Research Article

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Alcohol drinking pattern and risk of alcoholic liver cirrhosis: A prospective cohort study

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Background & Aims: Alcohol is the main contributing factor of alcoholic cirrhosis, but less is known about the significance of drinking pattern.

Methods: We investigated the risk of alcoholic cirrhosis among 55,917 participants (aged 50–64 years) in the Danish Cancer, Diet, and Health study (1993–2011). Baseline information on alcohol intake, drinking pattern, and confounders was obtained from a questionnaire. Follow-up information came from national registers. We calculated hazard ratios (HRs) for alcoholic cirrhosis in relation to drinking frequency, lifetime alcohol amount, and beverage type.

Results: We observed 257 and 85 incident cases of alcoholic cirrhosis among men and women, respectively, none among lifetime abstainers. In men, HR for alcoholic cirrhosis among daily drinkers was 3.65 (95% CI: 2.39; 5.55) compared to drinking 2–4 days/week. Alcohol amount in recent age periods (40–49 and 50–59 years) was associated with an increased risk, whereas the amount in 20–29 and 30–39 years was not. In men drinking 14–28 drinks/week, HR was 7.47 (95% CI: 1.68; 33.12), 3.12 (95% CI: 1.53; 6.39), and 1.69 (95% CI: 0.79; 3.65) in drinkers of little (<1% of weekly amount), some (1–15%), and mostly wine (50–100%), compared to drinking <14 drinks/week. In general, results were similar for women.

Conclusions: In men, daily drinking was associated with an increased risk of alcoholic cirrhosis. Recent alcohol consumption rather than earlier in life was associated with risk of alcoholic cirrhosis. Compared to beer and liquor, wine might be associated with a lower risk of alcoholic cirrhosis.

Keywords: Alcohol; Alcoholic beverages; Liver cirrhosis; Drinking pattern; Cohort study; Epidemiological methods.

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Abbreviation: HR, hazard ratio.

Introduction

Alcohol is the main risk factor of cirrhosis in Europe, where 1.8% of all deaths are attributable to liver disease [1]. Although alcohol *per se* is the most important risk factor for alcoholic cirrhosis, only about 35% of heavy drinkers develop the disease [2]. Moreover, even light drinkers, who consume one to two drinks a day, are at increased risk of alcoholic cirrhosis compared to abstainers [3]. Therefore, other risk factors besides the amount of alcohol must be important for alcoholic cirrhosis. For example, smoking, obesity, and chronic viral hepatitis C have been found to be associated with an increased risk [4–6]. Women have a higher risk of alcoholic cirrhosis compared to men for a given level of alcohol intake [3,7].

Few studies have investigated the influence of alcohol drinking patterns such as drinking frequency, binge drinking (drinking at least four or five drinks per occasion) [8,9], lifetime alcohol consumption, and beverage type, on the risk of alcoholic cirrhosis in the general population. Most studies on drinking frequency and risk of alcoholic cirrhosis have found that daily drinking compared to episodic or binge drinking is associated with an increased risk [7,12–14]. Moreover, death from cirrhosis might have explained the increased risk of overall mortality found in frequent drinkers (5–7 days per week) compared to infrequent drinkers (1–4 days per week) in a Japanese study, although a Danish study reached the opposite conclusion [10,11]. To our knowledge, no studies have evaluated in detail how drinking frequency is related to alcoholic cirrhosis, – for example, whether there is a difference between daily drinking compared to drinking four, five, or six days a week.

Earlier studies regarding lifetime alcohol consumption and risk of alcoholic cirrhosis reached opposite conclusions, for instance, whether a previous high level of alcohol amount predicted future risk, even after cut down [7,14–16]. From a clinical point of view, this is relevant to execute evidence-based counselling, and from a public health perspective, it may guide health interventions for the general population.

Lastly, due to the lower incidence of alcoholic liver disease *per capita* alcohol amount in Southern European compared to Northern European countries [2,17], it has been hypothesized that there is a lower risk of cirrhosis in wine drinkers compared to drinkers of other alcoholic beverages, but the evidence is inconsistent [7,18,19].

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In the present prospective study, we will test the three following hypotheses regarding alcohol drinking pattern and risk of alcoholic cirrhosis: (1) daily drinking is associated with an increased risk compared to drinking less frequently, (2) current, compared to lifetime alcohol consumption, is more strongly associated with the risk of alcoholic cirrhosis, and (3) drinking wine is associated with a decreased risk compared to drinking beer and liquor. With regard to binge drinking and risk of alcoholic cirrhosis, we had information only on the average number of drinks and drinking frequency, and were not able to explore this specific issue.

Materials and methods

Study population

We used data from a Danish prospective cohort study originally designed to investigate associations between diet and other lifestyle exposures and cancer in middle-aged individuals. From December 1993 to May 1997, 160,725 Danish men and women aged 50 to 64 years were invited to participate in the Diet, Cancer, and Health study, described in detail elsewhere [20]. Eligible cohort members were born in Denmark and not previously diagnosed with cancer. In all, 27,178 men and 29,875 women participated in the study (response rate 35%). At baseline, all participants completed a detailed food-frequency questionnaire along with a questionnaire regarding lifestyle and background factors (alcohol, smoking, physical activity, and years of education) as well as a brief physical examination, including measurement of waist circumference. For the present study of drinking pattern and risk of alcoholic cirrhosis, we excluded those subjects diagnosed with alcoholic cirrhosis before baseline (n = 86). We also excluded participants with missing information on alcohol amount (n = 105), smoking (n = 27), education (n = 27), and waist circumference (n = 50), and participants who reported conflicting answers on alcohol amount and frequency (n = 236) or smoking status and tobacco use (n = 7).

Information on alcohol consumption

The amount of alcohol intake was reported as the average amount per week of specific types of alcohol: beer (separately for light, regular, and strong beer, in bottles of 330 ml), wine (in glasses of 125 ml), and liquor (in drinks of 30 ml). The total amount was calculated and converted into number of standard drinks (containing 12 g of ethanol) [11]. Participants were furthermore asked to report their average amount of alcohol intake when they were 20–29, 30–39, 40–49, and 50–59 years old (referred to as age periods). This information was summed to give the total number of lifetime drinks until baseline, and the lifetime average amount of alcohol intake per week since age 20 years was also calculated. Information on frequency of alcohol consumption was obtained in the following response categories: never, less than one day a month, one to three days monthly, once a week, two to four days weekly, five to six days weekly, and daily.

Follow-up

We observed participants from baseline until diagnosis of alcoholic cirrhosis (n = 342), migration (n = 337), loss to follow-up (n = 2), death from other causes (n = 8132), or 31 December 2011 (end of follow-up), whichever came first. The total observation time was 831,285 person-years. Information on liver cirrhosis was obtained from the National Patient Register and the Danish Register of Causes of Death. The National Patient Register was established in 1977 and contains data on all somatic hospital admissions and, since 1995, data on outpatient contacts as well. The Danish Register of Causes of Death contains information on all causes of death in Denmark. In both registries, diagnoses are recorded according to the 8th and 10th international classification of diseases (codes for alcoholic cirrhosis, ICD-8: 571.0 and ICD-10: K70.3, and codes for unspecified cirrhosis, ICD-8: 571.9, 456.0, 785.3 and ICD-10: I85.0, I85.9, K74.6, R18.9), and the validity is considered to be high [21,22]. Data on vital status and migration was obtained from the Danish Civil Registration System. The registries were linked by a unique personal identifier assigned to all Danish residents [23].

Statistical analysis

We calculated hazard ratios (HRs) using a Cox proportional hazard regression model with age as the underlying time axis. The risk estimates were adjusted for known risk factors for alcoholic cirrhosis: smoking (never, former, <10 g tobacco/day, >10 g tobacco/day) [4], education ($\leqslant$7 years, 8–10 years, $\geqslant$11 years) [24], and obesity [5] measured as waist circumference according to WHO's guideline (men: <94 cm, 94–102 cm, >102 cm, women: <80 cm, 80–88 cm, >88 cm) [25,26]. The proportional hazard assumptions of the proportional hazard model were tested for each covariate, by evaluating the parallelism of the stratified survival curves. No violations were detected.

When alcohol amount or drinking frequency at baseline was assessed, lifetime abstainers (no alcohol consumption over lifetime or at baseline) and current abstainers (having drunk alcohol during life but no longer at baseline) were treated separately due to the potential heterogeneity in risk in these two categories [27].

We calculated Spearman's correlation coefficient to look for the magnitude of rank correlation between alcohol amount and drinking frequency at baseline.

Three approaches were carried out to study the first hypothesis that daily drinking is associated with an increased risk of alcoholic cirrhosis compared to less frequent drinking. First, we modelled a risk function for alcoholic cirrhosis according to drinking frequency, where alcohol amount was modelled continuously, and we performed a trend test among those who reported any alcohol consumption. Second, alcohol amount was modelled linearly within categories of drinking frequency, and we looked for interaction by testing whether the slopes could be considered equal. Third, alcohol amount was categorized, and we used nested log likelihood tests to test for interaction between alcohol amount and drinking frequency. To test the second hypothesis that current, compared to lifetime alcohol consumption, is more strongly associated with risk of alcoholic cirrhosis, we first calculated HRs for lifetime alcohol amount and risk of liver cirrhosis, with alcohol amount modelled as the average number of drinks per week over lifetime and by age period (20–29, 30–39, 40–49, and 50–59 years). Next, to explore the association between the level of alcohol amount at baseline (current alcohol consumption) and lifetime alcohol amount, HRs for lifetime alcohol amount were adjusted for current consumption.

To test the hypothesis that drinking wine is associated with a decreased risk compared to drinking beer and liquor (third hypothesis), we calculated HR in relation to the percentage of wine of weekly alcohol amount. We used a nested log likelihood test to test for interaction between alcohol amount and percentage of wine in the weekly alcohol amount. Furthermore, to evaluate the risk of alcoholic cirrhosis associated with wine, beer, and liquor, we calculated risk estimates for predefined categories of specific beverage types and controlled for consumption of other beverages [28].

All analyses were stratified by gender [3,7].

Finally, as a supplementary analysis, we ran analyses considering both unspecified cirrhosis and alcoholic cirrhosis as a combined outcome (n = 622). This was done to study alcohol drinking pattern and risk of a broader category of cirrhosis. We will refer to this as "risk of cirrhosis", and results can be found in the Supplementary material.

Results

Among the 55,917 participants, 257 men and 85 women developed alcoholic cirrhosis, corresponding to an incidence rate of alcoholic cirrhosis of 66 in men and 19 in women per 100,000 person-years. The median follow-up time was 14.9 years (14.6 years for men and 15.1 years for women). Drinking frequency was highly correlated with alcohol amount at baseline in men (r = 0.77) and women (r = 0.85). In men, the median alcohol amount was 8.9 (5th–95th percentiles: 3.6–13) drinks per week, in those drinking two to four days a week, and 26 (9.4–60) in daily drinkers (Table 1). In women, the median alcohol amount was 6.6 (3.0–19) drinks per week in those drinking two to four days a week and 19 (7.3–40) in daily drinkers. In both men and women, we found a large variation in the average lifetime alcohol amount in current abstainers, ranging from 0.20 to 71 (5th and 95th percentiles) drinks per week in men and 0.30 to 36 in women.

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Table 1. Baseline characteristics according to drinking frequency. Baseline characteristics of 26,696 men and 29,221 women participating in the Danish Diet, Cancer, and Health study according to alcohol frequency. Values are medians (5th–95th percentiles).

Characteristic	Not drinking alcohol at baseline		Drinking alcohol at baseline (drinking days/week)				
	Lifetime abstainers	Current abstainers	<1	1	2-4	5-6	7
Men							
Cohort	63	350	2946	2401	9165	4495	7276
Age, years	60 (51-65)	56 (51-64)	56 (51-64)	56 (51-64)	55 (51-4)	55 (51-64)	56 (51-64)
Alcohol amount at baseline, drinks/week	0	0	1.7 (0.3-13)	4.5 (1.3-13)	8.9 (3.6-13)	19 (7.0-42)	26 (9.4-60)
Average alcohol amount from twenties → baseline, drinks/week	0	18 (0.2-71)	3.8 (0.02-26)	4.8 (1.2-19)	7.6 (2.6-23)	11 (4.4-29)	15 (2.2-39)
No. of smokers	15 (24%)	191 (55%)	1319 (45%)	854 (36%)	3128 (34%)	1589 (35%)	3429 (47%)
Waist circumference, cm	98 (78-113)	94 (77-114)	96 (81-117)	95 (81-116)	95 (81-148)	95 (81-112)	95 (82-114)
No. education at school ≤7 years	26 (41%)	139 (40%)	1420 (48%)	961 (40%)	3040 (33%)	1281 (28%)	2401 (33%)
Women							
Cohort	265	370	7682	4345	9481	3147	3931
Age, years	58 (51-65)	56 (51-64)	57 (51-65)	56 (51-64)	55 (51-64)	56 (51-64)	57 (51-64)
Alcohol amount at baseline, drinks/week	0	0	1.0 (0.2-5.2)	3.5 (1.1-8.5)	6.6 (3.0-19)	13 (5.9-27)	19 (7.3-40)
Average alcohol amount from twenties → baseline, drinks/week	0	1.9 (0.3-36)	1.07 (0.01-26)	2.4 (0.6-7.5)	4.2 (1.4-11)	6.3 (2.4-15)	7.9 (2.4-20)
No. of smokers	75 (28%)	183 (49%)	2772 (36%)	1275 (29%)	2572 (27%)	977 (31%)	1688 (43%)
Waist circumference, cm	84 (66-112)	81 (67-109)	82 (67-107)	81 (68-102)	80 (67-101)	79 (67-99)	79 (67-100)
No. education at school ≤7 years	143 (54%)	144 (39%)	3338 (43%)	1490 (34%)	2487 (26%)	603 (19%)	910 (23%)

Alcohol amount

We observed no cases of alcoholic cirrhosis among lifetime abstainers. In current abstainers, the HR was 7.58 (95% CI: 3.39; 16.9) in men and 3.21 (95% CI: 0.77; 13.4) in women compared to those subjects drinking fewer than 14 drinks per week (Fig. 1). Overall, there was a clear dose-dependent association between level of alcohol amount and risk of alcoholic cirrhosis among both men and women. When compared to drinking fewer than 14 drinks per week, the HR for drinking 14–28 drinks per week was 2.33 (95% CI: 1.52; 3.58) for men and 3.49 (95% CI: 2.00; 6.12) for women; for 28–42 drinks per week, the HR was 6.98 (95% CI: 4.65; 10.5) in men and 16.2 (95% CI: 9.16; 28.7) in women. Since the number of women drinking more than 42 drinks per week was small, we grouped them in one category. By contrast, it was possible to estimate HR in men drinking 42–56, 56–70, and more than 70 drinks per week.

Alcohol drinking frequency

Table 2 lists HR for alcoholic cirrhosis according to drinking frequency with the following adjustments: (1) age, (2) age and alcohol amount, (3) age, alcohol amount, and potential confounders (smoking, education, and waist circumference). The highest number of cases was found among daily drinkers (171 in men and 30 in women). Among both men and women, the largest change in HR was seen when the age-adjusted estimates were further adjusted for alcohol amount, while adjusting for other potential confounders altered the estimates only a little.

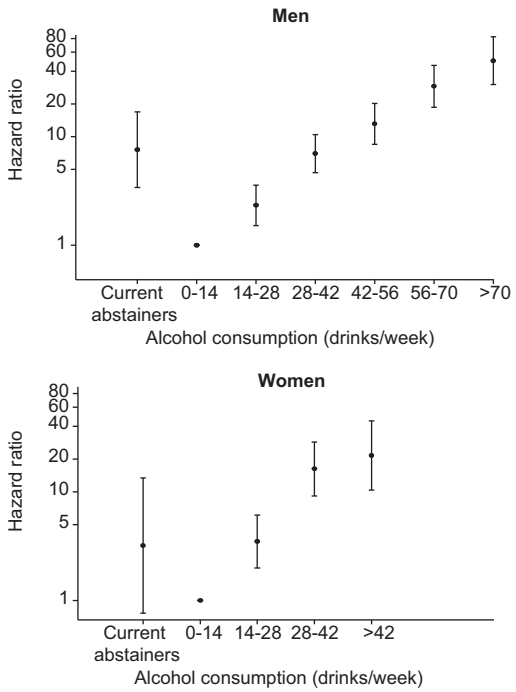

Fig. 1. Risk of alcoholic cirrhosis according to weekly alcohol amount. Hazard ratios (95% confidence intervals) of alcoholic cirrhosis in men and women according to weekly alcohol amount (in drinks) at baseline. Adjusted for confounders (smoking, education, and waist circumference).

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Table 2. Risk of alcoholic cirrhosis according to alcohol drinking frequency at baseline. Hazard ratios (95% confidence intervals) of alcoholic cirrhosis for men and women, according to alcohol drinking frequency at baseline.

	Not drinking alcohol at baseline		Drinking alcohol at baseline (drinking days/week)					
	Lifetime abstainers	Current abstainers	<1	1	2-4	5-6	7	*p* value**
Men								
No. of cases	0	7	14	8	27	30	171	
Person-years	926	4556	42,269	35,456	135,573	66,512	103,820	
Adjusted for age	n.a.	7.70 (3.35; 17.7)	1.67 (0.88; 3.19)	1.13 (0.52; 2.50)	1.00	2.26 (1.35; 3.81)	8.29 (5.52; 12.4)	<0.001
Adjusted for age and alcohol amount	n.a.	10.4 (4.50; 24.8)	0.89 (0.40; 1.98)	1.32 (0.60; 2.90)	1.00	1.69 (1.00; 2.85)	4.83 (3.20; 7.29)	<0.001
Adjusted for age, alcohol amount, and confounders*	n.a.	10.0 (4.32; 23.0)	1.34 (0.67; 2.67)	1.30 (0.59; 2.87)	1.00	1.43 (0.84; 2.43)	3.65 (2.39; 5.55)	<0.001
Women								
No. of cases	0	2	16	5	15	17	30	
Person-years	3920	5325	115,979	66,157	144,603	47,775	58,414	
Adjusted for age	n.a.	3.64 (0.83; 15.9)	1.34 (0.66; 2.72)	0.73 (0.27; 2.01)	1.00	3.44 (1.72; 6.88)	5.01 (2.69; 9.31)	<0.001
Adjusted for age and alcohol amount	n.a.	6.14 (1.40; 26.9)	1.99 (0.98; 4.05)	0.95 (0.35; 2.62)	1.00	2.07 (1.02; 4.18)	1.6 (0.81; 3.30)	0.57
Adjusted for age, alcohol amount, and confounders*	n.a.	4.03 (0.91; 17.8)	1.45 (0.71; 2.96)	0.81 (0.29; 2.24)	1.00	2.30 (1.14; 4.67)	1.73 (0.85; 3.52)	0.14

*Smoking, length of education, and waist circumference.
**Lifetime abstainers and current abstainers were not included in analyses for trend.

Table 3. Risk of alcoholic cirrhosis per additional drink, according to drinking frequency. Hazard ratios (95% confidence intervals) of alcoholic cirrhosis per additional drink of average weekly alcohol amount, according to drinking frequency at baseline in men and women. Adjusted for confounders.*

Drinking frequency (days/week)	<1	1-4	5-6	7
Men				
No. of cases	14	35	30	171
Person-years	42,269	171,029	66,512	103,820
HR	1.02 (1.01; 1.03)	1.03 (1.02; 1.05)	1.03 (1.02; 1.03)	1.05 (1.04; 1.05)
Women				
No. of cases	16	20	17	30
Person-years	115,979	210,760	47,775	58,414
HR	1.09 (1.05; 1.13)	1.06 (1.03; 1.10)	1.08 (1.06; 1.09)	1.05 (1.04; 1.06)

* Smoking, education, and waist circumference.

In men, compared to those drinking two to four days a week, the HR among current abstainers was 10.0 (95% CI: 4.32; 23.0), and among those who reported any alcohol consumption at baseline, 1.34 (95% CI: 0.67; 2.67), 1.30 (95% CI: 0.59; 2.87), 1.43 (95% CI: 0.84; 2.43), and 3.65 (95% CI: 2.39; 5.55) in those drinking less often than one day per week, one day per week, five to six days per week, and daily, respectively, in the model with adjustment for alcohol amount and confounders. The trend test was statistically significant (p <0.001). In women, when compared to those drinking two to four days a week, the HR was 4.03 (95% CI: 0.91; 17.8) in current abstainers and 1.45 (95% CI: 0.71; 2.96), 0.73 (95% CI: 0.27; 2.01), 2.30 (95% CI: 1.14; 4.67), and 1.73 (95% CI: 0.85; 3.52) in those drinking less often than one day per week, one day per week, five to six days per week, and daily, respectively. The test for trend was statistically insignificant (p = 0.14).

Table 3 presents HR for alcoholic cirrhosis per additional drink of alcohol weekly, at baseline in strata of drinking frequency. The HR of alcoholic cirrhosis per drink in men was lowest among those drinking less often than one day per week (HR 1.02 [95% CI: 1.01; 1.03]), and highest in daily drinkers (HR 1.05 [95% CI: 1.04; 1.05]). In women, HR were 1.09 (95% CI: 1.05; 1.13), 1.06 (95% CI: 1.03; 1.10), 1.08 (95% CI: 1.06; 1.09), and 1.05 (95% CI: 1.04; 1.06) in those drinking less often than one day per week, one day per week, five to six days per week, and daily, respectively. The tests for interaction between alcohol drinking frequency and alcoholic cirrhosis were statistically significant in both men (p <0.0001) and women (p = 0.0007).

Supplementary Table 5 presents HR of alcoholic cirrhosis in relation to alcohol amount (in categories) and alcohol drinking frequency. The mean alcohol amounts for daily drinkers were somewhat higher compared to those drinking less frequently in each category of alcohol amount, making it difficult to detangle the effect of drinking frequency and alcohol amount.

Lifetime alcohol amount

In men, we found a statistically significant increased risk of alcoholic cirrhosis per additional weekly drink in age periods 20–29, 30–39, 40–49, and 50–59 years (Table 4). However, after

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Table 4. Risk of alcoholic cirrhosis per additional drink in different exposure periods during life. Hazard ratios (95% confidence intervals) of alcoholic cirrhosis in men and women per drink of average weekly alcohol amount, according to different exposure periods.

	HR[1,2] (95% CI)	HR[1,3] (95% CI)	HR[1,4] (95% CI)
Men			
257 cases/389,112 person-years Previous consumption (age period)			
20-29	1.02 (1.02; 1.03)	1.00 (0.99; 1.01)	-
30-39	1.03 (1.02; 1.03)	0.99 (0.98; 1.01)	-
40-49	1.03 (1.02; 1.03)	1.01 (1.00; 1.02)	-
50-59	1.04 (1.03; 1.04)	1.03 (1.02; 1.03)	-
20-59	1.04 (1.04; 1.05)	-	1.03 (1.02; 1.03)
Current consumption			
Baseline	1.03 (1.03; 1.04)	1.03 (1.02; 1.03)	1.03 (1.02; 1.03)
Women			
85 cases/442,173 person-years Previous consumption (age period)			
20-29	1.04 (1.02; 1.06)	1.01 (0.98; 1.06)	-
30-39	1.03 (1.02; 1.04)	0.99 (0.95; 1.02)	-
40-49	1.03 (1.02; 1.04)	1.02 (1.00; 1.05)	-
50-59	1.06 (1.04; 1.07)	1.01 (0.98; 1.03)	-
20-59	1.05 (1.04; 1.07)	-	1.03 (1.01; 1.06)
Current consumption			
Baseline	1.05 (1.04; 1.06)	1.05 (1.03; 1.06)	1.05 (1.04; 1.06)

[1]Adjusted for age, smoking, education, and waist circumference; [2]alcohol amount in life periods 20–29, 30–39, 40–49, and 50–59 years was mutually adjusted; [3]mutually adjusted for alcohol amount in age periods 20–29, 30–39, 40–49, and 50–59 years and baseline alcohol amount; [4]mutually adjusted for alcohol amount in age period 20–59 years and baseline alcohol amount.

adjusting for alcohol amount at baseline, only alcohol amounts in age periods 40–49 and 50–59 years were associated with an increased risk. In women, we likewise found an increased risk of alcoholic cirrhosis per additional weekly drink in all age periods, but when adjusting for alcohol amount at baseline, only amount in age period 40–49 years was associated with an increased risk.

The HR for alcoholic cirrhosis per additional drink over lifetime was 1.04 (95% CI: 1.04; 1.05) in men and 1.05 (95% CI: 1.04; 1.07) in women, and adjusted for alcohol amount at baseline, 1.03 (95% CI: 1.02; 1.03) in men and 1.03 (95% CI: 1.01; 1.06) in women. The HR for alcohol amount at baseline was 1.03 (95% CI: 1.03; 1.04) in men and 1.05 (95% CI: 1.04; 1.06) in women, and was unchanged when adjusting for consumption over lifetime (overall and in age periods) in both sexes.

Beverage type

Men whose alcohol consumption consisted mostly of wine had a lower HR than men who drank no or little wine. For example, in men who drank on average 14–28 drinks/week, the HR was 7.47 (95% CI: 1.68; 33.12), 3.12 (95% CI: 1.53; 6.39), and 1.69 (95% CI: 0.79; 3.65) in drinkers of little (<1% of weekly amount as wine), some (1–15%), and mostly wine (50–100%), as compared to drinkers of mostly (50–100%) wine among those who drank fewer than 14 drinks weekly (Fig. 2). A test for interaction between the percentage of wine in weekly alcohol amount and the weekly alcohol amount on the risk of alcoholic cirrhosis was statistically insignificant ($p = 0.63$). Because there were few cases among women, it was not possible to perform similar analyses.

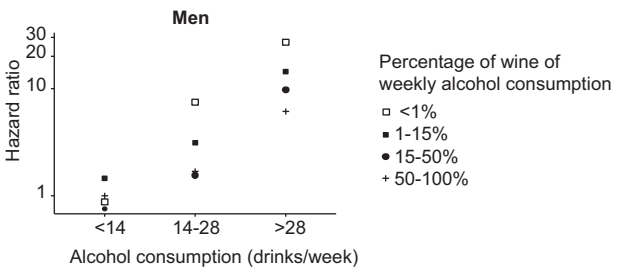

Fig. 2. Risk of alcoholic cirrhosis in relation to percentage of wine of weekly alcohol amount. Hazard ratios of alcoholic cirrhosis in relation to percentage of wine in weekly alcohol amount, stratified by weekly alcohol amount (in drinks) in men. Adjusted for confounders (smoking, education, and waist circumference).

In analyses controlled for consumption of other beverage types, the HR for alcoholic cirrhosis was lower for weekly amount of wine than for other beverage types (Supplementary Table 6), in both men and women drinking more than 14 drinks weekly.

Alcohol drinking pattern and risk of cirrhosis (supplementary analyses)

Among 55,917 participants included in the study, 393 men and 229 women were diagnosed with either alcoholic or unspecified cirrhosis during follow-up. Generally, analyses confirmed trends found for alcohol drinking pattern and alcoholic cirrhosis. Analyses on the risk of cirrhosis according to drinking frequency demonstrated an association between risk of cirrhosis and daily drinking in men, and an unclear pattern among women (Supplementary Table 2A, 3A, and 5A). Risk of cirrhosis associated with

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lifetime alcohol amount again remained stable after adjustment for alcohol amount at baseline (Supplementary Table 4A). The risk of cirrhosis in relation to beverage type was decreased for wine compared to beer and liquor in men whereas in women the trend was less clear (Supplementary Table 6A and Fig. 2A).

Discussion

This study confirmed the dose-response relationship between alcohol amount and alcoholic cirrhosis reported earlier, and we found no risk of alcoholic cirrhosis among lifetime abstainers. Among men, the risk of alcoholic cirrhosis was higher in daily drinkers compared to less frequent drinkers, when alcohol amount was taken into account. Furthermore, our results suggested that recent alcohol consumption, and not lifetime alcohol consumption, is the strongest predictor of alcoholic cirrhosis. Regarding beverage type, wine was associated with a lower risk of alcoholic cirrhosis compared to beer and liquor, for the same level of alcohol amount. Among women, we are unable to draw firm conclusions due to low statistical power, though, in general, we found the same trends.

Strengths and limitations

Strengths of this study are its large size, the prospective design, complete follow-up, and a high validity of the alcoholic cirrhosis diagnosis [21,22]. A possible limitation is that only 35% of the invitees actually participated, and precaution should be taken when generalizing our findings, since participants might practice a healthier lifestyle than non-participants. In women, the incidence of alcoholic cirrhosis in our cohort was somewhat lower compared to what would be expected from nationwide data [29]. Moreover, one could doubt the validity of self-reported alcohol consumption, though evidence supports the opposite [30]. Some studies suggest that women, in particular, might be more reluctant to report alcohol use than men [30,31]. Moreover, the low number of cases among women is a limitation of our study, making conclusions regarding drinking pattern and risk of alcoholic cirrhosis among women difficult.

Rehm *et al.* reported a different risk function between alcohol amount and alcoholic cirrhosis morbidity and mortality [3]. In our cohort, mortality accounted for only 11% of cases, and the lack of statistical power made it impossible to differentiate between the two outcomes. Since alcoholic cirrhosis has such a high mortality in Denmark, we regard this as a minor problem when interpreting the results [29]. Lack of information on hepatitis C status, as a contributing factor to alcoholic cirrhosis, is a minor limitation due to its low prevalence in Denmark [32].

Comparison with other studies

Several studies have reported a risk of alcoholic cirrhosis among abstainers that was higher than among light drinkers [18,21,27]. In this study, we differentiated between lifetime abstainers and current abstainers and found no risk of alcoholic cirrhosis among lifetime abstainers. Current abstainers, on the other hand, had an increased risk, which supports the hypothesis of problem-drinkers in this group [27].

Regarding alcohol drinking frequency, in men, our results confirmed our first hypothesis that daily drinking increases the risk compared to less frequent drinking. For the first time, our study points to a risk difference between daily drinking and drinking five or six days a week in the general male population, since earlier studies were conducted on alcohol misusers and patients referred for liver disease, and compared daily drinking to "binge pattern" or "episodic" drinking [7,12–14]. Since details of alcohol-induced liver injury are unknown, and no animal experiments have assessed the role of frequency of alcohol exposure, we can only speculate that daily alcohol exposure, in particular, might worsen liver damage or inhibit liver regeneration [33].

In women, an increased risk was found among those drinking less often than one day per week, which might also include problem drinkers. We also hypothesize that the observed elevated risk among women drinking five or six days per week compared to those drinking daily could be due to information bias. On the other hand, it might well be possible that women have a different risk profile than men since female hormones increase alcohol-mediated liver injury in an unknown fashion [34].

Regarding an independent influence of lifetime alcohol consumption, the present study supports our second hypothesis that it is the recent, rather than the lifetime alcohol amount, which is the strongest predictor of alcoholic cirrhosis, in line with prospective studies [7,14]. This finding may reflect reversibility in the preceding states of alcoholic cirrhosis, e.g., steatosis, steatohepatitis, and fibrosis [2].

Implications of our study for public health and clinical counselling are that there seems to be some gain when cutting down on alcohol amount, regardless of the high level of lifetime alcohol consumption, and that daily drinkers should be advised to drink less frequently.

Regarding beverage type, our data suggest a lower risk associated with wine compared to beer and liquor, at least in men, which supports our third hypothesis. This is in agreement with another prospective, population-based Danish study [18], but in conflict with studies on alcohol misusers [7,19]. Alcohol misusers might drink a considerably higher level of alcohol amount than the general population who develop alcoholic cirrhosis [12]. Therefore, the lower risk of alcoholic cirrhosis associated with wine most likely applies when the weekly amount does not exceed 28–35 drinks. Bellentani *et al.* reported an increased risk of liver cirrhosis when drinking outside meals [35], and wine is probably more often consumed with a meal than beer and liquor. We do not have information on meal-related drinking in our cohort, but find it unlikely that this could account for the entire observed risk difference between wine and the other beverage types.

Conclusions

In conclusion, there is a dose-response relationship between alcohol amount and alcoholic cirrhosis, with no risk of alcoholic cirrhosis among lifetime abstainers. Daily drinking appears to increase the risk of alcoholic cirrhosis, regardless of alcohol amount, at least among men. Recent alcohol consumption rather than earlier in life is the most significant risk factor of alcoholic cirrhosis. Compared with beer and liquor, wine seems to be

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associated with a lower risk of alcoholic cirrhosis, up to a moderate level of weekly alcohol amount.

Conflict of interest

The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

GA, MG, MSK, AT, and JST contributed to the conception and design of the study. AT contributed to the acquisition of data. GA and JST analysed and interpreted the data and wrote the manuscript. GA, MG, MSK, AT, and JST critically revised the manuscript and approved the final version.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.12.005.

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