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Obesity and liver cancer mortality in Asia: the Asia Pacific Cohort Study Collaboration

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Abstract

While obesity is associated with liver cancer in studies from western societies, the paucity of data from Asia limits insights into its aetiological role in this population. We examined the relationship

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between body mass index (BMI) and liver cancer using data from the Asia Pacific Cohort Studies Collaboration. In 309,203 Asian study members, four years of follow-up gave rise to 11,135 deaths from all causes, 420 of which were ascribed to liver cancer. BMI, whether categorised according to current guidelines for Asian groups or World Health Organisation recommendations, was not associated with liver cancer in any of our analyses.

Introduction

Although liver cancer is a relatively uncommon malignancy, owing to a very high case-fatality, it is the third most lethal malignancy worldwide [1]. With treatments being largely ineffective, identification of environmental risk factors is key for successful primary prevention. A recent, comprehensive systematic review of prospective cohort studies reported an almost doubling of liver cancer risk in obese relative to normal weight persons [2]. This observation is biologically plausible: in obese individuals, non-alcoholic fatty liver disease is common and the spectrum of pathological alterations occurring within the liver as a consequence range from fat accumulation, to non-alcoholic steatohepatitis, and cirrhosis which may in turn give rise to carcinoma [2]. However, in this review [2], only two [3;4] of the eleven studies were drawn from Asian populations where there are strong *prima facie* reasons to anticipate that weight may have a different influence on liver malignancy to that apparent in western populations. Thus, Asian societies are characterised by different body composition, environmental exposures, genetic background, and socio-economic circumstances. Indeed, in the two Asian studies [5;6] featured in the afore-described review [2] the evidence of an effect of overweight and obesity on liver cancer was less unconvincing than in western populations.

Given the clear paucity of extant studies on obesity and liver cancer in Asian populations, and the plausible suggestions for a differential obesity-liver cancer effect in this group, we examined this association using data from the Asia Pacific Cohort Study Collaboration which has pooled individual participant data from over forty studies so resulting in unusually high statistical power.

Methods

The Asia Pacific Cohort Study Collaboration is a pooling project of individual participant data from 44 existing cohort studies in the region. Methods of study identification and their characteristics have been reported in detail elsewhere [7]. Cohorts were classified as Asian if the participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan or Thailand; and as Australasian if the participants were drawn from Australia or New Zealand. This classification largely represented a dichotomy by ethnicity into Asians and non-Asians. Height and weight were measured directly and body mass index (BMI) was calculated using the usual formulae (weight, kg, divided by squared height, m^2). Standard protocols were used to determine blood pressure and blood cholesterol [7]. The presence of diabetes in individual participants was determined from either reported history of diabetes or measured blood glucose levels. Study members also responded to enquiries about cigarette smoking habits and alcohol intake. Liver disease deaths occurring over median of four years of follow-up were ascertained from death certificates. These were coded as either liver cancer (155 [ICD 9]) or 'other' liver disease (70, 570-573, [ICD 9]; K70-K77 [ICD10].

Statistical analyses

Analyses were restricted to individuals aged 20 years or over at study entry with information on height and weight. Participants at extreme ends of the BMI spectrum (i.e., <15 or >50 kg/m^2) were assumed to have incorrectly entered data and were therefore excluded from the analysis (N=409). Studies that did not record any liver death were also dropped. This resulted in an analytical sample of 405,799 men and women (96,596 participants from Australasia, 309,203 from Asia) with complete data on age, sex, study, BMI and mortality experience. With only 25 cancer deaths occurring in the Australian population, it was not possible to compute robust survival models in this group; these study members were therefore excluded from analyses.

Having first ascertained that the proportional hazards assumption had not been violated, Cox proportional hazards regression models[8] were used to regress time until death due to liver disease in relation to baseline BMI. All the Cox models included age and stratification variables for study and sex (there was no evidence of sex interaction). For hazards ratios in each BMI category, 95% confidence intervals were estimated by the 'floating absolute risk' method [9]. In these analyses, BMI was categorised according to recommendations for Asian populations (underweight: 15-18.4; normal weight (referent): 18.5-22.9; overweight: 23-24.9; and obese: 25-50 kg/m^2) [10], and, for the purposes of comparison, also using existing World Health Organization (WHO) guidelines (underweight: 15-18.4; normal weight (referent): 18.5-24.9; overweight: 25-29.9; and obese: 30+ kg/m^2) [11].

Results

In table 1 we provide an overview of the principal data from each of the studies contributing to the present analyses. A median of four years of follow-up (1,637,082 person-years) gave rise to 11,135 deaths from all causes, 420 of which were ascribed to liver cancer. In table 2 we present the relation of categories of BMI, based on guidelines for Asian populations, with death from liver cancer and 'other' liver disease. In analyses adjusted for age, sex and study, while there was a suggestion of an upturn in risk in the lowest BMI group, overall there was little evidence of an association between body mass index and later risk of liver cancer. Statistical adjustment for a range of confounding factors, which included smoking and alcohol intake, essentially flattened this relationship. When we re-categorised the BMI data according to existing WHO guidelines and repeated these analyses, our conclusions about this association were unchanged (results not shown but available upon request). When other causes of liver disease (principally comprising hepatitis and cirrhosis) was the outcome of interest, a suggestion of a protective effect in the higher weight groups was lost after control for a series of covariates. Reanalyses following left censoring, whereby deaths due to liver cancer occurring in the first three years of follow-up were excluded in order to explore reverse causality, did not materially change these results.

Finally, we explored the country-specific association between BMI and liver cancer. There were sufficient liver cancer deaths in China (N=155), Japan (N=54), and Korea (N=199) to facilitate analyses. While there was no evidence of a BMI-liver cancer association in Korea (HR per one SD increase in BMI; 95% CI: 0.98; 0.80, 1.20) in age-, sex-, and study-adjusted analyses, in China, increased BMI was associated with reduced risk (0.75; 0.60, 0.95) and in Japan a positive gradient was apparent (1.58; 1.15, 2.17).

Discussion

In the present study, there was essentially no evidence that obesity or overweight were associated with liver cancer mortality. Findings from the two Asian studies [12;13] featured in an existing systematic review [2] accord with our own, whereas in large study of Korean men and women appearing subsequently [14] a dose-response effect was seen across five weight groups. Taking these results together, in contrast to data from Western populations,[2;15] the balance of evidence in studies from Asia points towards a null obesity-liver cancer association. This is consistent with the observation in Asian groups that the relationship between obesity and risk factors for liver cancer, such as smoking [16] and alcohol intake, are null [17]. Our data are not without there limitations. We did not, for instance, have information on hepatitis virus infection, although it is unlikely that control for this potential confounding factor would have substantially altered an already null BMI-liver cancer relation.

In conclusion, given the modestly-sized and apparently conflicting literature, the association between BMI and liver cancer warrants further investigation in prospective cohort studies.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer. 2007; 97:1005–1008. [PubMed: 17700568]
3. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol. 2005; 23:4742–4754. [PubMed: 16034050]
4. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer. 2005; 113:148–157. [PubMed: 15386435]
5. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol. 2005; 23:4742–4754. [PubMed: 16034050]
6. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer. 2005; 113:148–157. [PubMed: 15386435]

7. Woodward M, Barzi F, Martiniuk A, Fang X, Gu DF, Imai Y, Lam TH, Pan WH, Rodgers A, Suh I, Jee SH, Ueshima H, Huxley R. Cohort profile: the Asia Pacific Cohort Studies Collaboration. Int J Epidemiol. 2006; 35:1412–1416. [PubMed: 17060333]
8. Cox DR. Regression models and life-tables. J R Stat Soc [Ser B]. 1972; 34:187–220.
9. Woodward, M. Epidemiology: study design and data analysis. Chapman and Hall/CRC; Boca Raton, Florida: 2004.
10. World Health Organization IAftSoOIOT. The Asia-Pacific Perspective: Redefining Obesity and its Treatment. Health Communications; Sydney: 2000.
11. World Health Organisation. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. WHO; Geneva: 1995. Who Tech. Rep. Ser.
12. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol. 2005; 23:4742–4754. [PubMed: 16034050]
13. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer. 2005; 113:148–157. [PubMed: 15386435]
14. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, Ohrr H, Samet JM. Body mass index and cancer risk in Korean men and women. Int J Cancer. 2008; 123:1892–1896. [PubMed: 18651571]
15. Batty GD, Shipley MJ, Kivimaki M, Barzi F, Smith GD, Mitchell R, Marmot MG, Huxley R. Obesity and overweight in relation to liver disease mortality in men: 38 year follow-up of the original Whitehall study. Int J Obes (Lond). 2008; 32:1741–1744. [PubMed: 18794897]
16. Batty GD, Kivimaki M, Gray L, Smith GD, Marmot MG, Shipley MJ. Cigarette smoking and site-specific cancer mortality: testing uncertain associations using extended follow-up of the original Whitehall study. Ann Oncol. 2008; 19:1002.
17. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer. 2005; 113:148–157. [PubMed: 15386435]

Table 1

Baseline summary statistics and details of studies included in the analyses of body mass index and site-specific cancer mortality in the Asia-Pacific Cohort Studies Collaboration (APCSC)

Study name	Sample size	Years of baseline survey	Age at baseline (yr)		% female	BMI (kg/m^2)		Median follow-up	Liver cancer deaths	All liver disease deaths
			Mean	SD		Mean	SD			
Akabane	1833	85-86	54	8	55.7	22.5	3.0	11	2	2
Anzhen	8344	91	54	13	55.1	23.9	3.7	4	6	6
CISCH	2164	92-93	44	7	50.8	24.7	3.4	3	2	2
Civil Serivce Workers	9312	90-92	47	5	33.1	22.5	2.7	7	7	8
CVDFACTS	5704	88-96	47	15	55.3	23.5	3.4	6	0	5
Fangshan	2606	91-92	47	10	66.6	24.4	3.6	4	0	2
Guangzhou Occupational	20524	85-97	42	6	31.7	22.5	2.9	8	0	5
Hisayama	1516	61	56	11	56.1	21.6	2.6	25	14	25
Hong Kong	2767	85-91	78	7	56.8	22.1	3.7	3	10	11
Huashan	1852	90-92	53	12	52.0	23.4	3.4	3	0	2
Kinmen	1266	93-96	63	9	46.9	23.4	3.4	3	0	2
KMIC	183368	92	44	7	37.0	23.0	2.5	4	199	379
Konan	1192	87-95	52	16	55.3	21.9	3.0	6	3	5
Miyama	1031	88-90	60	9	55.3	22.1	2.9	7	0	4
Saitama	3599	86-90	54	12	62.1	22.4	2.9	11	11	12
Seven Cities Cohorts	10705	87	54	12	54.4	22.7	3.6	3	6	11
Shibata	2328	77	57	11	57.7	22.4	3.0	20	10	20
Shigaraki Town	3731	91-97	57	14	59.4	22.5	3.1	4	0	1
Shirakawa	4636	74-79	48	12	54.3	21.5	2.7	18	7	17
Singapore Heart	2304	82-97	41	13	49.0	23.6	4.3	15	1	5
Singapore NHS92	3293	92	39	12	51.7	23.3	4.1	6	1	1
Six Cohorts	19329	82-86	45	7	46.7	21.2	2.6	9	111	146
Tianjin	9228	84	54	12	51.1	23.6	3.9	6	17	38
Yunnan	6571	92	56	9	3.1	21.6	2.9	4	13	25
Total Asia	**309203**	**61-97**	**53**	**14**	**40.5**	**22.7**	**2.9**	**4**	**420**	**734**

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Study name	Sample size	Years of baseline survey	Age at baseline (yr)		% female	BMI (kg/m^2)		Median follow-up	Liver cancer deaths	All liver disease deaths
			Mean	SD		Mean	SD			
Melbourne	41240	90-94	55	9	58.9	26.9	4.4	8	11	18
Busselton	7439	66-81	45	17	52.0	24.6	3.8	27	5	18
Fletcher Challenge	10329	92-94	44	15	28.0	26.4	4.1	6	2	3
Perth	10222	78-94	45	13	48.2	25.2	3.9	14	3	8
ANHF	9256	89-90	43	13	50.9	25.4	4.2	8	0	2
Newcastle	5920	83-94	52	10	50.2	26.7	4.5	9	1	1
Western AAAA Screenees	12190	96-99	72	4	0.0	26.9	3.7	3	3	8
Total ANZ	**96596**	**66-99**	**53**	**14**	**45.2**	**25.9**	**4.3**	**8.3**	**25**	**58**
Overall total	**405799**	**61-99**	**48**	**11**	**41.6**	**23.7**	**3.6**	**4**	**445**	**792**

Abbreviations: ANZ, Australia and New Zealand; SD, standard deviation. Study abbreviations: WA AAA Screenees, Western Australian Abdominal Aortic Aneurysm Screening Program; CISCH, Capital Iron and Steel Company Hospital Cohort; CVDFACTS, Cardiovascular Disease Risk Factors Two-Township Study; KMIC, Korean Medical Insurance Company; Singapore NHS92, Singapore National Health Survey 1992; EGAT, Electricity Generating Authority of Thailand

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Table 2

Hazard ratios (95% confidence intervals) for body mass index in relation to liver disease mortality in Asian study members in the Asia Pacific Cohort Study Collaboration (N=309,203)

	Body Mass Index[a]				P-value for linear trend
	Underweight (15-18.4 kg/m^2)	**Normal weight[e] (18.5-22.9)**	**Overweight 23-24.9**	**Obese 25+**	
Number of subjects	14483	152817	75694	66209	
Liver cancer					
Number of deaths	42	204	96	78	
Age-, sex- & study-adjusted	1.49 (1.07-2.07)	1.00 (0.87-1.14)	1.09 (0.88-1.33)	1.07 (0.85-1.34)	0.64
Age-, sex-, study- & alcohol-adjusted[b]	1.50 (1.06-2.10)	1.00 (0.86-1.16)	1.08 (0.85-1.36)	1.14 (0.89-1.48)	0.86
Fully Adjusted[c,d]	0.95 (0.41-2.20)	1.00 (0.81-1.24)	1.21 (0.91-1.59)	1.27 (0.93-1.74)	0.19
'Other' liver disease					
Number of deaths	20	164	71	59	
Age-, sex- & study-adjusted	1.12 (0.71-1.77)	1.00 (0.86-1.16)	0.82 (0.65-1.05)	0.78 (0.60-1.01)	0.057
Age-, sex-, study- & alcohol-adjusted	1.09 (0.66-1.80)	1.00 (0.84-1.19)	1.00 (0.63-1.11)	0.89 (0.66-1.20)	0.33
Fully Adjusted	1.03 (0.41-2.59)	1.00 (0.79-1.26)	0.95 (0.69-1.32)	0.75 (0.51-1.11)	0.24

[a]Categorisation is based on existing guidelines for Asia [10].

[b]Analyses based on a subgroup (N=286,470) with age, sex, study and alcohol intake data (584 deaths due to all liver disease - 233 due to non-cancer liver disease, 351 due to cancer liver disease);

[c]Analyses based on a subgroup (N=201,061) with all covariate data (312 deaths due to all liver disease - 136 due to non-cancer liver disease, 176 due to cancer liver disease);

[d]Fully-adjusted models are adjusted for: age, sex, study, alcohol, blood pressure, smoking, serum cholesterol & diabetes;

[e]Referent group.