who had quit smoking for 10–19 and ≥ 20 years, respectively.
Conclusions: Our cohort study confirmed that cigarette smoking was associated with an increased risk of death from pancreatic cancer.

Introduction

The mortality and incidence of pancreatic cancer have been continuously increasing during the past three decades in Japan [1]. Pancreatic cancer is now the fifth leading cause of cancer death among males and the seventh among females, accounting for over 16,000 deaths annually [2]. The etiology of pancreatic cancer remains unknown. Epidemiological studies form European countries and the United States have consistently shown that cigarette smoking is associated with an increased risk or pancreatic cancer [3–24], but the dose–response relationship is not consistently observed among these studies.

There have been very few epidemiological studies searching into the environmental etiology of pancreatic cancer in Japan. The first large-scale cohort study on lifestyle factors and cancer was conducted by Hirayama between 1965 and 1980 [25]. Daily cigarette smoking and meat consumption were revealed to be the most important risk factors for pancreatic cancer. In another multi-institute case–control study Mizuno *et al.*

Address for correspondence: Akiko Tamakoshi, Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8550, Japan. Ph.: 0081-52-744-2132; Fax: 0081-52-744-2971; E-mail: tamaa@med.nagoya-u.ac.jp

† See Acknowledgements for the members of this JACC study.

reported that the odds ratio for current smokers was 2.4 (95% confidence interval (CI) 1.1–5.3), relative to non-smokers, after adjustment for sex, age, and place of enrollment [26].

Since around 1970, there have been remarkable changes in lifestyles and living conditions in Japan, which may have brought about new variations in environmental factors. We therefore report the results obtained from another large-scale prospective study of 110,792 Japanese with approximately 8 years of follow-up, focusing on the effect of cigarette smoking on pancreatic cancer.

Materials and methods

Study cohort

We analyzed the dataset from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (the JACC study). The design and conduct of the JACC study has been described elsewhere in detail [27]. In brief, this cohort study began in 1988, with the aim of evaluating risk factors for cancer among Japanese. From 1988 to 1990, a baseline questionnaire survey was conducted for the inhabitants who were enrolled from 45 areas throughout Japan. A total of 110,792 inhabitants aged 40–79 years (46,465 men and 64,327 women) completed the questionnaire, and were subsequently followed for mortality to the end of 1997.

At baseline, a self-administered questionnaire was used to collect information on demographic characteristics, medical history of diabetes mellitus and gallbladder diseases, tobacco and alcohol use, coffee drinking, and dietary habits. For cigarette smoking, subjects were asked to describe their smoking status (never/former/current), age at starting smoking, average number of cigarettes smoked per day, years of smoking, depth of smoke inhalation, and years of smoking cessation.

During the follow-up period, the vital status of the subjects were determined using resident registration records available from the municipalities, and causes of death were confirmed by the death certificate. The endpoint in this cohort study was defined as death from pancreatic cancer (*International Statistical Classification of Diseases and Related Health Problems*, 10th revision [ICD-10]: C25) [28]. Person-time of follow-up for each subject was computed from the enrollment to the day of death from pancreatic cancer or any other causes, the time of moving out of the study area, or the end of 1997, whichever occurred first. Subjects who moved out of the study field or died from causes other than pancreatic cancer were treated as censored cases. This investigation was approved by the Ethical Board of the Nagoya University Graduate School of Medicine.

In this study we excluded subjects who reported a history of cancer at baseline and those with unknown smoking status. This left 99,527 subjects (44,646 men and 54,881 women) eligible for the present analysis. The mean age ± standard deviation of the subjects was 57.3 ± 10.2 years at entry.

Statistical analysis

All data were analyzed using the SAS procedure [29]. The strength of association between cigarette smoking and risk of death from pancreatic cancer was examined using the relative risks (RRs) derived from the Cox proportional hazards model [30]. All RRs were adjusted for such potentially confounding factors as age, body mass index, and history of diabetes mellitus and gallbladder diseases. The cumulative amount of cigarette smoking, measured as pack-years, was calculated by multiplying the number of packs smoked per day by years of smoking. Trends in risk were evaluated among current smokers by treating ordinal score variables as continuous variables in the proportional hazards model. The proportion of pancreatic cancer attributable to cigarette smoking was calculated as the proportion of cases among ever smokers (former and current smokers) that was attributable to smoking ([RR−1]/RR) multiplied by the prevalence of ever smokers in the Japanese population in 1998 [31]. All p-values were based on two-sided tests and, if less than 0.05, considered statistically significant.

Results

At the initiation of the JACC study the proportions of never, former, and current smokers were 15.8%, 27.5% and 56.7% in males and 87.6%, 3.8%, and 8.6% in females, respectively. A total of 225 pancreatic cancer deaths were observed during the follow-up of 807,407 person-years. The mean follow-up period ± standard deviation was 8.1 ± 1.8 years. Table 1 shows the RRs of death from pancreatic cancer in relation to smoking status. After adjustment for age, body mass index, and history of diabetes mellitus and gallbladder diseases, cigarette smoking was associated with an increased risk of death from pancreatic cancer in both males and females. Compared with non-smokers the RR for current smokers was 1.6 (95% CI: 0.95–2.6) in males, and 1.7 (95% CI: 0.85–3.4) in females. For males and females combined the RR was 1.8 (95% CI: 1.3–2.4). Male ex-smokers did not experience a significant eleva-