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Running title

Alcohol use and early mortality in women

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Abstract

Aims: The majority of prospective studies on alcohol use and mortality risk indicate that non-drinkers are at increased risk of death compared to moderate drinkers. This paper investigates the association between middle-aged women's alcohol use and mortality, controlling for socio-demographic and health variables. An association between alcohol use and hospital in-patient care is also analysed.

Methods: Baseline data were collected 1995-2000 in a population-based cohort of 6917 women aged 50-59 years living in southern Sweden, the Women's Health in Lund Area (WHILA). After nine years a register follow-up was performed from the National cause-of-death register and the Swedish hospital discharge register. Cox proportional hazards regression were used to analyse differences in survival.

Results: During the observation period 201 (2.9%) women died. In a crude model non-drinkers had a significantly increased risk for death. When including socio-demographic predictors in the model there was a strong indication that non-drinkers were at increased risk for death compared to moderate drinkers. Adding health predictors, not drinking alcohol was no longer a risk factor for death. Further, analyses of in-patient care indicate that non-drinkers had poorer health during their entire adult life.

Conclusions: This study underlines the importance of including health status at base-line when prospectively studying the association between alcohol use and mortality, otherwise moderate alcohol consumption may appear more beneficial than is the case.

Key words

Alcohol, mortality, women, middle aged, population, Sweden

Introduction

The association between alcohol consumption and health is complex. Alcohol consumption is causally related to more than 60 different medical conditions, in most but not all cases detrimentally [1-2]. The relation between alcohol consumption and mortality is usually reported as J- or U-shaped with lower all-cause mortality observed among light-to-moderate drinkers as compared to non-drinkers and heavy drinkers [3-6]. This relation has been explained by harmful implications of heavy drinking, such as liver cirrhosis and cancer, but beneficial effect of light drinking in particular on the cardiovascular system [1,5-6]. Several studies point to benefits associated with light to moderate drinking in middle-aged and older individuals. White et al found that in women aged 16-54 there was a direct dose-response relationship between alcohol consumption and risk of death, but at older ages a U-shaped relationship appeared [7]. Fuchs et al found that the benefit associated with light-to-moderate drinking was most apparent among women 50 years of age or older [4]. In an Australian study alcohol use in women was associated with reduced mortality in all groups older than 64 years [8]. In a Danish study light alcohol intake was associated with lower mortality than abstention or heavy drinking both in middle-aged (50-64 years) as well as in elderly (>64 years) men and women [9]. On the other hand, older individuals run considerable risks associated with alcohol use due to pre-existing health conditions, heavier use of prescribed medications, greater risk of balance problems, and/or cognitive dysfunction compared to younger people [10]. Furthermore, in a large meta-analysis Fillmore et al concluded that the cardiac protection afforded by alcohol may be over-estimated [11]. Based on the material from a health survey of a total population of 50-59 year old women living in the Lund area of southern Sweden, we have in previous studies shown that three out

of four women drank alcohol weekly [12]. More than one out of ten were drinking at a level that might be hazardous for women (>9 drinks/week) [13, 14].

The aim of this nine-year follow-up study is to highlight a perceived association between the women's alcohol use and mortality, controlling for a large number of socio-demographic and health variables. To further illuminate health factors in relation to the women's alcohol use at baseline in-patient hospital care before and after investigation is analysed.

Methods

Participants

All women (n=10,766) aged 50-59, born between 2 December 1935 and 1 December 1945, and on 1 December 1995 living in the Lund area in southern Sweden (172,005 inhabitants), received a mailed invitation to a health survey called Women's Health in Lund Area (WHILA). The WHILA study included a physical and laboratory examination and a self-administered questionnaire. It ran from 2 December 1995 until 3 February 2000, and in total 6917 women (64.2%) participated. The Ethics Committee at Lund University approved the study. An attrition analysis has been published previously [15].

Material

The basic questionnaire, distributed to all 6917 women, has been described in previous papers [12,15]. The response rate to the questions varied from 95.7%-100%.

Alcohol consumption was reported by 6623 women (95.7%). Each of them stated the number of glasses/bottles (specified in centilitres) of wine, beer and liquor that she drank in an ordinary week, or indicated the option "no alcohol". Total alcohol intake was converted into grams of pure alcohol and number of drinks (12 grams of pure alcohol equals one drink). As in the previous papers alcohol consumption was divided into categories, while in this paper the level of risk consumption was lowered according to recent recommendations for women in Sweden [13-15]. Based on weekly alcohol consumption the subjects were grouped into: Non-drinkers (0 g, 0 drinks, n = 1722), Moderate Drinkers (1-108 g, <9 drinks, n = 4148), or Risk drinkers (>109 g, >9 drinks, n = 753).

Socio-demographic variables included: age, household composition, highest level of education, employment, social network, immigrant status.

Health variables included: smoking, regular medical control for a physical or mental disease, regular medication, occurrence of hypertension, diabetes, thrombosis, heart attack, cerebral haemorrhage/stroke, occurrence of mental and physical symptoms late classified as absent/slight, moderate or severe [15].

Register follow-up

Using Sweden's unique national personal identification numbers we linked data from all women participating in the WHILA-study to the registries on file at the National Board of Health and Welfare. The national cause-of-death register comprises all deaths among Swedish residents, whether occurring in Sweden or abroad. All cases of death up to 25 March 2009 were collected. Causes of death are coded according to the International Classification of Disease (ICD-10), and had at the time been registered for death cases up to and including 31 December 2006.

To further illuminate health factors in relation to the women's alcohol use at baseline in-patient hospital care before and after investigation was analysed. The Swedish hospital discharge register includes each individual's hospitals discharge records. All cases of in-patient hospital care from 1 January 1964 until 31 December 2007 were collected. Each woman's number of hospital admissions and days spent in hospital was calculated. All in-patient care was categorised as "before" or "after" the WHILA-study baseline. As this was based on each woman's individual date for participation the timeframe "before" ranged from 11658 to 13182 days (approximately 32 to 36 years), and "after" from 2888 to 4412 days (approximately 8 to 12 years).

Statistical methods

Statistical calculations were performed using SPSS, version 11.0 (Chicago Illinois). Chi-square tests, and when required, Fishers exact test, were used to analyse differences in proportions. As continuous variables were assumed to be non-normally distributed, non-parametric tests were applied to those variables. For two-group comparisons, as well as post-hoc analyses when the Kruskal-Wallis test showed a statistical significance, the Mann-Whitney U-test was used. Bonferroni corrections were applied for multiple comparisons. Results are presented as median (min-max). $P <0.05$ were considered significant.

In order to identify alcohol consumption as risk factor for premature death, survival analyses were employed; Kaplan-Meier (univariate) and subsequent Cox regression (multivariate) analyses were carried out. The variables reaching statistical significance as possible risk factors for death in Kaplan-Meier analyses (log-rank test) were entered in a Cox regression analysis (Backward LR) as control variables. Cox regression analyses were performed, one crude model controlling only for age, one controlling for age and socio-demographic predictors, and one controlling fore age, socio-demographic and health predictors (presented in Table I). When the follow-up study was performed time since participation in the WHILA study varied between women. Minimum time since participation was 3340 days (approximately 9.2 years), so this figure was set as the observation period. Thus, all women were included in the analyses and followed-up for the same time period. If a woman had died after the follow-up period of 3340 days (which was the case for 77 women) they were included in the analysis as "alive").

Results

Alcohol use and risk factors for death

Of all 6917 women that participated in the WHILA-study 201 (2.9%) had died during the observation period. Out of the 6623 women that stated alcohol consumption, death within the observation period occurred in 71 (4.1%) of 1722 non-drinkers, in 102 (2.5%) of 4148 moderate drinkers and in 19 (2.5%) of 753 risk drinkers. Median (range) weekly alcohol consumption for moderate drinkers was 34 (3-108) gram and for risk drinkers 150 (109-1036) gram.

In a crude model (controlling only for age) not drinking alcohol was a significant risk factor for premature death compared to moderate drinking. Risk drinkers had no increased risk for death (Table I). When socio-demographic control variables were included the variable alcohol consumption was not fully significant but there was a strong indication that non-drinkers were at increased risk for death compared to moderate drinkers ($p = 0.024$). When also health predictors were included as control variables non-drinkers were no longer at increased risk for death compared to moderate drinkers ($p = 0.185$).

Suggested position of Table I

Of the 201 women who died during the observation period, 184 (92%) had a classified cause of death; neoplasm were by far the most common cause of death (n = 139), followed by diseases of the circulatory system (n = 22). One woman died of alcohol intoxication and four due to suicide. Eighteen women died from other causes. Causes of death, categorised as neoplasm, diseases of the circulatory system, alcohol/suicide, and other causes, did not differ between non-, moderate- and risk drinkers ($p = 0.850$).

Alcohol use and in-patient care

In patient care before and after participation in the WHILA-study was compared between non-, moderate- and risk drinkers (Table II). Non-drinkers had a higher number of hospital admissions and more days in hospital before as well as after their participation in the WHILA-study compared to moderate and risk drinkers (the *p*-values in the tests ranged from <0.001 to 0.003). There were no significant differences between moderate and risk drinkers (the *p*-values ranged from 0.41-0.90).

Suggested position of Table II

Discussion

Most studies find lower mortality associated with light to moderate drinking in middle-aged and older women [4,7-9]. Also in this study not drinking alcohol was a significant risk factor for premature death compared to moderate drinking in the crude model. However, it was no longer a significant predictor of mortality, when controlling for health status at baseline. Our results are in line with another Swedish population study of women aged 38-60 years. In that study, women who reported a high intake of beer or wine at the initial examination had a significantly lower mortality during the 32-year follow-up when controlling for age, but this observation did not remain significant when several social and health covariates were added in the multivariate analysis [16]. In our study the need to consider health when analysing alcohol use and mortality risk is strengthened by the finding that non drinkers had higher use of in-patient care both before and after their participation in the WHILA-study. Since the WHILA-study took place, national studies show an increase in alcohol consumption among Swedish women aged 50 years and beyond [17]. A study of age-related changes in drinking patterns shows that heavy drinking decreases from midlife to older age, but more frequent moderate drinking may occur [18]. Thus, in general the participants may have increased their consumption, but not necessarily risk drinking.

Cogency of the studies lies in the access to hospital discharge records showing each individual´s number of hospital admissions and days spent in hospital during their adult life. Reliable information of mortality and in-patient care was possible to collect for the whole study group during 1964 to 2007. All in-patient care were categorised as before or after participation in the WHILA-study based on each woman's individual date for participation. Hence there were individual differences in duration. As women were born between 2 December 1935 and 1 December 1945, and data on in-patient care were collected from 1

January 1964 the youngest subject at that particular day was 18 years and the oldest 28 years. These limitations should be considered.

The magnitude of the study (nearly 7000 women), in combination with its narrow age range makes the WHILA-study quite unique, while it complicates comparisons with mortality studies of women in general.

The study has limitations. Alcohol use was measured only at baseline and no information of earlier alcohol use was collected [19]. Thus life-long abstainers could not be distinguished from former drinkers, and we do not know the women's reason for abstinence, e.g. "sick quitters". In some studies the "protective effect" of alcohol use may be explained by the fact that former drinkers have been included among non-drinkers [11,20]. However, others have observed J- or U-shaped associations even after separating former drinkers from life-long abstainers [21-22]. Nor could past heavy drinkers, which usually have risks similar to those for current heavy drinkers be analysed in detail [23].

Further, in our study the categorisation of consumption had to be limited to three to reach statistical power. The moderate drinking category is fairly wide. A study by Rehm et. al. a shows that a more detailed categorisation is preferable [24]. According to the definitions recommended in Sweden cut-off for risk-drinking was set at >9 drinks/week [14]. Several studies find a significant increased risk of mortality for women only at much higher levels of drinking [3-4,7]. Grønbaek et al found significantly increased risk only among those drinking >42 beverages/week [3]. Fuchs et al found an increased risk for women only when consuming at least 30 grams per day, approximately 3 drinks daily [4]. White et al found that the level at which the risk of death significantly increases differed by age, being 8 units/week in women aged 16-24 and 20 units/week in women over 65 [7]. In our study only 1.6% (n = 106) of the women had >20 drinks/week of whom four had died.

Alcohol consumption is mostly, but not in all cases, adversely related to different medical conditions [1-2]. As pointed out in the Global Burden of Disease study 2010, mortality linked to substance abuse is largely captured under other causes, and is rarely listed as the primary cause of death. However, mental- and substance use disorders are the leading global causes of non-fatal burden of disease [25]. Lower mortality among light- and moderate drinkers has mainly been explained by the potential beneficial influence of alcohol on coronary heart disease, stroke and diabetes mellitus, usually reported as a J-shaped curve, while the curve is linear for cancer with no protective effect by alcohol [1,5-6]. However, Fillmore et. al. argue that the cardiac protection afforded by alcohol may have been over-estimated [11]. An association between breast cancer and alcohol use has been shown in other studies. The risk of breast cancer is doubled among heavy drinking women compared to non drinking women, but even a small, frequent intake has been found to imply an increased risk [6]. In this study analyses of different causes of death were not performed due to small numbers. Further follow-up of this population is planned, when also causes of death will be analysed.

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Table I. Risk factors for death in multivariate Cox regression analyses.

Risk factor	Deaths n (%)	Crude Model HR	CI (95%)	*p*-value	Socio-demographic predictors[a] HR	CI (95%)	*p*-value	Socio-demographic and health predictors[b] HR	CI ((95%)	*p*-value
Alcohol consumption				0.002			0.077			0.413
Moderate drinker (Ref)	102 (2.5%)	1.0			1.0			1.0		
Non drinker	71 (4.1%)	1,7	1.3-2.3	0.001	1.5	1.1-2.0	0.024	1.3	0.9-1.8	0.185
Risk drinker	19 (2.5%)	1,0	0.6-1.7	0.923	1.2	0.7-1.9	0.546	1.1	0.7-1.9	0.682

Non-significant variables were: immigrant status, severity of physical symptoms, severity of mental symptoms, thrombosis, heart-attack, and cerebral haemorrhage/stroke.

[a] This model included alcohol consumption, age and all significant socio-demographic predictors (household composition, highest level of education, employment and social network).

[b] This model included alcohol consumption, age, all significant socio-demographic and health predictors variables (household composition, highest level of education, employment, social network, smoking, regular medical control for a physical or mental disease, regular medication, hypertension and diabetes).

Table II. In patient care before and after participation in the WHILA study; comparisons between Non-, Moderate- and Risk drinkers.

	Non-drinkers $n = 1722$	Moderate drinkers $n = 4148$	Risk drinkers $n = 753$	p-value
Number of hospital admissions[a]				
Before WHILA	2 (0-226)	1 (0-85)	1 (0-33)	<0.001
After WHILA	1 (0-58)	0 (0-30)	0 (0-27)	<0.001
Number of days in hospital[a]				
Before WHILA	9 (0-1867)	7 (0-1397)	7 (0-389)	<0.001
After WHILA	2 (0-1454)	0 (0-352)	0 (0-225)	<0.001

[a] Kruskal-Wallis test was used to compare all three groups (p-value presented in table). As it showed a statistical significance, the Mann-Whitney U-test was used for two-group comparisons, results presented in text. Data presented as median (min-max).