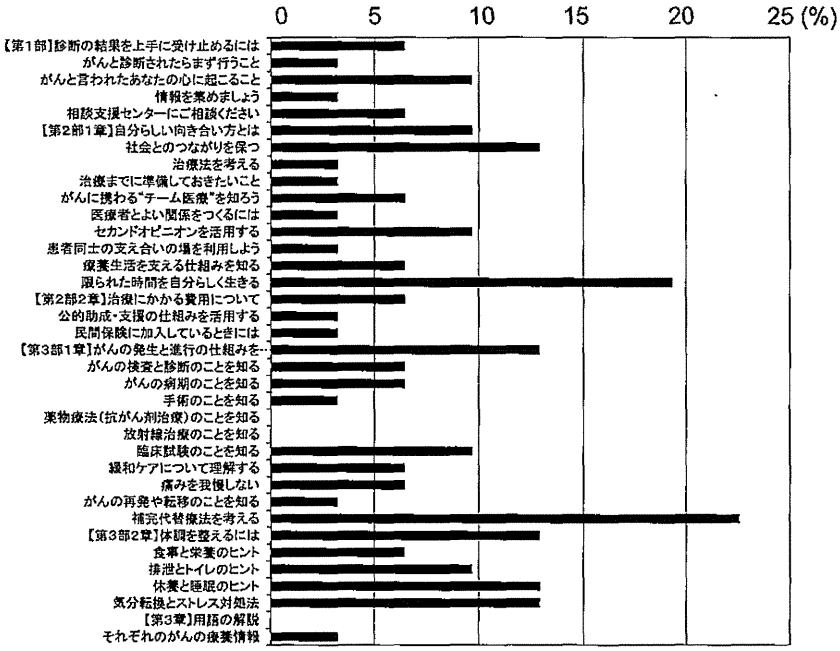

図6　患者・家族が全く使わないと思うところ．もし，自分自身や子どもが小児がんと診断されたとき，この「患者必携　がんになったら手にとるガイド」を手にして1～2か月後に「まったく使わないと思う」ところに○を付けて下さい．

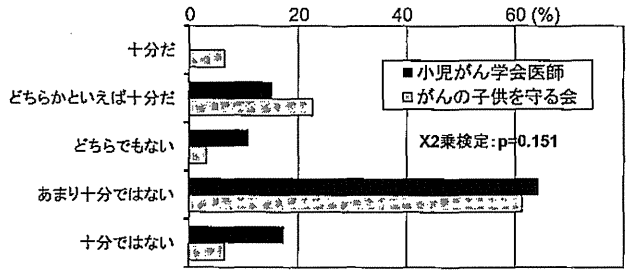

図7　小児がん患者や家族・支援者への情報提供．小児がん患者さんやご家族・支援者への情報提供は，総合的にみて十分であると思いますか．

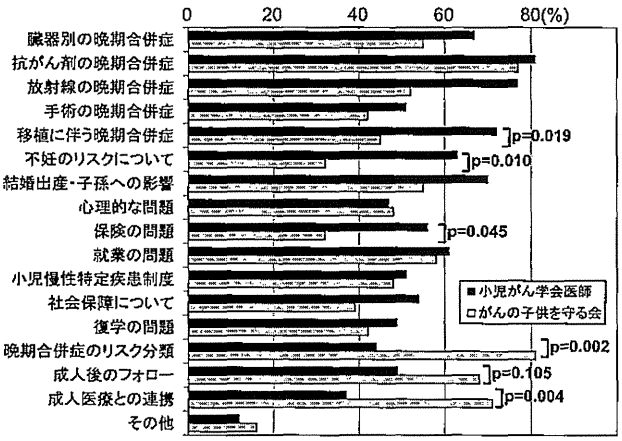

図8　ぜひほしい長期フォローアップ情報．「小児がん患者必携」に，もし治療終了後の長期フォローアップに関する情報を盛り込むとしたら，あなたがもっとも優先するもの1つに◎，ぜひ欲しい情報に○をつけてください（○はいくつでも）．

に高かったこと，移植に伴う晩期合併症，不妊のリスク，保険の問題に関しては医師群が有意に高い結果であった．その中でも特に優先すべき情報は，医師群では臓器別身体的合併症とリスク分類，守る会群ではリスク分類，抗がん剤合併症，結婚出産・子孫への影響，心理的な問題であった．

成人後のフォローと成人医療との連携の両者とも重要と考えた人を「成人期の移行を重要」と考えた群と判断して，医師群と守る会群の背景因子（年齢と性別）を調整してロジスティク回帰分析をした結果を表2に示した．単変量分析では，守る会群と女性であることが，「成人期の移行を重要」と考えることと有意に関連していたが，多変量解析の結果では性別よりも守る会群であることがより関連が強いと判断された．

自由記載では，医師群は小児がん登録，データ管理，信頼ある情報発信，心理・生活支援などが必要であるという意見，守る会群では，小児がん自体の社会的認知，信頼ある情報発信，心理社会・生活支援などが必要であるという意見が多かった．

IV　考　察

小児がん関係の医師と経験者・家族・支援者の両者の「患者必携　がんになったら手にとるガイド」[3]に対する意

表2　成人期の移行を重要と考えるグループ

	グループ	重要である	χ^2（p値）	オッズ比（95%信頼区間）	p値
分類	医師群	11/43	0.010	Reference	—
	守る会群	17/31		3.90（1.01–15.0）	0.048
年齢	40歳代以下	16/23	0.929	Reference	—
	50歳代	15/32		2.83（0.72–9.62）	0.145
	60歳代以上	4/19		0.60（0.13–2.77）	0.516
性別	男性	12/45	0.014	Reference	—
	女性	16/29		1.64（0.46–5.90）	0.449

* Hosmer & Lemeshow: χ^2=2.99（p-value=0.701）

見・感想をまとめたが両者の結果は酷似していた．両者とも8割は診断時に医療者を通じて情報提供を受けるのが望ましいと考えており，医師の説明の補助として振り返りに役立てたいと考えていた．両冊子の情報提供[3]を歓迎し，特に「患者必携」の総論部分では小児がんでも参考になる部分が多いという意見がある一方で，小児がんのような稀少疾患に関しての各疾患別の情報については，今回の「患者必携」では情報が不足していると感じており，疾患各論については成人がんとは別にもう少し詳細な情報を提供する必要があると思われた[1]．

小児がんに関する一般向けの情報としては，公益財団法人がんの子どもを守る会の配布冊子ならびにホームページの情報が一番充実していると考えられる[5]．これまで既に「子どものがん～病気の知識と療育の手引き～」「がんとたたかう子とともに」「病期別のリーフレット」「この子のためにやれること」「各種ガイドライン」（緩和ケア，家族の支援，教育支援，小児がん経験者，病気の子どもの気持ちなど）が存在し，ホームページからpdfでダウンロード可能である[5]．そのような中で，「がんになったら手にとるガイド」の意義を考えるとすれば，これまで小児がんでは情報が乏しかった「セカンドオピニオンを活用する」「がんの発生と進行の仕組みを知る」「治療までの準備」「医療者とのよい関係」「がんの病期」「がんの地域での療養情報」などが比較的新しい視点だと思われた．国立成育医療研究センターでも，小児がん情報ステーションという医療情報，支援活動，研究活動の提供サイトが存在する[6]が長期フォローアップに関する情報はまだ不十分である．最近著者等は，このギャップを埋めるべく『よくわかる小児がん経験者のために～よりよい生活の質（QOL）を求めて～』という本を小児がん経験者と家族向けに出版したが[7]，今後はもう少し手軽にインターネット等で情報を入手できる環境が望まれる[8,9]．

本調査の「患者必携」の内容に関しての意見で興味深かったのは，セカンドオピニオンの活用に関して，医師群では約80%が活用するだろうと予想していたのに対して，守る会群では約50%に留まっていたこと，がんの発生や進行の仕組みに関しては，医師群の予想に反して守る会群で60%以上が活用すると答えていたことである．また守る会群では「治療までの準備」「チーム医療」「医療者とのよい関係」「がんの病期」「臨床試験」「がんの療養情報」など多くの項目が不安解消に役立つと答えており，医師群の予想する以上にがん診療に普遍的な基本的な情報のニーズが高いことが浮き彫りにされた[10]．

小児がんでは，長期フォローアップ（サバイバーシップ）に関する関心は極めて高く，両群の希望する項目の割合も比較的似ており，情報提供を十分に行う必要がある[11–15]．その中で守る会群で，晩期合併症のリスク分類，成人後のフォローや成人医療との連携が有意に高かったことから，特に成人期移行の問題に関してロジスティク回帰分析を用いて年齢・性別という交絡因子を調整して分析したところ，医師群に比べて守る会群は調整オッズ比で3.90（p=0.048）と有意な関連を示した．小児がん経験者・家族・支援者にとって成人期移行の問題は医師群以上に切実であると考えられた[16,17]．一方移植に伴う晩期合併症，不妊のリスク，保険の問題に関しては医師群の関心がより高く，両群で多少の関心のギャップはありそうである[15,18]．

本研究の一番の限界は，回収率は比較的良かったもののアンケート回答者数が少なく，対象者に選択バイアスがあると推定されること，また検定した項目が多かったため，統計的には多重性が問題であり検証的な研究にはならなかったことである．本研究には以上の様な限界はあるものの，主に成人がん患者を想定して作成された「患者必携」について，小児がん関係者の視点から評価を行った貴重な報告と考えられ，今後小児がんに関する情報提供の方向性を考えていく上で貴重なデータになると思われる[18]．将来的には，今回の調査結果を反映した「患者必携」の小児がんバージョンが完成されることを願っている．

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Original Article

Body Mass Index and Weight Change During Adulthood Are Associated With Increased Mortality From Liver Cancer: The JACC Study

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ABSTRACT

Background: We investigated the association of baseline body mass index (BMI) and weight change since age 20 years with liver cancer mortality among Japanese.

Methods: The data were obtained from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). A total of 31 018 Japanese men and 41 455 Japanese women aged 40 to 79 years who had no history of cancer were followed from 1988 through 2009.

Results: During a median 19-year follow-up, 527 deaths from liver cancer (338 men, 189 women) were documented. There was no association between baseline BMI and liver cancer mortality among men or men with history of liver disease. Men without history of liver disease had multivariable hazard ratios (HR) of 1.95 (95%CI, 1.07–3.54) for BMI less than 18.5 kg/m^2 and 1.65 (1.05–2.60) for BMI of 25 kg/m^2 or higher, as compared with a BMI of 21.0 to 22.9 kg/m^2. BMI was positively associated with liver cancer mortality among women and women with history of liver disease. Weight change since age 20 years was positively associated with liver cancer mortality among women regardless of history of liver disease. Women with history of liver disease had a multivariable HRs of 1.96 (1.05–3.66) for weight gain of 5.0 to 9.9 kg and 2.31 (1.18–4.49) for weight gain of 10 kg or more, as compared with weight change of −4.9 to 4.9 kg.

Conclusions: Both underweight (BMI <18.5 kg/m^2) and overweight (BMI ≥25 kg/m^2) among men without history of liver disease, and weight gain after age 20 (weight change ≥5 kg) among women with history of liver disease, were associated with increased mortality from liver cancer.

Key words: weight change; body mass index; liver cancer; mortality; prospective study; epidemiology

INTRODUCTION

According to the World Health Organization, liver cancer was responsible for 700 000 deaths worldwide in 2008 and was the third leading cause of cancer death after lung cancer (1.4 million deaths) and stomach cancer (740 000 deaths).[1]

Meta-analyses[2] and systematic reviews[3,4] reported associations between excess body weight and higher risk of liver cancer among both men and women. However, few studies have examined the association of weight change with risk of liver cancer.[5,6]

In a population with a high prevalence of chronic infection with hepatitis C virus (HCV),[7] it is important to determine whether body weight and weight change are associated with risk of liver cancer irrespective of viral infection (a major contributor to liver cancer).[8] Thus, we chose to examine these associations in relation to the presence or absence of liver disease.

We conducted a prospective study of the associations of BMI at age 20 years, BMI at baseline, and weight change since age 20 years with mortality from liver cancer in a large cohort of Japanese men and women aged 40 to 79 years at baseline.

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METHODS

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) was initiated during 1988–1990.[9,10] Self-administered questionnaires with items on lifestyle and medical history of cancer, liver disease, gallbladder disease, diabetes mellitus, other diseases, and blood transfusion were completed by 110 588 people (46 398 men and 64 190 women) aged 40 to 79 years from 45 communities across Japan. Among them, 73 463 people (31 321 men and 42 142 women) provided self-reported data on weight and height at baseline and weight at age 20 years. We excluded 303 men and 687 women with a reported history of cancer at baseline, leaving 31 018 men and 41 455 women for the present analysis.

Mortality surveillance was conducted systematically by reviewing death certificates. Participants were followed-up until death or until they moved away from their original community, through the end of 2009 (follow-up of 4, 4, and 2 communities finished at the end of 1999, 2003, and 2008, respectively). The median follow-up period was 19.0 years. Underlying cause of death according to the International Classification of Diseases (ICD-10) was obtained centrally from the Ministry of Health and Welfare. Death from liver cancer was defined as ICD-10 codes C22.0 to C22.9. The present study was approved by the Ethical Committees of Nagoya University and Osaka University.

Variables

Weight (kg) and height (m) were self-reported at baseline. BMI was calculated as weight (kg) divided by height (m) squared and then divided into 5 categories (<18.5, 18.5–20.9, 21.0–22.9, 23.0–24.9, and ≥25 kg/m^2); a BMI of 21.0–22.9 kg/m^2 served as the reference group. Weight change since age 20 years was calculated by subtracting weight at age 20 years from weight at baseline. Weight change was grouped into 5 categories (≤−10, −9.9 to −5.0, −4.9 to 4.9, 5.0 to 9.9, and ≥10 kg); stable weight (−4.9 to 4.9 kg) was used as the reference group. We asked the subjects, "Do you have a history of physician-diagnosed liver disease such as hepatitis?". Potential confounding variables were smoking status (never, former, current smoker of <20 cigarettes per day, and current smoker of ≥20 cigarettes per day), ethanol consumption (never, former, current [1–22, 23–45, 46–68, and ≥69 g per day]), hours of walking (<0.5, 0.5, 0.6–0.9, and ≥1.0 h per day), hours of exercise (<1, 1–2, 3–4, and ≥5 per week), frequency of coffee intake (seldom, 1–2 cups per month, 1–2 cups per week, 3–4 cups per week, and almost every day), frequency of fish intake (seldom, 1–2 times per month, 1–2 times per week, 3–4 times per week, and almost every day), education level (<10, 10–12, 13–15, and ≥16 years), area of residence (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu regions), and histories of diabetes mellitus, gallbladder disease, and blood transfusion. A positive history of liver disease, with or without present treatment, was also considered.

Statistical analyses

Sex-specific, age-adjusted means (SD) and proportions of potential confounding factors were calculated by a general linear model.

Cox proportional hazards models were used to calculate sex-specific age- and multivariable-adjusted hazard ratios (HRs) and 95% CIs for liver cancer mortality associated with BMI at baseline, BMI at age 20, and weight change since age 20 years. Multivariable-adjusted Cox modeling included continuous age at baseline, smoking status, ethanol consumption, hours of walking and exercise, frequencies of coffee and fish intake, education level, area of residence, and histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment. For the analysis of weight change, the model was further adjusted for height (continuous) and weight (continuous) at age 20. The P values for linear trends were calculated by assigning the median value of each category to corresponding individuals and treating it as a continuous variable in the model. Testing for trends was performed across the upper 3 categories of BMI (ie, ≥21.0 kg/m^2) and weight change (>−5 kg). Testing for overall trends was performed across all 5 categories of BMI and weight change. Multivariable-adjusted HRs were also calculated for a 5-kg increment of weight change if necessary. To identify effect modification of the association between body weight or weight change and risk of liver cancer, additional stratified analyses were conducted based on the presence or absence of history of liver disease at baseline in men and women.

Because lower body weight and weight loss could be due to preclinical liver cancer, and higher body weight or weight gain could be a consequence of ascites associated with liver cancer, we excluded early deaths from liver cancer (ie, those that occurred during the first 10 years after baseline) to reduce reverse causation in our analyses.

All analyses were conducted using SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, North Carolina, USA). Two-tailed probability values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Mean age at baseline, BMI at baseline, and weight change since age 20 years, in men and women, were 57.2 (10.2) and 56.8 (9.8) years, 22.7 (2.8) and 23.0 (3.2) kg/m^2, and 1.7 (8.9) and 2.7 (8.5) kg, respectively (Table 1). We identified 527 deaths (338 men, 189 women) from liver cancer during 1 168 909 follow-up person-years (486 745 in men, 682 164 in women).

There was no association between baseline BMI and mortality from liver cancer among men or men with liver

Table 1. Sex-specific, age-adjusted means and proportions in all subjects and subjects with and without a self-reported history of liver disease at baseline (JACC study, 1988–2009)

	Men			Women		
	Total	History of liver disease[a]		Total	History of liver disease[a]	
		+	−		+	−
No. at risk	31 018	2438	25 793	41 455	2304	35 378
Age, years	57.2 (10.2)	58.4 (9.4)	56.6 (10.2)	56.8 (9.8)	58.9 (9.0)	56.1 (9.8)
Weight at baseline, kg	60.3 (8.8)	60.6 (9.1)	60.5 (8.8)	52.6 (7.8)	53.3 (8.5)	52.6 (7.8)
Weight at age 20, kg	58.6 (7.6)	58.4 (7.3)	58.6 (7.5)	49.9 (6.8)	49.7 (6.9)	49.9 (6.7)
Height at baseline, m	163.0 (6.6)	163.1 (6.3)	163.1 (6.6)	151.3 (5.8)	151.3 (5.7)	151.3 (5.8)
BMI at baseline, kg/m^2	22.7 (2.8)	22.7 (2.9)	22.7 (2.8)	23.0 (3.2)	23.2 (3.3)	23.0 (3.1)
BMI at age 20, kg/m^2	22.1 (2.8)	21.9 (2.6)	22.1 (2.7)	21.8 (3.0)	21.7 (3.0)	21.8 (3.0)
Weight change after age 20, kg	1.7 (8.9)	2.3 (9.2)	1.8 (8.7)	2.7 (8.5)	3.6 (9.1)	2.7 (8.3)
Never smoker, %	20.4	17.3	21.1	93.3	90.8	93.9
Current smoker, %	53.2	50.8	53.5	5.2	6.2	4.8
Never drinker, %	19.4	15.5	19.7	80.8	76.5	81.5
Current drinker, %	73.8	70.2	74.8	17.3	24.7	17.0
Walk 30 min or more/day, %	68.6	64.3	69.1	71.5	68.8	71.7
Exercise 3 hours or more/week, %	14.9	15.4	14.6	9.9	9.2	9.9
Coffee 1 cup or more daily, %	36.6	36.5	36.1	36.1	37.0	35.1
Fish almost daily, %	1.3	1.3	1.3	1.6	1.5	1.6
College or higher education, %	18.6	21.9	18.3	10.7	12.0	10.7
History of diabetes mellitus, %	7.1	15.9	5.3	4.0	9.4	3.1
History of gallbladder disease, %	4.3	10.7	3.2	5.6	18.9	4.1
History of blood transfusion, %	9.4	19.7	7.6	10.3	20.9	9.1
Present treatment of liver disease, %	—	28.8	—	—	22.0	—

Abbreviation: BMI, body mass index.
[a]Information on history of liver disease was missing for 2787 men and 3773 women.
Values are means (SD) or proportions.

disease. In contrast, among men without a history of liver disease the association was U-shaped: as compared with a BMI of 21.0 to 22.9 kg/m^2, the multivariable HR (95% CI) was 1.95 (1.07–3.54) among those with a BMI less than 18.5 kg/m^2 and 1.65 (1.05–2.60) among those with a BMI of 25 kg/m^2 or higher. BMI was positively associated with mortality from liver cancer among women ($P = 0.04$ for overall trend) and women with a history of liver disease ($P = 0.02$ for overall trend), but not among women without a history of liver disease ($P = 0.23$ for overall trend) (Table 2).

No associations were found for BMI at age 20 in either sex (Table 3). Weight change since age 20 years was positively associated with mortality from liver cancer among women, women with a history of liver disease, and women without a history of liver disease ($P = 0.01$, 0.02, and 0.03, respectively). Among women with a history of liver disease, weight gain of 5.0 to 9.9 kg was associated with a multivariable HR of 1.96 (95% CI, 1.05–3.66) for mortality from liver cancer, and weight gain of 10 kg or more was associated with an HR of 2.31 (1.18–4.49), as compared with women with a weight change of −4.9 to 4.9 kg. The multivariable HRs associated with a 5-kg increment in weight were 1.11 (1.00–1.28), 1.14 (1.00–1.30), and 1.17 (1.00–1.36) among women, women with a history of liver disease, and women without a history of liver disease, respectively. There was no association between weight change and mortality from liver cancer in men (Table 4). The results of the analyses that excluded early deaths from liver cancer were essentially identical. Among overweight men without a history of liver disease the multivariable HR was 1.67 (0.90–3.12), versus a BMI of 21.0 to 22.9 kg/m^2. Analysis of the overall trend for BMI categories among women and women with and without a history of liver disease yielded P values of 0.009, 0.02, and 0.06, respectively, in the multivariable model. Analysis of overall trend for weight change in women, women with a history of liver disease, and women without a history of liver disease yielded P values of 0.007, 0.03, and 0.02, respectively (data not shown in table).

DISCUSSION

In this large-scale prospective study of Japanese men and women, we observed that overweight and underweight were associated with liver cancer mortality in men without liver disease and that weight change positively correlated with liver cancer mortality in women, regardless of history of liver disease.

Our results showing an excess risk of mortality from liver cancer in overweight men without a history of liver disease are in line with those from studies of men from the general populations of East Asian countries,[11] European countries,[5,6] and the United States.[12] Among women, we found a weak positive association between BMI categories and liver cancer mortality, which supports previous findings for women from

Table 2. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to body mass index (BMI) categories at baseline (JACC study, 1988–2009)

	BMI at baseline (kg/m^2)					*P* for trend[a]	*P* for overall trend[b]
	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	≥25.0		
Men							
No. at risk	1669	7116	8892	7583	5758		
No. of person-years	21 231	107 857	140 791	123 112	93 753		
No. of deaths	32	82	88	73	63		
Crude death rate[c]	151	76	63	59	67		
Age-adjusted HR (95% CI)	1.87 (1.25–2.82)	1.15 (0.85–1.55)	1	1.01 (0.74–1.37)	1.20 (0.86–1.65)	0.33	0.21
Multivariable HR (95% CI)[d]	1.42 (0.93–2.15)	1.09 (0.81–1.48)	1	1.04 (0.76–1.42)	1.15 (0.83–1.60)	0.37	0.99
Men with liver disease							
No. at risk	139	544	690	558	507		
No. of person-years	1376	7055	9404	7940	7494		
No. of deaths	13	30	39	34	22		
Crude death rate[c]	945	425	415	428	294		
Age-adjusted HR (95% CI)	1.86 (0.99–3.51)	0.94 (0.59–1.52)	1	1.06 (0.67–1.67)	0.75 (0.44–1.26)	0.27	0.09
Multivariable HR (95% CI)[d]	0.99 (0.51–1.95)	0.91 (0.55–1.48)	1	1.03 (0.64–1.66)	0.83 (0.48–1.44)	0.38	0.80
Men without liver disease							
No. at risk	1303	5838	7396	6446	4810		
No. of person-years	17 660	91 245	120 182	107 098	79 876		
No. of deaths	16	39	39	33	37		
Crude death rate[c]	91	43	32	31	46		
Age-adjusted HR (95% CI)	2.24 (1.25–4.03)	1.25 (0.80–1.96)	1	1.00 (0.63–1.59)	1.58 (1.01–2.48)	0.05	0.75
Multivariable HR (95% CI)[d]	1.95 (1.07–3.54)	1.22 (0.78–1.91)	1	1.08 (0.68–1.72)	1.65 (1.05–2.60)	0.03	0.78
Women							
No. at risk	2560	8527	11 094	9598	9676		
No. of person-years	38 047	138 984	184 657	159 579	160 898		
No. of deaths	8	36	42	41	62		
Crude death rate[c]	21	26	23	26	39		
Age-adjusted HR (95% CI)	0.73 (0.34–1.57)	1.10 (0.71–1.72)	1	1.14 (0.74–1.75)	1.63 (1.10–2.41)	0.01	0.01
Multivariable HR (95% CI)[d]	0.74 (0.35–1.60)	1.08 (0.69–1.68)	1	1.16 (0.75–1.79)	1.42 (0.95–2.13)	0.10	0.04
Women with liver disease							
No. at risk	136	448	572	527	621		
No. of person-years	1722	6176	8157	7546	8749		
No. of deaths	1	16	19	17	30		
Crude death rate[c]	58	259	233	225	343		
Age-adjusted HR (95% CI)	0.23 (0.03–1.73)	1.11 (0.57–2.15)	1	1.02 (0.53–1.96)	1.49 (0.84–2.66)	0.14	0.05
Multivariable HR (95% CI)[d]	0.23 (0.03–1.74)	1.14 (0.57–2.29)	1	1.20 (0.60–2.40)	1.72 (0.93–3.18)	0.09	0.02
Women without liver disease							
No. at risk	2121	7282	9572	8196	8207		
No. of person-years	32 776	121 678	163 208	139 737	139 789		
No. of deaths	7	14	19	22	28		
Crude death rate[c]	21	12	12	16	20		
Age-adjusted HR (95% CI)	1.44 (0.60–3.45)	0.96 (0.48–1.92)	1	1.36 (0.74–2.52)	1.64 (0.91–2.93)	0.10	0.14
Multivariable HR (95% CI)[d]	1.32 (0.55–3.18)	0.97 (0.49–1.94)	1	1.33 (0.72–2.46)	1.49 (0.83–2.69)	0.27	0.23

[a]Test for trend refers to a baseline BMI of ≥21.0 kg/m^2.
[b]Test for overall trend refers to a baseline BMI of <18.5 kg/m^2.
[c]Mortality rate is expressed as rate per 100 000 person-years.
[d]Multivariable adjustment: age, smoking status, ethanol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.

the general populations of the United States[12] and Korea.[11] The positive association between BMI and liver cancer risk in women with a history of liver disease was in line with previous findings in patients with liver disease, namely, that a higher baseline BMI was predictive of incident liver cancer.[13–19]

Two prospective studies investigated the association of weight change during adulthood with liver cancer risk.[5,6] A study of 107 815 Swedish men with a small number of incident liver cancers ($n = 55$) reported no association between weight gain and risk of liver cancer, as compared with stable weight.[5] Another study of 191 927 European men and women found a positive dose-dependent association between weight change after age 20 years and risk of incident liver cancer.[6] However, in sex-specific analysis, there was a positive association only among men, perhaps due to the small number of incident liver cancers among women ($n = 54$). Nonetheless, we found a positive relationship between weight change and liver cancer mortality in women, regardless of history of liver disease, which confirms previous findings among men. Because the

Table 3. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to body mass index (BMI) categories at age 20 years (JACC study, 1988–2009)

	BMI at age 20 (kg/m^2)					*P* for trend[a]	*P* for overall trend[b]
	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	≥25.0		
Men							
No. at risk	1805	9180	10 300	6372	3361		
No. of person-years	28 079	148 241	164 069	97 587	48 768		
No. of deaths	14	91	115	75	43		
Crude death rate[c]	50	61	70	77	88		
Age-adjusted HR (95% CI)	0.78 (0.45–1.36)	0.99 (0.75–1.30)	1	0.96 (0.72–1.29)	1.02 (0.72–1.45)	0.92	0.65
Multivariable HR (95% CI)[d]	0.74 (0.42–1.29)	0.89 (0.68–1.18)	1	0.92 (0.69–1.24)	0.91 (0.64–1.31)	0.54	0.66
Men with liver disease							
No. at risk	170	735	785	474	274		
No. of person-years	2249	10 227	11 072	6248	3474		
No. of deaths	8	34	48	31	17		
Crude death rate[c]	356	332	434	496	489		
Age-adjusted HR (95% CI)	0.86 (0.41–1.82)	0.83 (0.53–1.28)	1	1.02 (0.65–1.61)	0.97 (0.55–1.69)	0.98	0.49
Multivariable HR (95% CI)[d]	0.91 (0.42–1.97)	0.68 (0.43–1.07)	1	0.98 (0.61–1.56)	0.75 (0.41–1.35)	0.36	0.68
Men without liver disease							
No. at risk	1456	7667	8625	5294	2751		
No. of person-years	23 539	127 328	141 043	83 287	40 864		
No. of deaths	4	48	57	33	22		
Crude death rate[c]	17	38	40	40	54		
Age-adjusted HR (95% CI)	0.78 (0.45–1.36)	0.99 (0.75–1.30)	1	0.96 (0.72–1.29)	1.02 (0.72–1.45)	0.85	0.61
Multivariable HR (95% CI)[d]	0.50 (0.18–1.39)	1.05 (0.71–1.54)	1	0.81 (0.53–1.25)	0.98 (0.60–1.62)	0.76	0.99
Women							
No. at risk	4061	12 936	11 996	7364	5098		
No. of person-years	64 811	214 456	199 655	122 099	81 143		
No. of deaths	20	49	58	37	25		
Crude death rate[c]	31	23	29	30	31		
Age-adjusted HR (95% CI)	1.23 (0.74–2.05)	0.90 (0.61–1.32)	1	0.95 (0.63–1.43)	0.77 (0.48–1.23)	0.28	0.25
Multivariable HR (95% CI)[d]	0.98 (0.58–1.64)	0.85 (0.58–1.25)	1	0.91 (0.60–1.38)	0.73 (0.45–1.18)	0.18	0.49
Women with liver disease							
No. at risk	289	721	582	410	302		
No. of person-years	3746	10 014	8348	6049	4192		
No. of deaths	11	17	28	13	14		
Crude death rate[c]	294	170	335	215	334		
Age-adjusted HR (95% CI)	1.04 (0.52–2.10)	0.56 (0.31–1.02)	1	0.64 (0.33–1.24)	0.84 (0.44–1.60)	0.60	0.99
Multivariable HR (95% CI)[d]	0.91 (0.43–1.94)	0.53 (0.29–1.00)	1	0.61 (0.31–1.21)	0.75 (0.37–1.50)	0.32	0.98
Women without liver disease							
No. at risk	3337	11 081	10 396	6311	4253		
No. of person-years	55 240	188 811	176 982	106 855	69 299		
No. of deaths	9	27	25	20	9		
Crude death rate[c]	16	14	14	19	13		
Age-adjusted HR (95% CI)	1.23 (0.74–2.05)	0.90 (0.61–1.32)	1	0.95 (0.63–1.43)	0.77 (0.48–1.23)	0.25	0.14
Multivariable HR (95% CI)[d]	1.28 (0.59–2.76)	1.24 (0.72–2.15)	1	1.22 (0.68–2.21)	0.62 (0.29–1.34)	0.30	0.13

[a]Test for trend refers to a baseline BMI of ≥21.0 kg/m^2.
[b]Test for overall trend refers to a baseline BMI of <18.5 kg/m^2.
[c]Mortality rate is expressed as rate per 100 000 person-years.
[d]Multivariable adjustment: age, smoking status, ethanol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.

numbers of deaths were relatively small in the first 2 weight-change groups (ie, ≤−10.0 and −5 to −9.9 kg) in the analyses of women in the present study, we examined whether combining the first 2 weight-change groups would alter the results; however, the *P* values were very similar for overall trend. We found no association between weight change since age 20 years and risk of liver cancer in men.

The mechanism linking excess body weight or weight gain during adulthood with higher mortality from liver cancer may be mediated via progression of nonalcoholic fatty liver disease (NAFLD), a clinicopathologic condition that encompasses a wide spectrum of liver tissue changes, ranging from steatosis alone to nonalcoholic steatohepatitis, advanced fibrosis, cirrhosis, and, in the most severe cases, liver cancer.[20] Level of obesity was found to be correlated with NAFLD development: a study of 39 151 Japanese adults reported that 12.8% of nonobese subjects (BMI <25 kg/m^2), 51.4% of overweight subjects (25 ≤ BMI < 30 kg/m^2), and 80.4% of highly obese subjects (BMI ≥30 kg/m^2) had fatty liver disease, as determined by abdominal ultrasonography.[21] In addition,

Table 4. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to categories of weight change since age 20 years to baseline (JACC study, 1988–2009)

	Weight change from age 20 to baseline (kg)					*P* for trend[a]	*P* for overall trend[b]
	≤−10.0	−5 to −9.9	−4.9 to 4.9	5.0 to 9.9	≥10.0		
Men							
No. at risk	2454	4831	12279	5666	5788		
No. of person-years	30812	70268	197516	93608	94540		
No. of deaths	27	76	124	55	56		
Crude death rate[c]	88	108	63	59	59		
Age-adjusted HR (95% CI)	0.94 (0.61–1.43)	1.32 (0.99–1.77)	1	1.06 (0.77–1.46)	1.09 (0.80–1.50)	0.59	0.85
Multivariable HR (95% CI)[d]	0.68 (0.43–1.08)	1.08 (0.80–1.46)	1	1.06 (0.77–1.47)	0.98 (0.70–1.37)	0.88	0.54
Men with liver disease							
No. at risk	193	390	882	436	537		
No. of person-years	1942	4895	12357	6322	7752		
No. of deaths	11	29	49	23	26		
Crude death rate[c]	566	592	397	364	335		
Age-adjusted HR (95% CI)	1.09 (0.56–2.12)	1.26 (0.79–2.00)	1	1.03 (0.62–1.69)	0.97 (0.60–1.56)	0.89	0.48
Multivariable HR (95% CI)[d]	0.59 (0.28–1.23)	0.93 (0.56–1.54)	1	1.08 (0.64–1.81)	1.03 (0.61–1.72)	0.63	0.33
Men without liver disease							
No. at risk	1908	3880	10406	4818	4781		
No. of person-years	24969	58307	171105	81354	80327		
No. of deaths	13	33	65	28	25		
Crude death rate[c]	52	57	38	34	31		
Age-adjusted HR (95% CI)	0.95 (0.52–1.73)	1.15 (0.75–1.76)	1	1.03 (0.66–1.61)	0.94 (0.59–1.50)	0.84	0.73
Multivariable HR (95% CI)[d]	0.69 (0.36–1.34)	0.98 (0.64–1.52)	1	1.08 (0.69–1.70)	1.00 (0.61–1.61)	0.95	0.52
Women							
No. at risk	2269	5811	16186	8986	8203		
No. of person-years	32934	92910	270774	150616	134929		
No. of deaths	10	24	62	46	47		
Crude death rate[c]	30	26	23	31	35		
Age-adjusted HR (95% CI)	0.77 (0.39–1.52)	0.82 (0.51–1.32)	1	1.44 (0.98–2.10)	1.60 (1.10–2.34)	0.01	0.0006
Multivariable HR (95% CI)[d]	0.68 (0.34–1.40)	0.83 (0.51–1.35)	1	1.31 (0.89–1.94)	1.41 (0.94–2.11)	0.08	0.01
Women with liver disease							
No. at risk	135	308	789	508	564		
No. of person-years	1750	4400	11184	7488	7528		
No. of deaths	3	15	21	22	22		
Crude death rate[c]	171	341	188	294	292		
Age-adjusted HR (95% CI)	0.67 (0.20–2.26)	1.56 (0.80–3.04)	1	1.64 (0.90–2.98)	1.70 (0.94–3.10)	0.06	0.11
Multivariable HR (95% CI)[d]	0.55 (0.15–2.03)	1.47 (0.72–3.00)	1	1.96 (1.05–3.66)	2.31 (1.18–4.49)	0.02	0.02
Women without liver disease							
No. at risk	1812	4880	14141	7720	6825		
No. of person-years	27205	79851	241627	132498	116006		
No. of deaths	4	6	36	22	22		
Crude death rate[c]	15	8	15	17	19		
Age-adjusted HR (95% CI)	0.54 (0.19–1.52)	0.35 (0.15–0.84)	1	1.22 (0.72–2.08)	1.36 (0.80–2.30)	0.24	0.003
Multivariable HR (95% CI)[d]	0.50 (0.17–1.49)	0.35 (0.15–0.85)	1	1.16 (0.68–1.99)	1.14 (0.65–2.00)	0.58	0.03

[a]Test for trend refers to weight change ≥−4.9 kg.
[b]Test for overall trend refers to weight change ≤−10.0 kg.
[c]Mortality rate is expressed as rate per 100 000 person-years.
[d]Multivariable adjustment: age, weight at age 20, height at age 20, smoking status, ethanol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.

weight gain during an average of 414 days was found to be an independent risk factor for incident NAFLD in Japanese men and women.[22]

Second, overweight (BMI ≥25 kg/m^2) was associated with a 5-fold risk of fibrosis progression in liver during a 1-year period among people with HCV infection,[23] which suggests that overweight increases the risk of liver cancer via progression of liver fibrosis.

Third, it is possible that overweight was confounded by hepatitis C infection. However, according to a nested case-control study[24] of a JACC study subsample of approximately 12 000 adults, BMI tended to be inversely associated with HCV infection. For example, among men without liver disease, the proportion of those with HCV infection was 8.9% for a BMI less than 18.5 kg/m^2, 7.3% for a BMI of 18.5 to less than 21.0 kg/m^2, 6.9% for a BMI of 21.0 to less than 23.0 kg/m^2, 6.7% for a BMI of 23.0 to less than 25.0 kg/m^2, and 4.7% for a BMI of 25.0 kg/m^2 or higher. Thus, it is unlikely that the excess risk of mortality from liver cancer in adults with a BMI of 25.0 kg/m^2 or higher was due to HCV

infection. However, the excess risk of mortality from liver cancer in those with a BMI less than 18.5 kg/m^2 could be confounded by HCV infection.

In the present study, men without liver disease and a baseline BMI less than 18.5 kg/m^2 had excess mortality from liver cancer as compared with those with a BMI of 21.0 to 22.9 kg/m^2, perhaps because underweight men without liver disease were in a preclinical disease state. Indeed, in our study the proportion of former drinkers was higher among underweight men without liver disease than among men with a BMI of 21.0 to 22.9 kg/m^2 (10% vs 5%). However, the associations were weaker in sensitivity analyses that excluded deaths from liver cancer within 10 years ($n = 77$) and former drinkers ($n = 1277$) from men without liver disease: the multivariable HRs were 1.80 (95% CI, 0.72–4.53) and 1.86 (95% CI, 0.96–3.58), respectively. Therefore, the increased risk of mortality from liver cancer associated with low BMI is unlikely to be due to reverse causation. The mechanisms responsible should be investigated in future studies.

Our study benefited from a long follow-up period and a large population-based sample, which allowed us to examine associations with liver cancer in narrow ranges of BMI and weight change in both men and women. However, some limitations of the present study should be discussed. First, the lack of information on HCV infection, a major risk factor for liver cancer,[8] is a major limitation of the current study. Because most individuals with hepatitis virus infection are asymptomatic, the use of a questionnaire to exclude hepatitis would be insufficient. Second, we used mortality data rather than incidence data as an endpoint. However, the prognosis of liver cancer is generally poor: relative 5-year survival rates were 21.2% to 27.1% from 1993–1996 to 2000–2002, according to statistics by the Japan National Cancer Center,[25] which means that most incident cases are detected as mortality cases.[25] Third, weight and height were self-reported in the current study and were not validated by actual measurements. However, a previous validation study of a Japanese population indicated that self-reported weight and height strongly correlated with previously measured weight and height: the reported Pearson correlation coefficients for men and women were 0.979 and 0.998 for height and 0.961 and 0.959 for weight, respectively, ie, the differences were immaterial.[26] Fourth, weight at age 20 was also self-reported. However, 1 study found that long-term recall of past body weights was reasonably accurate in Japanese adults[27] and that people who had experienced weight loss after age 25 years underestimated their past weights, whereas those with stable weight or weight gain overestimated them.[27] Recall bias resulting in misclassification of weight changes would likely lead to overestimation of real associations. Fifth, only 70% of the present cases reported their weight at age 20 and at baseline. However, any selection bias caused by missing data is unlikely to affect the results because age (57.0 vs 58.2 years), baseline BMI (22.8 vs 22.7 kg/m^2), and other baseline variables were similar between the included and excluded subjects.

In conclusion, underweight (BMI <18.5 kg/m^2) and overweight (BMI ≥25 kg/m^2) in men without liver disease, and weight gain (weight change ≥5 kg) after age 20 in women with liver disease, were associated with increased mortality from liver cancer. Higher BMI tended to be associated with higher mortality from liver cancer among women and women with a history of liver disease. Weight change was positively associated with increased risk of liver cancer mortality in women with or without liver disease.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Conflicts of interest: None declared.

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Study Profile

Cohort Profile of the Japan Collaborative Cohort Study at Final Follow-up

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ABSTRACT

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in the late 1980s to evaluate the risk impact of lifestyle factors and levels of serum components on human health. During the 20-year follow-up period, the results of the study have been published in almost 200 original articles in peer-reviewed English-language journals. However, continued follow-up of the study subjects became difficult because of the retirements of principal researchers, city mergers throughout Japan in the year 2000, and reduced funding. Thus, we decided to terminate the JACC Study follow-up at the end of 2009. As a final point of interest, we reviewed the population registry information of survivors. A total of 207 (0.19%) subjects were ineligible, leaving 110 585 eligible participants (46 395 men and 64 190 women). Moreover, errors in coding date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Although such errors were unexpected, their impact is believed to be negligible because of the small numbers relative to the large total study population. Here, we describe the final cohort profile at the end of the JACC Study along with selected characteristics of the participants and their status at the final follow-up. Although follow-up of the JACC Study participants is finished, we will continue to analyze and publish study results.

Key words: JACC Study; cohort study; Japan; follow-up

INTRODUCTION

To evaluate the risk impact of lifestyle factors and levels of serum components on human health, in the late 1980s we established a large-scale cohort study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). During a follow-up period of approximately 20 years, data on deaths from major causes such as stomach cancer, lung cancer, and cardiovascular diseases enabled examination of risk factors. We subsequently published results regarding associations between lifestyle factors and health status in almost 200 original research articles in peer-reviewed English-language journals. Additionally, we are currently developing a website to increase public awareness.[1]

The enthusiasm of researchers is always important in promoting a cohort study, but enthusiasm is not enough since such work takes many years to bear fruit. A substantial budget is also required. The JACC Study was started after receiving a promise of funds for 10 years; however, after the initial 10 years had passed, it became necessary to apply for small public grants to maintain and follow cohort participants. In addition, administrative mergers of cities, towns, and villages throughout Japan in the year 2000 sometimes caused further difficulties in following subjects in the study area, due to changes in partnerships between local governmental offices and researchers. Moreover, with the retirement of key researchers, it was not always easy to transfer their work to their successors. As a result of these challenges, we decided to

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terminate follow-up of participants in the JACC Study at the end of 2009.

As a final point of interest, we used population registers in the study area to review the list of survivors. Some subjects were found to be no longer living in the study area, although the overall number of such participants was small. Moreover, a small number of errors in the coding of date of birth and sex were identified during follow-up data collection. Here we describe the final cohort profile obtained upon completion of the JACC Study. Data on cancer incidence have not yet been compiled because of the time lag of the cancer registry system. This process is expected to continue until 2013, at which point incidence information until 2009 will be made available.

METHODS

Study subjects

Details of the study design and concept have been described elsewhere.[2–4] Briefly, the JACC Study was a multicenter collaborative study in which 24 institutions voluntarily participated. Recruitment of study subjects living in 45 areas was managed by individual investigators whose responsibility was to construct the cohort in that area. Data were collected from 1988 through 1990. However, although most baseline surveys were performed during this 3-year period, some subjects were recruited before and after this period because of the need for a preliminary study in 3 areas and later collaboration in 1 area. Individual informed consent before participation in the study was obtained in 36 of the 45 study areas (written consent in 35 areas and oral consent in 1 area); in the remaining 9 areas, group consent from the area leader was obtained. Participant eligibility was verified by individual investigators, who confirmed that (1) the participant was living within the study area and (2) was aged 40 to 79 years at baseline. In addition, date of birth and sex were further verified using official documents and/or a completed self-administered questionnaire.

Follow-up

As follow-up information, dates and causes of death were annually or biannually confirmed, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) and/or the Ministry of Health, Labor and Welfare, Japan. The date of move-out of cohort members from the study area was also annually or biannually verified by the investigator in cooperation with key members of the local governmental office. In 24 of the 45 areas, data on cancer incidence such as date of diagnosis and primary site were also collected through population-based cancer registers or by reviewing the records of local major hospitals. In most areas, follow-up was completed at the end of 2009; however, it was stopped at the end of 1999 in 4 areas, at the end of 2003 in another 4 areas, and at the end of 2008 in 2 areas.

Final data setup: correction of birth date and sex information, identification of decedents and subjects who had moved, and deletion of ineligible participants

To confirm if study participants had survived and were living in the study area at the end of follow-up, we conducted a systematic review of population registers of cohort members in 17 areas followed until 2009. In the remaining 18 areas followed until 2009, annual or biannual follow-up surveys were routinely performed using population registers; thus, no further reviews were conducted. If data from participants presumed to survive were found to be missing at the end of 2009, attempts were made to obtain information on their mortality status or current location, and relevant information was added to the follow-up data. A few participants were found to have never lived in the study area and were thus excluded from the baseline data.

This review process revealed some errors in coding of date of birth and sex. Moreover, during the merge of follow-up data with baseline identifiable data (name, date of birth, and sex), further errors in date of birth and sex were found. All such errors were corrected.

RESULTS

Of 110 792 participants aged 40 to 79 years at baseline, 207 (0.19%) were found to have never lived in the study area. As a result, 110 585 participants (46 395 men and 64 190 women) were ultimately deemed eligible as subjects for the JACC Study, with 707 136 and 1 025 703 person-years of follow-up for men and women, respectively. Errors in the coding of date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Table 1 shows the age and sex distribution of study participants. There were no subjects from the Shikoku region. As compared with the overall distribution of the Japanese population in 1989, our cohort participants were slightly older and included a higher percentage of women.

Table 2 shows the follow-up results, and Table 3 shows the major causes of death up to 2009. These values include the follow-up information (death or move-out from the study area) that was reported in 10 of 17 areas for 516 subjects (0.5%) through a systematic review of population registers of cohort members. Finally, 27 410 deaths (24.8%; 15 401 men, 12 009 women) and 6402 move-outs (5.8%; 2343 men, 4059 women) were identified during the median 18.0-year follow-up. The first cause of death was cancer among men (37.6%) and circulatory disease among women (33.7%), and the second cause of death was circulatory disease (27.8%) and cancer (30.8%), respectively (Table 3). Among those who died of cancer, the first, second, and third leading causes of death were cancer of the lung (23.2%), stomach (18.4%), and liver (10.7%) among men and cancer of the stomach (15.4%), lung (11.2%), liver, and pancreas (9.2% for both)

Table 1. Age distribution of cohort members at baseline by region

	Age at baseline								Total	%
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79		
Men										
Japan general population 1989 (×1000)	5022	4562	3967	3706	3122	2049	1507	1169	25 104	
	20.0	18.2	15.8	14.8	12.4	8.2	6.0	4.7	100.0	
JACC Study participants	5991	5794	6309	7690	8415	5516	4021	2659	46 395	100.0
%	12.9	12.5	13.6	16.6	18.1	11.9	8.7	5.7	100.0	
Hokkaido	191	182	211	267	284	201	86	43	1465	3.2
Tohoku	809	625	797	1050	1270	894	494	293	6232	13.4
Kanto	1325	1231	1219	1320	1446	1115	707	447	8810	19.0
Chubu	1736	1646	1560	1763	1804	1167	916	691	11 283	24.3
Kinki	960	908	1148	1456	1419	996	651	459	7997	17.2
Chugoku	220	374	452	886	1251	589	770	509	5051	10.9
Kyushu	750	828	922	948	941	554	397	217	5557	12.0
Women										
Japan general population 1989 (×1000)	4989	4613	4052	3852	3426	2825	2141	1770	27 668	
	18.0	16.7	14.6	13.9	12.4	10.2	7.7	6.4	100.0	
JACC Study participants	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190	100.0
%	11.7	12.3	14.2	16.8	17.3	13.4	8.6	5.6	100.0	
Hokkaido	310	310	433	436	382	257	93	37	2258	3.5
Tohoku	959	963	1412	1670	1670	1136	604	372	8786	13.7
Kanto	1428	1438	1442	1605	1744	1577	892	542	10 668	16.6
Chubu	1872	1669	1833	1933	2107	1613	1225	882	13 134	20.5
Kinki	1253	1219	1508	1784	1566	1300	876	623	10 129	15.8
Chugoku	300	796	828	1479	2194	1795	1289	844	9525	14.8
Kyushu	1414	1517	1632	1885	1439	911	569	323	9690	15.1

Table 2. Follow-up status until 2009 by sex and age

	Age at baseline								Total
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	
Men									
No. at baseline	5991	5794	6309	7690	8415	5516	4021	2659	46 395
No. of deaths	394	658	1113	2000	3252	3056	2782	2146	15 401
%	6.6	11.4	17.6	26.0	38.6	55.4	69.2	80.7	33.2
No. who left study area	539	377	303	298	292	242	180	112	2343
%	9.0	6.5	4.8	3.9	3.5	4.4	4.5	4.2	5.1
Person-years	107 048	102 338	108 465	124 421	123 896	74 267	43 689	23 012	707 136
Mortality rate (per 1000 person-years)	3.7	6.4	10.3	16.1	26.2	41.1	63.7	93.3	21.8
Women									
No. at baseline	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190
No. of deaths	242	368	637	1218	1982	2544	2632	2386	12 009
%	3.2	4.7	7.0	11.3	17.9	29.6	47.4	65.9	18.7
No. who left study area	605	488	479	522	606	592	483	284	4059
%	8.0	6.2	5.3	4.8	5.5	6.9	8.7	7.8	6.3
Person-years	134 927	139 091	159 465	182 347	174 721	125 510	71 076	38 566	1 025 703
Mortality rate (per 1000 person-years)	1.8	2.6	4.0	6.7	11.3	20.3	37.0	61.9	11.7

among women. When cancers of the colon and rectum were grouped together, that category was the second leading cause of death (12.7%) among women.

DISCUSSION

This final profile of the JACC Study Group describes the number of participants and their follow-up status. During the median 18-year follow-up, we found errors in the coding of date of birth and sex data as well as incorrectly registered cases. Accordingly, we would advise future researchers planning a field study to thoroughly check participant eligibility and basic information such as date of birth and sex; this can be performed at least twice, by using a population register and a self-questionnaire.

Although follow-up information was annually or biannually confirmed, 516 subjects who had died or moved out of the study area were not identified during routine follow-up. The

Table 3. Mortality distribution according to cause of death during entire follow-up period

Cause of death		Men											Women										
		Age at baseline								Total	%	%[a]	Age at baseline								Total	%	%[a]
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79				40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79			
All causes		394	658	1113	2000	3252	3056	2782	2146	15401	100.0		242	368	637	1218	1982	2544	2632	2386	12009	100.0	
A00–B99	Certain infectious and parasitic diseases	6	10	18	38	56	62	44	33	267	1.7		4	4	18	31	62	50	43	36	248	2.1	
C00–D49	Neoplasms	160	312	542	927	1425	1073	792	561	5792	37.6	100.0	147	182	319	563	740	714	618	414	3697	30.8	100.0
C15	Esophagus	12	14	28	42	55	38	17	10	216		3.7	0	1	5	3	4	7	8	7	35		0.9
C16	Stomach	32	62	87	176	252	199	151	109	1068		18.4	19	26	33	93	91	127	104	76	569		15.4
C18	Colon	12	14	36	41	67	59	44	35	308		5.3	2	13	29	45	62	65	65	52	333		9.0
C19–C20	Rectum	8	17	26	52	39	30	27	22	221		3.8	9	8	12	18	35	16	26	11	135		3.7
C22	Liver and intrahepatic bile ducts	21	46	79	128	167	77	66	37	621		10.7	8	12	29	65	81	77	33	35	340		9.2
C23	Gall bladder	1	5	6	16	17	32	12	12	101		1.7	4	7	11	15	17	28	35	13	130		3.5
C24	Other and unspecified parts of biliary tract	5	11	11	34	41	42	28	16	188		3.2	3	8	11	22	31	37	37	23	172		4.7
C25	Pancreas	13	20	29	50	78	63	43	42	338		5.8	7	16	26	48	82	66	62	33	340		9.2
C33–C34	Lung	27	50	114	205	364	290	181	114	1345		23.2	18	20	39	54	96	78	70	40	415		11.2
C50	Breast	0	1	0	0	0	0	1	0	2		0.0	28	26	28	37	29	18	17	9	192		5.2
C53	Cervic uteri												6	2	10	5	9	5	7	5	49		1.3
C54	Corpus uteri												2	2	7	7	9	3	4	2	36		1.0
C55	Uterus, part unspecified												2	3	1	3	13	9	8	7	46		1.2
C56	Ovary												13	8	15	16	22	10	9	5	98		2.7
C61	Prostate	2	4	20	21	68	49	59	56	279		4.8											
C64	Kidney	0	4	7	12	14	9	12	4	62		1.1	0	0	1	5	3	11	5	1	26		0.7
C65–C67	Urothelial tract	2	7	13	11	40	31	34	17	155		2.7	1	0	6	6	21	14	16	14	78		2.1
C82–C85	Non-Hodgkin's lymphoma	0	8	17	29	44	20	15	15	148		2.6	5	6	10	25	23	17	12	7	105		2.8
C90	Multiple myeloma	2	7	4	12	18	12	9	5	69		1.2	4	4	9	12	15	15	11	10	80		2.2
C92	Myeloid leukemia	5	10	11	16	17	7	9	3	78		1.3	1	4	4	12	15	9	8	3	56		1.5
E00–E89	Endocrine, nutritional and metabolic diseases	8	10	17	29	38	35	27	28	192	1.2		2	4	7	10	36	49	48	43	199	1.7	
G00–G99	Diseases of the nervous system	4	7	17	19	50	39	18	10	164	1.1		1	4	12	23	44	27	29	13	153	1.3	
I00–I99	Diseases of the circulatory system	86	132	252	460	857	908	919	673	4287	27.8		52	70	138	306	585	913	1001	978	4043	33.7	
I20–I25	Ischemic heart disease	34	45	69	124	199	204	181	147	1003			11	8	34	51	105	188	176	185	758		
I48	Atrial fibrillation and flutter	0	0	4	10	19	25	24	15	97			1	0	1	3	16	21	29	26	97		
I50	Heart failure	7	19	26	56	121	151	178	153	711			8	5	22	44	101	180	200	239	799		
I60–I69	Cerebrovascular disease	30	44	113	194	362	389	408	285	1825			24	43	63	130	256	393	461	407	1777		
I71	Aortic aneurysm and dissection	4	4	12	21	44	40	38	15	178			2	3	2	17	22	29	28	13	116		
J00–J99	Diseases of the respiratory system	14	40	62	219	408	501	550	500	2294	14.9		3	18	23	67	182	281	357	354	1285	10.7	
J09–J18	Influenza and pneumonia	6	20	30	115	228	273	327	327	1326			2	11	15	39	110	173	247	245	842		
J43	Emphysema	0	1	6	19	58	58	64	44	250			0	0	0	2	2	4	4	4	16		
K00–K95	Diseases of the digestive system	28	35	53	78	82	109	80	46	511	3.3		1	12	13	54	54	106	91	82	413	3.4	
K74	Fibrosis and cirrhosis of liver	16	16	27	34	20	13	19	6	151			1	8	6	23	22	31	19	10	120		
N00–N99	Diseases of the genitourinary system	2	9	14	33	67	68	67	59	319	2.1		2	3	15	22	51	78	82	81	334	2.8	
N17–N19	Acute kidney failure and chronic kidney disease	2	7	12	22	50	52	52	53	250			1	2	12	17	38	50	63	60	243		
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	4	4	6	7	26	52	99	109	307	2.0		1	1	1	7	26	84	172	234	526	4.4	
R54	Age-related physical debility	0	0	0	4	19	37	87	99	246			0	0	1	2	18	71	150	224	466		
S00–T88	External causes	78	86	113	150	170	150	126	93	966	6.3		22	57	72	97	143	147	117	73	728	6.1	
	Others	4	13	19	40	73	59	60	34	302	2.0		7	13	19	38	59	95	74	78	383	3.2	

[a]Percentage of deaths per neoplasm.

use of population registers to verify that subjects are living in the study area is therefore necessary because it enables identification of deceased individuals and those who have moved out of the study area. Furthermore, 356 (0.32%) and 59 (0.05%) cases of incorrect coding of date of birth and sex, respectively, were found during routine follow-up and final review. Miscoding of data can occur by verification only once, and miscoding of date of birth and sex information may cause errors such as merging of the follow-up information of 1 participant with the baseline data of another participant. Thus, careful efforts such as independent double-entry are essential to reduce such miscoding.

The JACC Study is one of the largest cohort studies in Japan. Selected characteristics of study participants were similar to those of the Japanese general population, and thus, the JACC Study can be regarded as representative of the Japanese population, though it should be noted that no subjects were recruited from the Shikoku region. Almost 200 original articles on the risk factors for cancer, cardiovascular disease, and other diseases have been published using the results of the JACC Study. It was not an easy task to establish and maintain such a large collaborative cohort study with a limited budget; the voluntary efforts of the collaborators were essential. Although unexpected errors were found, we believe that the impact of these errors was negligible because the number of ineligible cases and amount of missing data were small relative to the large total study population.

Cohort studies need to continue over a long period if they are to yield fruitful results. Moreover, because all study participants must be followed up carefully and thoroughly, considerable funding is required. The JACC Study received systematic support for the first 10 years, at which point this funding ceased and maintenance and follow-up of cohort participants was accomplished by means of smaller grants. The retirements of principal researchers and city mergers throughout Japan made it difficult to continue follow-up. Thus, we decided to terminate the follow-up of participants in the JACC Study at the end of 2009. Our experience indicates that the development and maintenance of an appropriate long-term management system is essential when launching a cohort study and that adequate and steady support from funding bodies is also important.

We would like to express our sincere thanks to all participants and researchers related to the JACC Study, and to all the funding bodies that supported our study. Hereafter, we plan to use the final dataset and remaining sera to examine the risk impact of lifestyle factors and levels of serum components on human health.

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Conflicts of interest: None declared.

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大阪府におけるAYA（adolescents and young adults）世代のがんの実態

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要旨：

目的：米国では、15歳～29歳のAYA（adolescents and young adults）世代の悪性リンパ腫および白血病の罹患割合が20%超と報告されているが、わが国におけるAYA世代のがんの現状は殆ど把握されていない。また、がん医療水準の均てん化は、わが国に多いがんを中心に進められているが、AYA世代に多くみられる悪性リンパ腫や白血病は考慮されておらず、この世代におけるがん医療の均てん化は遅れていると推測される。そこで、AYA世代のがんの現状と受療動態を明らかにする。方法：対象は、1996年～2005年に診断された15歳～29歳の患者で、大阪府がん登録資料に基づき、罹患、生存率、国指定／府指定がん拠点病院におけるカバー率を算出した。カバー率は、「当該医療機関における主治療件数」を「大阪府全体の罹患数」で除して得た。結果：15歳～29歳では、悪性リンパ腫と白血病が多くみられ、その罹患割合は23.3%であった。15歳～19歳から20歳～29歳に年齢が上がるに伴い、全がんに占める固形腫瘍の割合は増加し、悪性リンパ腫および白血病の割合は減少した。5年相対生存率は0歳～14歳と異なり、AYA世代の白血病の生存率向上は鈍かった。AYA世代のがんにおける国指定がん拠点病院及び府指定がん拠点病院のカバー率は60%超であった。結論：AYA世代のがんでは悪性リンパ腫や白血病が多いことから、国指定がん拠点病院及び府指定がん拠点病院以外の医療機関でのカバー率は約40%も認められた。生存率向上に向けて、AYA世代の特殊事情を考慮した医療体制の構築が重要である。

1．はじめに

米国では、15歳～29歳のAYA（adolescents and young adults）世代の悪性リンパ腫および白血病の罹患割合が20%超と報告[1]されているが、わが国におけるAYA世代のがんの現状は殆ど把握されていない。また、がん医療水準の均てん化を推進するためにがん診療連携拠点病院の整備が進められているが、これらの医療機関はわが国に多いがん（胃、

大腸、肝、肺、乳がん）の診療実績等を考慮して指定されており、AYA世代に多い悪性リンパ腫や白血病は考慮されていない。AYA世代におけるがん医療の均てん化は遅れていると推測されるため、本研究では、大阪府におけるAYA世代のがんの現状と受療動態を明らかにする。

2．方法

対象は、1996年～2005年にがんと診断された15歳～29歳の大阪府在住の患者である。大阪府がん登録資料に基づき、罹患数及び年齢調整罹患率（標準人口は1985年日本人モデル人口）、罹患割合、5年相対生存率を算出した。5年相対生存率[2)]は、Kaplan-Meier法で算出した5年累積実測生存率を、日本人のコホート生命表に基づき算出した期待生存率で除して得た。受療動態については、厚生労働省指定がん診療連携拠点病院（都道府県がん診療連携拠点病院及び地域がん診療連携拠点病院。以下、「国指定がん拠点病院」とする）及び大阪府指定がん診療拠点病院（以下、「府指定がん拠点病院」とする）における、初回治療の治療件数及びカバー率を算出した。2010年7月現在、大阪府における国指定がん拠点病院は計14施設、大阪府指定がん拠点病院は計36施設である。カバー率は、「当該医療機関における主治療件数」を「大阪府全体の罹患数」で除して得た。治療について複数の医療機関から届出のあった場合は、主治療を担当した医療機関で集計し、主治療は、手術＞放射線治療＞TAE＞エタノール注入＞レーザー治療＞化学療法＞ホルモン療法＞免疫療法、の順番で判定した。

3．結果

1）15歳～29歳におけるがんの現状

図1に年齢階級別罹患数及び罹患率の推移を示した。罹患数は減少傾向であるが、15歳～19歳および20歳～29歳の罹患率は横ばいで、20歳～29歳の罹患率は15歳～19歳の約2倍であった。

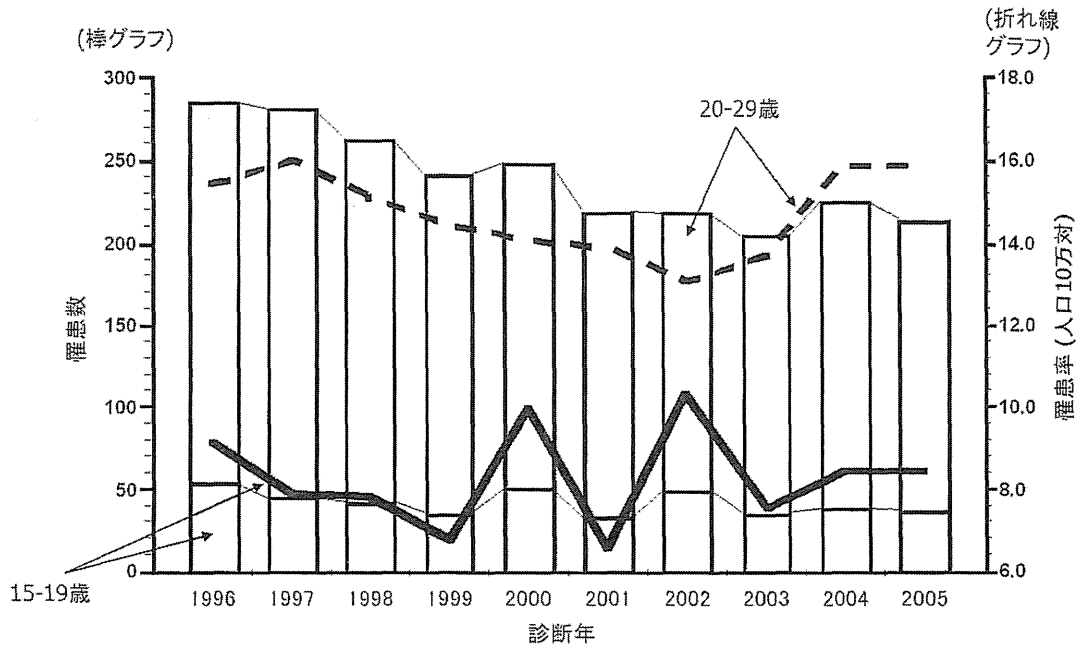

図1　年齢階級別罹患数と罹患率の推移

表 1 に部位別罹患数及び罹患割合を示した。罹患割合は、15 歳～19 歳では白血病、骨及び関節軟骨、悪性リンパ腫の順に、20 歳～29 歳では白血病、悪性リンパ腫、乳房の順に多く、悪性リンパ腫と白血病の占める割合は前者で 36.1%、後者で 20.6%であった。15 歳～19 歳から 20 歳～29 歳に年齢が上がるに伴い、全がんに占める固形腫瘍の割合は増加し、悪性リンパ腫及び白血病の割合は減少した。