Fatty liver incidence and predictive variables

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Running title: Fatty liver incidence and predictive variables

Abstract

Background: While fatty liver predicts ischemic heart disease, the incidence and predictors of fatty liver need examination.

Objective: To determine fatty liver incidence and predictive variables.

Method: Using abdominal ultrasonography, we followed biennially through 2007 (mean follow-up, 11.6±4.6 years) 1,635 Nagasaki atomic bomb survivors (606 men) without fatty liver at baseline (November 1990 through October 1992).   We examined potential predictive variables with the Cox proportional hazard model and longitudinal trends with the Wilcoxon rank sum test.

Results: 323 (124 male) new fatty liver cases were diagnosed.   The incidence was 19.9/1000 person-years (22.3 for men, 18.6 for women) and peaked in the sixth decade of life. After controlling for age, sex, and smoking and drinking habits, obesity (relative risk [RR], 2.93; 95% confidence interval [CI], 2.33 - 3.69, $p<0.001$), low HDL-cholesterol (RR, 1.87; 95%CI, 1.42 - 2.47; $p<0.001$), hypertriglyceridemia (RR, 2.49; 95%CI, 1.96 - 3.15; $p<0.001$), glucose intolerance (RR, 1.51; 95%CI, 1.09 - 2.10; $p=0.013$), and hypertension (RR, 1.63; 95%CI, 1.30 - 2.04; $p<0.001$) were predictive of fatty liver.   In multivariate analysis including all variables, obesity (RR, 2.55; 95%CI, 1.93 - 3.38; $p<0.001$), hypertriglyceridemia (RR, 1.92; 95%CI, 1.41 - 2.62; $p<0.001$), and hypertension (RR, 1.31; 95%CI, 1.01 - 1.71; $p=0.046$) remained predictive.

In fatty liver cases, body mass index and serum triglycerides, but not systolic or diastolic blood pressure, increased significantly and steadily up to the time of the diagnosis.

Conclusion: Obesity, hypertriglyceridemia and, to a lesser extent, hypertension might serve as predictive variables for fatty liver.

Key words: Fatty liver, Incidence, Obesity, Hypertriglyceridemia, Hypertension

Introduction

The recent increase in obesity caused by excess food intake has led to an increased incidence in metabolic syndrome and visceral fat accumulation[1-3], both of which are associated with non-alcoholic fatty liver disease[4-11]. Since non-alcoholic fatty liver disease is also associated with the classical coronary risk factors of obesity, hypertension, dyslipidemia, and glucose intolerance[4,7,8,10-15], non-alcoholic fatty liver disease serves as a surrogate marker for visceral fat accumulation or metabolic syndrome.

Non-alcoholic fatty liver disease correlates with the remodeling of coronary artery lesions or lipid core plaques when evaluated by multislice computed tomography and with coronary artery stenosis evaluated by coronary angiography[16,17]. Moreover, non- alcoholic fatty liver disease might be a stronger predictor than metabolic syndrome of cardiovascular disease[18]. In obese children, non-alcoholic fatty liver disease is associated with dyslipidemia, hypertension, and glucose intolerance, and predicts development of these conditions[5,7]. Few reports, however, describe the incidence of fatty liver and its predictive variables[19,20]. In this study, we selected atomic bomb survivors in Nagasaki who were confirmed by abdominal ultrasonography during 1990 to 1992 (baseline) as not having fatty liver and followed them through 2007 to examine the incidence of, and predictive variables for, fatty liver.

Methods

Subjects

As part of the follow-up program of the Radiation Effects Research Foundation (RERF, formerly the Atomic Bomb Casualty Commission), 7,564 atomic bomb survivors (3,374 male) have undergone biennial examinations in Nagasaki since 1958.   A detailed description of this program has been published elsewhere (Atomic Bomb Casualty Commission, Technical Report and Radiation Effects Research Foundation, Research Plan for RERF Adult Health Study, Hiroshima and Nagasaki, RERF Research Protocol 2-75, 1975).   RERF's Research Protocol Review Committee and the Human Investigation Committee approved the original program in 1975 and the present study in 2008 (RP-A 08-08).

At the baseline examination (November 1990 through October 1992), 2,015 subjects underwent clinical examination, biochemical measurements, and abdominal ultrasonographic examination.   The 123 fatty liver cases that were detected then were excluded from this study, as were subjects who were positive (n = 167) or indeterminate (n = 90) for hepatitis B virus surface antigen and/or anti-hepatitis C virus antibody.   We included the remaining 1,635 subjects in this study.

Baseline data collection

At each examination, a trained nurse collected clinical and life-style (past and current

smoking and alcohol consumption) information.   The nurse also measured sitting blood

pressure (mm Hg) on the left arm with a sphygmomanometer after a sufficient sedentary period

using the first Korotkoff phase for systolic blood pressure (SBP) and the fifth for diastolic blood

pressure (DBP).   We classified subjects as having hypertension if their SBP was ≥130 mm Hg

and/or their DBP was ≥85 mm Hg from a preventive point of view based on Guidelines for the

Management of Hypertension (JSH2009) and metabolic syndrome[21,22].

Standing height (in m) and body weight (in kg) were measured without socks and outer

clothing.   Body mass index (BMI) was calculated as body weight divided by the square of the

standing height (kg/m^2).   Obesity was defined as a BMI of ≥25, in accordance with the

definition of the Japan Society for the Study of Obesity.

Fasting blood samples were drawn for biochemical measurements.   Serum total

cholesterol (mg/dL), high-density lipoprotein cholesterol (HDL-cholesterol, mg/dL), serum

triglyceride (mg/dL), and fasting blood glucose (FBG, mg/dL) were measured by an automated

procedure (Hitachi 7050 and 7170S; Hitachi Ltd., Tokyo, Japan) with quality control monitored in

accordance with the College of American Pathologists (Northfield, IL, USA).

Hypercholesterolemia was defined as total serum cholesterol ≥220 mg/dL, low HDL-cholesterol

as serum HDL-cholesterol <40 mg/dL, and hypertriglyceridemia as serum triglyceride ≥150

mg/dL.   Subjects with an FBG ≥110 mg/dL and those undergoing medical treatment for

diabetes mellitus or impaired glucose tolerance were defined as having glucose intolerance.

Radiologists, without making reference to the subjects' history or data, conducted abdominal ultrasonographic examinations using an Aloka SSD-650, SSD-2000 (Aloka Co., Ltd., Tokyo) and GE LOGIQ-500 (GE Healthcare Japan Co., LTD., Tokyo) and diagnosed fatty liver when there was accentuation of liver-kidney contrast, blurring of the hepatic vessel wall, or deep attenuation of echogenicity[23].   Ultrasonography is a sensitive and reasonably accurate diagnostic tool for assessing fat infiltration of the liver.   Others have found 83% sensitivity and 100% specificity in comparison to histology, and 100% sensitivity and 56% specificity in comparison to CT[23,24].   In the present study, a second radiologist blindly reviewed 40 films originally classified as fatty liver and 80 films from age-sex matched persons that were not so classified.   The positive agreement rate by the second rater was 80% and the negative agreement rate was 95%, yielding a kappa coefficient of agreement of 0.77.[25]

Follow-Up

All subjects visited RERF biennially and underwent the same clinical, biochemical, and ultrasonographic examinations as at the baseline examination.   Follow-up began on the date of the baseline examination and ended on the date of the diagnosis of fatty liver, the date of death, or December 31, 2007, whichever came first.   The criteria for fatty liver were the same as at baseline examination.

Radiation dose

We based total radiation dose on Dosimetry System 2002 (DS02) with a weighting

factor of 10 for neutrons relative to γ rays[26].   To reduce radiation effect estimation bias[27], we

adjusted the gamma and neutron doses for 35% dose error after truncation at 4 Gy for doses

over 4 Gy..   The mean radiation dose was 0.517 Gy (range, 0 - 3.455).

Statistical Analysis

We calculated the incidence of fatty liver using the person-year method.   We used the

Wilcoxon rank sum test to compare continuous variables (age, BMI, total cholesterol,

HDL-cholesterol, serum triglycerides, SBP, DBP, and radiation dose) and the chi-square test to

compare prevalences (sex, smoking and drinking habits, and glucose intolerance) between

incident fatty liver cases and non-incident fatty liver cases at baseline.   We used the Cox

proportional hazard model to examine the predictive variables (obesity, hypercholesterolemia,

low HDL-cholesterolemia, hypertriglyceridemia, glucose intolerance, and hypertension) for

incident fatty liver after controlling for age, sex, smoking and drinking habits, and atomic bomb

radiation dose.

When fatty liver was diagnosed in someone for the first time at follow-up, we randomly

selected two sex- and age- matched controls from non-incident fatty liver cases.   For example,

if fatty liver was diagnosed for the first time in 1995 in a 63-year-old male, we randomly selected

two male controls who were aged 60 to 64 years in 1995.   Because the predictive variables for

fatty liver were obesity, hypertriglyceridemia, and hypertension (see multivariate analysis in

results section), we plotted BMI, serum triglycerides, SBP, and DBP at -6, -4, -2 (before the

diagnosis), 0 (at the diagnosis), 2, 4, and 6 years after the diagnosis in cases and at the

corresponding times in controls, and we used the Wilcoxon rank sum test to compare the

values.   We set a *p* value of <0.05 for over-all significance and of <0.0084 ($\fallingdotseq$0.05/6) for a

Bonferroni-type multiple comparison in the analysis of BMI, triglycerides, SBP, and DBP.   We

conducted all analyses using SAS software running on a UNIX System (SAS/STAT Software,

Release 9.0. Cary, North Carolina, SAS Inst., Inc.).

Results

Table 1 shows the baseline characteristics of the 1,635 subjects by sex.   As indicated

from the mean age of our study subjects, our study cohort consisted of middle aged / elderly

subjects (- 49 year old; 113 subjects, 50 – 59 yeas old; 284 subjects, 60 – 69 years old; 863

subjects, 70 – 79 years old; 289 subjects, 80 – years old; 86 subjects).   Among them, 323 (124

men) were newly diagnosed with fatty liver during the follow-up period.   The mean follow-up

period was 11.6 years (SD, 4.6; median, 14.0; range, 1.3 - 17.1).

Table 2 shows the baseline characteristics of subjects who did and did not develop

fatty liver.   The two groups did not differ in sex ratio, smoking or drinking habits, prevalence of

glucose intolerance, or radiation dose.   The group that developed fatty liver, however, had

higher mean values for BMI, total cholesterol level, and triglyceride level, a higher prevalence of

hypertension, and lower mean values for age and HDL-cholesterol level.   The incidence of

fatty liver per 1,000 person-years was 19.9 (22.3 for men, 18.6 for women).   It peaked in the

sixth decade of life and decreased thereafter in both sexes (**Figure 1**).

In Cox's proportional hazard model adjusted for age, sex, and smoking and drinking

habits, obesity, low HDL-cholesterol, hypertriglyceridemia, glucose intolerance, and

hypertension were statistically significant predictors of fatty liver (**Table 3**).   In multivariate

analysis including all variables, obesity, hypertriglyceridemia, and hypertension remained

positive predictors (**Table 3**).   Radiation dose was not a predictive variable.

Subjects who developed fatty liver had significantly higher BMIs and serum triglyceride

levels than control subjects throughout the 12-year study period (**figure 2, panel A and B**).

Moreover, their BMI levels increased steadily and significantly during the 6 years before the

diagnosis to the diagnosis (23.9 ± 2.8 at -6 years and 24.1 ± 3.0 at -4 years to 25.0 ± 3.0 at 0

years [$p < 0.001$ for 2 intervals]) and remained elevated, while the level remained constant in

controls (**figure 2, panel A**).   Similarly, serum triglycerides levels in those who developed fatty

liver increased steadily and significantly up to the time of diagnosis (130.0 ± 54.6 mg/dL at -6

years to 159.2 ± 71.9 mg/dL at 0 years, $p < 0.001$) and remained elevated, while the level

remained constant in controls (**figure 2, panel B**).   Although hypertension was a predictive

variable, SBP and DBP were not consistently higher in cases than in controls and did not increase significantly during the observation period (**figure 2, panel C and D**).

Discussion

In this study of 1,635 Nagassaki atomic bomb survivors who were followed for 12 years, our finding of an incidence of fatty liver of 19.9 / 1,000 person-years was similar to the incidence of 18.5 / 1,000 person-years reported by Bedogni and colleagues for a general Italian population followed for a median time of 8.5 years[19].   In a study of 3,147 Japanese adults who consumed less than 20g of ethanol per day, Hamaguchi and colleagues reported that 10% of subject developed non-alcoholic fatty liver disease at follow-up examination (1.13 ± 0.35 years later)[20].   And while we did not find a sex difference in the development of fatty liver, Hamaguchi and colleagues reported a higher incidence among men, which might be explained by the fact that the mean age of participants at baseline examination in their cohort study (48.1 years for men, 46.6 for women) was younger than it was in our study (62.4 years for men, 63.4 for women).   Indeed, as shown in figure 1, the incidence of fatty liver in participants <50 years old was higher in men than in women.

Our finding that the incidence of fatty liver in both sexes peaked in the sixth decade of life and decreased thereafter may follow from that fact that BMI generally follows that age pattern[28,29].   Our calculation of fatty liver incidence in participants <50 years old, however, was

based on only 4 male and 2 female incident cases.   That may have biased our results, leading

to the possibility that peak fatty liver incidence might occur in the fifth decade instead of the

sixth.   Cohort studies including younger subjects are needed to confirm the age of peak fatty

liver incidence.

That obesity, low HDL-cholesterol, hypertriglyceridemia, glucose intolerance, and

hypertension—classic risk factors for cardiovascular disease—were predictive of fatty liver in

Cox regression analysis (after controlling for age, sex, and smoking and drinking habits) and

that obesity, hypertriglyceridemia, and hypertension remained predictive in multivariate Cox

regression analyses fit in with our understanding of the pathophysiological pathway of fatty

liver[12,30].   Obesity (from excess nutrition intake) leads to visceral fat accumulation.   Visceral

fat has high metabolic activity and releases free fatty acids (FFAs) and adipokines such as

leptin, tumor necrosis factor–α (TNF-α), and adiponectin[31-34].   Insulin resistance caused by

increasing TNF-α secretion or decreasing adiponectin secretion induces hypertension and

glucose intolerance[31].   Leptin and angiotensinogen secreted from visceral fat also induces

hypertension[33].   In this way, visceral fat accumulation associated with obesity serves as a risk

factor for hypertension and glucose intolerance.   On the other hand, FFAs released from

visceral fat enter the liver through the portal vein, and increased FFA influx from the portal vein

stimulates triglyceride synthesis in liver.   Fatty liver is the condition of triglyceride deposited in

liver, and fatty liver is thus a surrogate marker of visceral fat accumulation and clusters the

classic risk factors for cardiovascular disease—obesity, hypertension, dyslipidemia, and glucose intolerance.

Hamaguchi and colleagues reported that metabolic syndrome and weight gain were predictive of non-alcoholic fatty liver disease development[20]. Although we could not evaluate whether metabolic syndrome predicted the development of fatty liver because we did not measure waist circumference at baseline examination, our results are consistent with their results in the following aspects; (1) coronary risk factors associated with metabolic syndrome, i.e., obesity, dyslipidemia, and hypertension, predict the development of fatty liver, and ; (2) increases in BMI and serum triglycerides are related to the development of fatty liver as suggested by observed trends (figure 2).

Limitations

(1) The mean age of study participants was 63.1 ± 8.9 at baseline (November 1990 through October 1992), which means that many of our study participants had taken excess nutrition since their middle age. Thus, our calculated age of peak incidence may shift to older age and our overall incidence estimate (19.9 / 1000 person-years) may be calculated to be low. Further studies including younger subjects are necessary to evaluate fatty liver incidence in the contemporary era of excess nutrition intake.

(2) Our subjects were atomic bomb survivors in Nagasaki, Japan, which means that our

results might not be generalizable.   Radiation dose was not a predictive variable for

incident fatty liver, however, so we believe that the present results can be generalized,

although further studies in non-atomic bomb survivors are necessary.

(3)   While we incorporated alcohol intake into the analysis and found it not to be a predictive

variable for incident fatty liver, we could not negate the possibility that fatty liver cases

related to alcohol intake were included in the study because we did not take amount of

alcohol intake into account. (For the diagnosis of non-alcoholic fatty liver, alcohol intake

should not exceed 20g/day[35]).

Conclusion

In this middle aged / elderly subjects cohort, fatty liver incidence (19.9 / 1000

person-years) peaked in the sixth decade of life and decreased thereafter.   While obesity,

hypertriglyceridemia, and hypertension were predictive of fatty liver, BMI and serum triglyceride

level, but not SBP or DBP, increased steadily up to the time of diagnosis.   These data suggest

that obesity and hypertriglyceridemia, rather than hypertension, are closely associated with

development of fatty liver.

Acknowledgements

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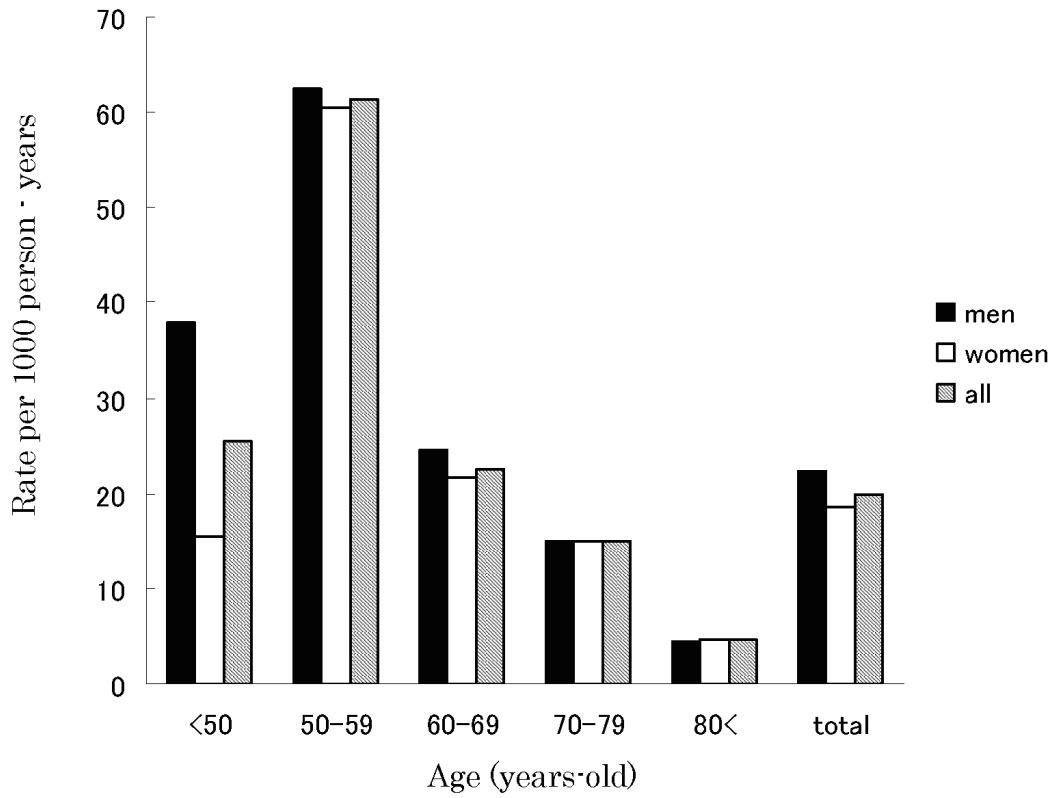
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Figure 1.   Incidence of fatty liver. Black bars represent men, white bars women, gray bars
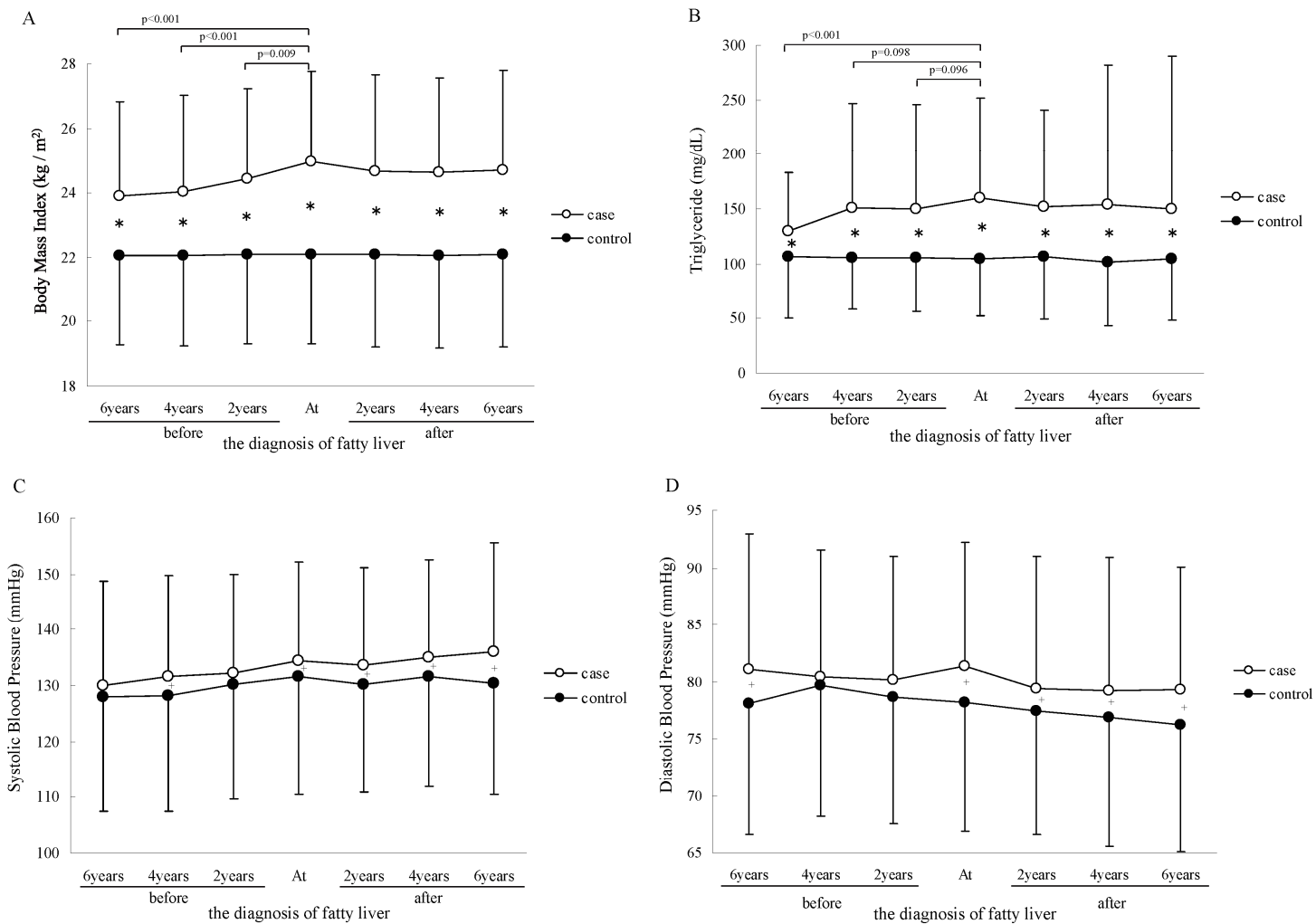
all subjects.

Figure 2.

Panel A. Body mass index trends. Values are expressed as means ± SD.

Comparisons were made by means of analysis of covariance. *p < 0.001 between fatty

liver cases and controls.

Panel B. Triglyceride trends. Values are expressed as means ± SD. Comparisons

were made by means of analysis of covariance. *p < 0.001 between fatty liver cases and

controls.

Panel C. Systolic blood pressure trend. Values are expressed as means ± SD.

Comparisons were made by means of analysis of covariance. $^+p < 0.05$ between fatty liver

cases and controls.

Panel D. Diastolic blood pressure trend. Values are expressed as means ± SD.

Comparisons were made by means of analysis of covariance. $^+p < 0.05$ between fatty liver

cases and controls.

Table 1. Baseline Characteristics of the Study Population by Sex

Risk Factors	Total n = 1635	Men n = 606	Women n = 1029	p
Age	63.1 ± 8.9	62.4 ± 9.6	63.4 ± 8.4	0.002
Smoking (%)	34.6	76.9	9.7	< 0.001
Drinking (%)	41.0	78.7	18.8	< 0.001
BMI (kg/m2)	22.5 ± 3.0	22.2 ± 2.7	22.7 ± 3.1	0.003
T-chol (mg/dL)	206.5 ± 34.7	193.1 ± 30.6	214.4 ± 34.5	< 0.001
HDL-C (mg/dL)	54.9 ± 14.5	52.0 ± 14.7	56.7 ± 14.0	< 0.001
TG (mg/dL)	115.3 ± 61.0	122.6 ± 72.3	110.9 ± 52.9	0.004
Glucose intolerance (%)	10.5	14.2	8.4	< 0.001
SBP (mmHg)	127.3 ± 19.4	129.4 ± 18.2	126.1 ± 20.0	< 0.001
DBP (mmHg)	79.3 ± 11.0	81.2 ± 10.4	78.1 ± 11.2	< 0.001
*Atomic radiation dose (mGy)	522.6 ± 741.7 (n=1077)	527.0 ± 719.8 (n=403)	520.0 ± 754.8 (n=674)	0.42

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-Chol, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; Atomic radiation dose, atomic bomb radiation dose estimated by RERF 2002 criterion. Unless otherwise indicated, values are expressed as the mean ± SD.

*Because radiation dose was not determined in all subjects, the numbers of subjects was reduced to 1,077 (403 men, 674 women).

Table 2. Baseline Characteristics of Incident Fatty Liver Cases and Non-incident

Fatty Liver Cases

	Incident fatty liver	Non-incident fatty liver	p
Number	323	1312	
Age	59.0 ± 7.3	64.1 ± 9.0	< 0.001
Sex (men %)	38.4	36.7	0.58
Smoking (%)	34.4	34.7	0.92
Drinking (%)	45.2	39.9	0.09
BMI (kg/m2)	24.1 ± 2.8	22.1 ± 2.9	< 0.001
T-chol (mg/dL)	210.2 ± 35.1	205.6 ± 34.5	0.029
HDL-C (mg/dL)	50.9 ± 13.1	56.0 ± 14.6	< 0.001
TG (mg/dL)	143.1 ± 85.0	108.4 ± 51.3	< 0.001
Glucose intolerance (%)	13.0	9.9	0.10
Hypertension (%)	56.3	47.4	0.004
Atomic radiation dose (mGy)	510.1 ± 726.6 (n=214)	525.6 ± 745.6 (n=863)	0.92

Abbreviations are the same as in Table 1. Unless otherwise indicated, values are expressed

as the mean ± SD.

Table 3.   Relative Risk of Predictive Variables for Fatty Liver by means of Multiple

Cox's Regression Analysis.

	*RR (95% CI)	p	**RR (95% CI)	p
Age (older decade)			0.54 (0.45 - 0.64)	< 0.001
Sex (women)			0.93 (0.61 - 1.42)	0.73
Smoking			0.92 (0.64 - 1.34)	0.67
Drinking			0.95 (0.68 - 1.32)	0.75
Obesity (BMI≧25)	2.93 (2.33 - 3.69)	< 0.001	2.55 (1.93 - 3.38)	< 0.001
Hypercholesterolemia (T-chol≧220mg/dL)	1.12 (0.88 - 1.42)	0.35	0.98 (0.73 - 1.30)	0.88
Low HDL-cholesterolemia (HDL-C<40mg/dL)	1.87 (1.42 - 2.47)	< 0.001	1.19 (0.83 - 1.70)	0.35
Hypertriglyceridemia (TG≧150mg/dL)	2.49 (1.96 - 3.15)	< 0.001	1.92 (1.41 - 2.62)	< 0.001
Glucose intolerance	1.51 (1.09 - 2.10)	0.013	1.31 (0.90 - 1.90)	0.16
Hypertension	1.63 (1.30 - 2.04)	< 0.001	1.31 (1.01 - 1.71)	0.046
Atomic radiation dose (mGy) (n=1077)	0.99 (0.83 - 1.18)	0.89	0.92 (0.78 - 1.10)	0.38

RR, relative risk; CI, confidence interval. Other abbreviations are the same as in Table 1.

*Adjusted for age, sex, smoking, and alcohol habits.

** All variables are included.