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Original Contribution

Separate and Joint Effects of Alcohol and Smoking on the Risks of Cirrhosis and Gallbladder Disease in Middle-aged Women

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The separate and joint effects of alcohol and smoking on incidences of liver cirrhosis and gallbladder disease were examined in a prospective study of 1,290,413 United Kingdom women (mean age, 56 years) recruited during 1996–2001. After a mean follow-up of 6.1 years (1996–2005), incidence rates of cirrhosis and gallbladder disease were 1.3 per 1,000 persons ($n = 2{,}105$) and 15 per 1,000 persons ($n = 23{,}989$), respectively, over 5 years. Cirrhosis risk increased with increasing alcohol consumption, while the risk of gallbladder disease decreased ($P_{trend} < 0.0001$ for each). Comparing women who drank ≥15 units/week with those who drank 1–2 units/week, the relative risk was 4.32 (95% confidence interval (CI): 3.71, 5.03)) for cirrhosis and 0.59 (95% CI: 0.55, 0.64) for gallbladder disease. Increasing numbers of cigarettes smoked daily increased the risk of both conditions ($P_{trend} < 0.0001$ for each). Comparing current smokers of ≥20 cigarettes/day with never smokers, the relative risk was 3.76 (95% CI: 3.25, 4.34) for cirrhosis and 1.29 (95% CI: 1.22, 1.37) for gallbladder disease. Effects of alcohol and smoking were more than multiplicative for cirrhosis ($P_{interaction} = 0.02$) but not for gallbladder disease ($P_{interaction} = 0.4$). Findings indicate that alcohol and smoking affect the risks of the 2 conditions in different ways. For cirrhosis, alcohol and smoking separately increase risk, and their joint effects are particularly hazardous. For gallbladder disease, alcohol reduces risk and smoking results in a small risk increase.

alcohol drinking; gallbladder diseases; liver cirrhosis; liver diseases, alcoholic; prospective studies; smoking

Abbreviations: CI, confidence interval; ICD-10, *International Classification of Diseases,* Tenth Revision; NHS, National Health Service; RR, relative risk.

Both alcohol consumption and cigarette smoking are believed to affect the hepatobiliary system. Studies have consistently found an increased risk of liver cirrhosis with increasing alcohol consumption (1, 2), whereas the reverse has been reported for gallbladder disease, with some evidence that alcohol may be protective against symptomatic gallstones and cholecystitis (3). Some studies on the effects of smoking suggest a modest increase in the risks of both cirrhosis and gallbladder disease (4–9); however, since alcohol drinking is associated with smoking and vice versa, it is often difficult to disentangle the effects of the 2 exposures. Because studies suggest opposing effects of alcohol on the risks of liver and gallbladder disease (harmful and protective, respectively) but similar effects for smoking (harmful for both conditions), we examined the separate and joint effects of alcohol use and smoking on these 2 outcomes in a large prospective study of middle-aged women.

MATERIALS AND METHODS

Study population

The Million Women Study is an ongoing prospective study of 1.3 million middle-aged women in England and Scotland who were recruited through the United Kingdom National Health Service (NHS) Breast Screening Service during 1996–2001 (10). At the time recruitment, the study included an estimated 25% of all women in this age range in

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the United Kingdom, and participants were of marginally higher socioeconomic status than nonparticipants (11). At recruitment, women provided details on the amount of alcohol they were drinking, their smoking status, and the number of cigarettes they smoked daily, as well as information on anthropometric factors, sociodemographic factors, reproductive history, use of exogenous hormones, and medical history. Repeat surveys were conducted an average of 3 years and 7 years following recruitment into the study. Information was collected via self-completed questionnaires. The questionnaires can be viewed at the study's Web site (www.millionwomenstudy.org).

Follow-up of study participants is carried out through record linkage to the NHS central registries for deaths, cancers, and emigrations (12) and to the Hospital Episode Statistics for England (13) and Scottish Morbidity Records (14) for hospital admission data. Study participants are linked using their NHS number (a unique personal identifier) and other personal details. The NHS central registries hold records on all registered deaths, including the cause of death and the date of death. The hospital admission data contain a record of all inpatient admissions to NHS hospitals starting from April 1997 in England and from January 1981 in Scotland. Each record includes the date of hospital admission, the primary reason for hospital admission, and up to 13 additional diagnoses. Throughout the follow-up period of this study, all linked records were coded according to the *International Classification of Diseases*, Tenth Revision (ICD-10) (15). Women were classified as having cirrhosis if they had either a death or a hospital admission record with an ICD-10 diagnosis code of K70, K73, or K74 (16). They were classified as having gallbladder disease if they had either a death or a hospital admission record with an ICD-10 diagnosis code of K80 or K81.

This study was approved by the Eastern Multicentre Research Ethics Committee, and all study participants provided written consent. Access and linkage to hospital records was approved by the Information Centre for Health and Social Care in England and the Information Services Division in Scotland.

Statistical analysis

Women were excluded if they had had a hospital admission for or reported a history of either of the diagnoses of interest (liver cirrhosis or gallbladder disease) before recruitment or if they had had a diagnosis of cancer (except nonmelanomatous skin cancer (ICD-10 code C44)) before recruitment. Also excluded were women who self-reported hepatitis or had a record of viral hepatitis (ICD-10 codes B15–B19) at recruitment or during follow-up. Each of the 2 conditions of interest was considered as a separate endpoint, and in the analyses cirrhosis and gallbladder disease were not considered to be competing risks. Person-years for each endpoint were calculated from the date of recruitment to the date of death or hospital admission for the endpoint of interest or the last date of follow-up, whichever came first. We had complete data on all deaths occurring up to December 31, 2006. The last date of follow-up was set as December 31, 2003, for women recruited in Scotland and March 31, 2005, for women recruited in England; these were the last dates by which hospital data were complete in each country. For a small proportion of women (5%) recruited in England before April 1, 1997, person-years were calculated from this date, since hospital records were not available in England before this time.

Cox regression was used to estimate the relative risk of death or hospital admission for liver cirrhosis or gallbladder disease according to alcohol intake or cigarette smoking. Reported alcohol consumption was converted into units, where a unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits). Women were then categorized into the following groups for alcohol intake: none (never or former drinker), 1–2 units/week, 3–6 units/week, 7–14 units/week, and $\geq$15 units/week. Smoking was categorized as never, past, or current smoking, and current smokers were also categorized according to reported number of cigarettes smoked per day (1–9, 10–19, or $\geq$20). In analyses, the reference category for alcohol drinking was 1–2 units/week, and for smoking it was never smokers. Attained age was used as the underlying time variable, and all results were routinely stratified by region of recruitment (10 regions) and adjusted for socioeconomic status (in quintiles, according to the deprivation index, as defined previously (12)), body mass index (weight (kg)/height (m)^2; $<$22.5, 22.5–24.9, 25–27.4, 27.5–29.9, or $\geq$30), and alcohol drinking and smoking as appropriate. The effect of additional adjustment for parity, hormone therapy, and other medical illnesses (heart disease, diabetes, high blood pressure, high cholesterol) reported at recruitment was examined.

Cigarette smoking and alcohol drinking are correlated. In order to distinguish their effects, we examined the effect of alcohol intake in predefined subgroups of smoking status (never smoking vs. current smoking) and the effect of smoking in predefined subgroups of alcohol consumption (1–6 units/week vs. $\geq$7 units/week). The likelihood ratio test statistic was used to test for heterogeneity between subgroups. We also conducted additional analyses to examine the robustness of certain assumptions. We repeated the analyses among women who were recruited in Scotland only, because, unlike the situation in England (where hospital records were available only from 1997), women recruited in Scotland had complete hospital records from 1981 (an average of 20 years preceding recruitment). We also censored the first 2 years of follow-up in our sensitivity analyses, since women may have changed their alcohol or smoking behavior because of preexisting illness. Coffee consumption has been reported to be associated with both liver cirrhosis (6, 7, 17) and gallbladder disease (18). However, because women were only asked about coffee consumption at the first resurvey, we repeated the analyses after adjusting for reported coffee consumption (0, 1, 2, 3, or $\geq$4 cups/day) among women who participated in the resurvey, calculating person-years starting from the date of the resurvey.

The STATA 9.2 statistical package was used for all analyses (Stata Corporation, College Station, Texas). To account for regression dilution bias (19), in the figures we plotted relative risks against mean alcohol and smoking values based on categories reported at recruitment, using means calculated from what was reported at the resurvey.

RESULTS

We excluded 10,954 women who had reported a history of cirrhosis or gallbladder disease or had a hospital admission record for cirrhosis or gallbladder disease before recruitment. We also excluded 42,268 women who had had cancer before recruitment and 636 women with hepatitis. This left 1,290,413 women in our analyses. Over a mean of 6.1 years of follow-up, 2,105 women were first diagnosed with cirrhosis and 23,989 first diagnosed with gallbladder disease. During the follow-up period, 22% ($n = 458$) of women with cirrhosis and 0.1% ($n = 32$) of women with gallbladder disease also had a death registration for the disease. The incidence rates of first hospital admission for cirrhosis and gallbladder disease were 1.3 per 1,000 persons and 15 per 1,000 persons, respectively, over 5 years.

Table 1 shows the baseline characteristics of the study cohort according to categories of alcohol use. The majority of women in the cohort were moderate alcohol drinkers, with 24% reporting drinking no alcohol at recruitment; 52% consumed 1–6 units/week. Only 5% reported drinking more than 15 units/week. Women reporting no alcohol intake at recruitment differed from the cohort with regard to almost all baseline characteristics, with a greater age and mean body mass index, a higher proportion of current smokers, a higher rate of high blood pressure, and lower socioeconomic status. In women who reported drinking alcohol, increasing intake was associated with decreasing age and mean body mass index, decreasing rate of high blood pressure, and increasing socioeconomic status and proportion of current smokers.

Table 2 shows characteristics according to cigarette smoking. Current smokers were younger and of lower socioeconomic status than never and past smokers, and there was a decreasing trend with amount smoked for both age and socioeconomic status. Current smokers were also less likely to be treated for high blood pressure and had a lower body mass index. Past smokers and smokers of ≥20 cigarettes/day had the highest mean weekly alcohol intake (5.4 units/week and 5.6 units/week, respectively), while never smokers had the lowest (3.7 units/week). In general, women drinking more alcohol were more likely to be smokers and smoked more cigarettes (Table 1), while women who smoked more cigarettes were more likely to drink more alcohol (Table 2).

Table 3 shows the relative risk of hospital admission or death for liver cirrhosis according to alcohol intake and cigarette smoking. Among drinkers, increasing alcohol consumption was associated with significant increases in the risk of cirrhosis, despite the relatively low levels of consumption ($P_{trend} < 0.0001$). Women who reported drinking ≥15 units/week had approximately 4 times the risk of cirrhosis as women drinking 1–2 units/week. Women who reported at recruitment that they drank no alcohol had a significantly higher risk of cirrhosis (relative risk (RR) = 1.41, 95% confidence interval (CI): 1.23, 1.61), but it is unknown how many of these women were ex-drinkers. Regarding the relation with smoking, current smokers had an increased risk of cirrhosis compared with never smokers, and the risk increased with number of cigarettes smoked ($P_{trend} < 0.0001$). Past smokers also had a slightly higher risk than never smokers (RR = 1.36, 95% CI: 1.21, 1.53).

Table 1. Baseline Characteristics of Study Participants According to Alcohol Consumption, United Kingdom, 1996–2001

	Alcohol Intake, units/week[a]												Total	
	0 (Never/ Former Drinker)		1–2		3–6		7–14		≥15		Unknown			
	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%
No. of women	305,652		372,065		294,353		241,307		67,360		9,676		1,290,413	
Mean age, years	56.7 (4.7)		56.2 (4.7)		55.8 (4.6)		55.4 (4.6)		55.2 (4.5)		56.7 (4.7)		56.0 (4.7)	
Mean body mass index[b]	27.1 (5.4)		26.4 (4.7)		25.9 (4.4)		25.4 (4.0)		25.3 (4.1)		26.9 (5.2)		26.2 (4.7)	
Upper third of socioeconomic status	74,944	25	128,102	35	109,091	37	91,156	38	25,328	38	1,895	20	430,516	34
Mean parity	2.3 (1.4)		2.1 (1.2)		2.1 (1.2)		2.0 (1.2)		2.0 (1.2)		2.3 (1.5)		2.1 (1.2)	
Treatment for high blood pressure	60,418	20	59,855	16	40,907	14	32,183	13	9,380	14	1,685	17	204,428	16
Current smoking	73,693	26	57,418	17	47,558	17	51,279	22	16,693	26	3,520	37	250,161	21
Current smoking of ≥20 cigarettes/day	19,489	6	12,220	3	9,821	3	13,086	5	6,681	10	922	10	62,219	5
Mean alcohol intake, units/week	0 (0)		1.6 (0.5)		4.3 (1.0)		9.9 (2.2)		20.1 (5.0)				4.4 (5.3)	

Abbreviation: SD, standard deviation.

[a] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).

[b] Weight (kg)/height $(m)^2$.

Table 2. Baseline Characteristics of Study Participants According to Current Cigarette Smoking, United Kingdom, 1996–2001

	Never Smoking		Past Smoking		Current Smoking, cigarettes/day								Total	
					1–9		10–19		≥20		Unknown			
	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%
No. of women	621,185		343,990		63,349		124,593		62,219		75,077		1,290,413	
Mean age, years	56.2 (4.7)		56.1 (4.7)		55.7 (4.6)		55.3 (4.4)		54.7 (4.2)		56.7 (4.7)		56.0 (4.7)	
Mean body mass index[a]	26.2 (4.6)		26.7 (4.8)		25.3 (4.3)		25.4 (4.4)		26.2 (4.9)		26.7 (4.9)		26.2 (4.7)	
Upper third of socioeconomic status	236,271	38	114,601	34	17,461	28	26,994	22	12,137	20	23,052	31	430,516	34
Mean parity	2.1 (1.2)		2.1 (1.2)		2.2 (1.3)		2.3 (1.3)		2.3 (1.4)		2.2 (1.3)		2.1 (1.2)	
Treatment for high blood pressure	101,931	16	57,266	17	8,239	13	15,449	12	7,986	13	13,557	18	204,428	16
Mean alcohol intake, units/week[b]	3.7 (4.6)		5.4 (5.9)		4.6 (5.5)		4.3 (5.5)		5.6 (7.2)		3.5 (4.7)		4.4 (5.3)	

Abbreviation: SD, standard deviation.
[a] Weight (kg)/height (m)^2.
[b] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).

For gallbladder disease (Table 4), among drinkers, the relative risks became significantly lower as alcohol consumption increased ($P_{trend} < 0.0001$). Women reporting ≥15 units/week had an approximately 40% lower risk of gallbladder disease than women reporting 1–2 units/week. Current smokers had a higher risk of gallbladder disease than never smokers, with an increase in risk as the quantity smoked increased ($P_{trend} < 0.0001$). Past smokers also had a marginally higher risk than never smokers (RR = 1.10, 95% CI: 1.06, 1.13); however, risks were not as great as that observed for smoking and cirrhosis. All of the risk estimates in Tables 3 and 4, for both alcohol and tobacco, changed by less than 5% when additional adjustment was made for parity, hormone replacement therapy, and medical illnesses. Hence, in all subsequent analyses we did not adjust for these additional factors.

Given that both alcohol drinking and cigarette smoking had significant associations with cirrhosis and gallbladder disease and are known to be associated with one another, we examined the joint effect of these exposures using women who never smoked and who drank 1–6 units of alcohol per week as the baseline group. The relative risks of incident cirrhosis in subgroups of alcohol consumption (1–6 units/week vs. ≥7 units/week) and smoking (never smoking vs. current smoking) are given in Table 5 and are illustrated (according to the different levels of alcohol and smoking) in Figure 1. There was a significant interaction on a multiplicative scale between the effects of alcohol and smoking ($P_{interaction} = 0.02$). Women who both smoked and consumed larger quantities of alcohol had a greater risk of cirrhosis than would be expected from the separate effects of each (RR = 8.02, 95% CI: 6.84, 9.40).

For gallbladder disease, however, there was no evidence of an interaction on a multiplicative scale ($P_{interaction} = 0.4$). This is illustrated in Table 5 and Figure 2. The relative risks of gallbladder disease among drinkers were consistently greater in smokers than in never smokers, regardless of the level of drinking. Similarly, risks of gallbladder disease

Table 3. Relative Risk of Liver Cirrhosis ($n = 2,105$) According to Alcohol Consumption and Cigarette Smoking, United Kingdom, 1996–2005

	No. of Cases[a]	Relative Risk[b]	95% Confidence Interval
Alcohol intake, units/week[c]			
0 (never/former drinker)	547	1.41	1.23, 1.61
1–2	380	1.00	Reference
3–6	363	1.24	1.08, 1.44
7–14	466	1.84	1.60, 2.11
≥15	322	4.32	3.71, 5.03
P for linear trend among drinkers			<0.0001
Cigarette smoking			
Never smoker	626	1.00	Reference
Current smoker			
1–9 cigarettes/day	128	1.83	1.52, 2.22
10–19 cigarettes/day	401	2.82	2.48, 3.22
≥20 cigarettes/day	297	3.76	3.25, 4.34
Former smoker	540	1.36	1.21, 1.53
P for linear trend (among current smokers)			<0.0001

[a] Numbers do not necessarily sum to totals because of missing values.
[b] Relative risks were adjusted for age, region of recruitment, socioeconomic status, body mass index, and alcohol intake and smoking as appropriate.
[c] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).

Table 4. Relative Risk of Gallbladder Disease ($n = 23,989$) According to Alcohol Consumption and Cigarette Smoking, United Kingdom, 1996–2005

	No. of Cases[a]	Relative Risk[b]	95% Confidence Interval
Alcohol intake, units/week[c]			
0 (never/former drinker)	7,239	1.09	1.06, 1.13
1–2	7,389	1.00	Reference
3–6	5,149	0.91	0.88, 0.95
7–14	3,272	0.74	0.71, 0.77
≥15	735	0.59	0.55, 0.64
P for linear trend among drinkers		<0.0001	
Cigarette smoking			
Never smoker	10,866	1.00	Reference
Current smoker			
1–9 cigarettes/day	1,140	1.12	1.05, 1.19
10–19 cigarettes/day	2,534	1.23	1.17, 1.28
≥20 cigarettes/day	1,391	1.29	1.22, 1.37
Former smoker	6,626	1.10	1.06, 1.13
P for linear trend (among current smokers)		<0.0001	

[a] Numbers do not necessarily sum to totals because of missing values.
[b] Relative risks were adjusted for age, region of recruitment, socioeconomic status, body mass index, and alcohol intake and smoking as appropriate.
[c] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).

among smokers were consistently lower in women drinking ≥7 units/week than in those drinking 1–6 units/week, regardless of the amount smoked.

Results from the sensitivity analyses are shown in the Appendix Table. When we included only the women who were recruited in Scotland (8% of the cohort), censored the first 2 years of follow-up, or adjusted the results for concurrent coffee drinking (in the 62% of the cohort who returned the first resurvey and did not have an event before the date of return of the resurvey), all of the alcohol-disease and smoking-disease relations were similar to those found in the main analysis.

DISCUSSION

In this large prospective study of women with moderate alcohol consumption, we confirmed previous findings that increasing alcohol consumption is associated with an increase in the risk of liver cirrhosis and a decrease in the risk of gallbladder disease. Current smoking was associated with increased risks of both cirrhosis and gallbladder disease, more so for cirrhosis than for gallbladder disease. With respect to the combined effects of alcohol and smoking, for cirrhosis there was an interaction between alcohol and smoking, with substantially higher relative risks being seen in women who both drank larger amounts of alcohol and smoked more cigarettes than would be expected by multiplying the separate effects of these factors. For gallbladder disease, there was no such interaction.

The association between alcohol use and mortality from liver cirrhosis is well established (1, 4, 20). In this cohort, women reported drinking moderate amounts of alcohol (mean consumption was 4.4 units/week, i.e., less than 1 unit/day), but we found that even for relatively small increases in alcohol intake, there was a significant dose-response effect, rising to a relative risk of approximately 4 for more than 15 units/week (i.e., >2 units/day) in comparison with 1–2 units/week. As has been previously described (1, 2), women who reported drinking no alcohol (which included never and former drinkers) had a higher risk of cirrhosis than women drinking very small amounts of alcohol (1–2 units/week). Such an association is not

Table 5. Relative Risks of Liver Cirrhosis and Gallbladder Disease According to Alcohol Consumption and Cigarette Smoking, United Kingdom, 1996–2005

	Alcohol Intake, units/week[a]					
	1–6			≥7		
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI
Cirrhosis[b]						
Never smoker	260	1.00	Reference	171	2.09	1.72, 2.53
Current smoker	236	2.92	2.44, 3.49	403	8.02	6.84, 9.40
Gallbladder disease[c]						
Never smoker	6,175	1.00	Reference	1,404	0.73	0.69, 0.78
Current smoker	2,160	1.20	1.14, 1.26	994	0.92	0.86, 0.98

Abbreviations: CI, confidence interval; RR, relative risk.
[a] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).
[b] Likelihood ratio test for interaction: $P = 0.02$.
[c] Likelihood ratio test for interaction: $P = 0.4$.

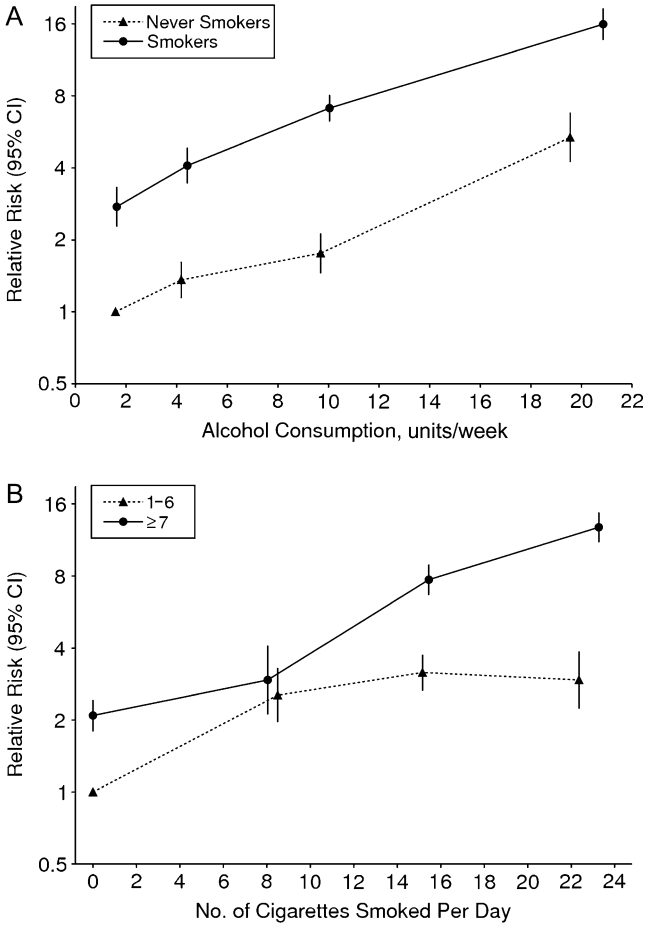

Figure 1. Relative risk of liver cirrhosis according to (A) alcohol consumption in never and current smokers and (B) number of cigarettes smoked per day in drinkers of 1–6 and ≥7 units of alcohol per week, United Kingdom, 1996–2005. Bars, 95% confidence interval (CI).

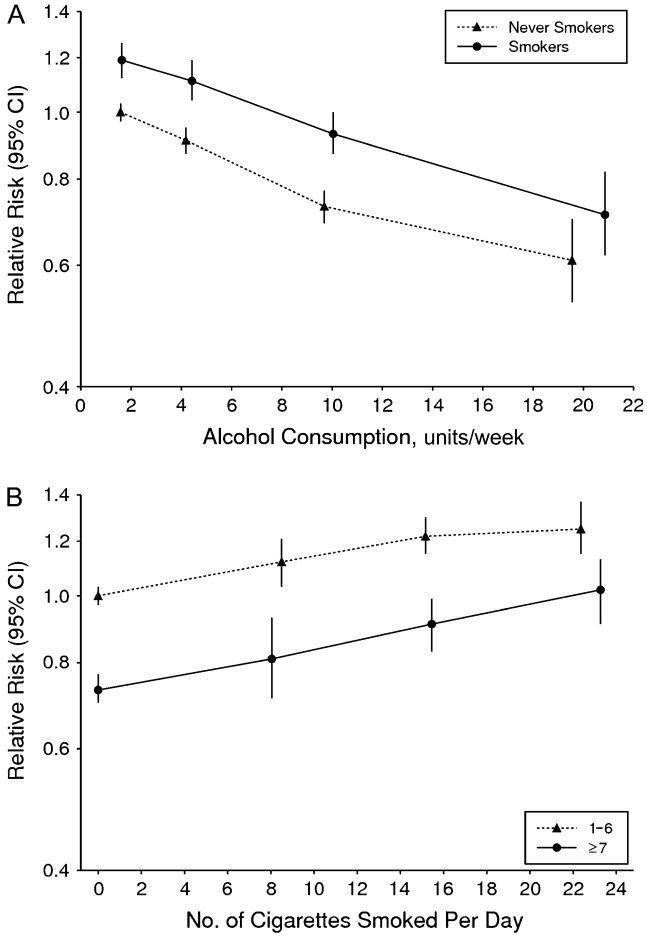

Figure 2. Relative risk of gallbladder disease according to (A) alcohol consumption in never and current smokers and (B) number of cigarettes smoked per day in drinkers of 1–6 and ≥7 units of alcohol per week, United Kingdom, 1996–2005. Bars, 95% confidence interval (CI).

unexpected, since past drinkers may have ceased drinking because of early signs of liver disease that occurred before hospital admission or death, thereby contributing to the higher relative risks found in this group.

It has been suggested that smoking also affects the liver (4, 6, 7). However, because of the correlation between alcohol drinking and cigarette smoking, in epidemiologic studies it has been difficult to separate the effects. When we controlled for alcohol consumption, we found a dose-response effect, with an increasing risk of cirrhosis with more cigarettes smoked. However, cross-classification by smoking and alcohol drinking demonstrated that while each separately increased risk, the joint effect of the 2 factors was greater than multiplying their separate risks. A possible explanation for this interaction between alcohol and smoking may be that smoking makes the liver more prone to alcohol-induced cirrhosis, as has been previously suggested (7).

With respect to gallbladder disease, while the published literature is not as extensive as that for cirrhosis, our findings are in general agreement with what has been previously reported. Other studies have suggested that alcohol intake is associated with a decreased risk of gallbladder disease (3, 21), and our findings agree with this. Most researchers have also found a small increase in the risk of gallbladder disease with cigarette smoking (5, 8, 9), and the magnitude of risk in our study was similar to that reported in the literature. However, in our study we were also able to demonstrate that the effects of drinking and smoking are multiplicative (i.e., no interaction on a multiplicative scale), with risks being consistently higher in current smokers than in never smokers for equivalent amounts of alcohol consumed and, similarly, risks of gallbladder disease being consistently lower at higher levels of alcohol consumption.

To our knowledge, this study is one of the largest prospective studies of cirrhosis and gallbladder disease to have been carried out among women. All women in the study were registered with the NHS, and by using linkage to national hospital admission and death registry data, we had

almost complete follow-up of study participants. There is minimal private hospital care in the United Kingdom (22), and we have previously demonstrated that in this cohort of women, who were recruited through the NHS Breast Screening Programme, follow-up using linkage to NHS hospital data is relatively complete (23). Outcomes were coded independently of study investigators. While hospital admission data will not capture events that do not require hospitalization, data from other sources suggest that these missed events are not substantial. Two general population studies of gallbladder disease using data from the years 2000 and 1996 found event rates for gallbladder disease of approximately 15–19 per 1,000 persons over a 5-year period among United Kingdom women aged 50–59 years (24, 25). Similarly, using data on cirrhosis mortality from 2002, Leon and McCambridge (16) estimated rates of approximately 0.75–1.7 per 1,000 persons among United Kingdom women aged 45–64 years over a 5-year period. Given differences between the age and population structures, our rates are broadly comparable.

Viral hepatitis is an important risk factor for liver cirrhosis, and we excluded women who had a record of hepatitis (either self-reported hepatitis or viral hepatitis in hospital records) from analyses. While exclusions based on self-report and hospitalization may result in some underascertainment of hepatitis infection among participants, in the United Kingdom estimated prevalence rates of hepatitis B and C are low (in 2003, they were 0.1% (26) and 0.4% (27), respectively), and because the women in this study would be classified as a predominantly low-risk population (26, 27)—that is, Caucasian, middle-aged United Kingdom women who underwent breast screening (10, 11)—this is unlikely to have caused significant bias in our analyses.

While alcohol consumption and smoking were self-reported, because information on these exposures was obtained prospectively, it should not have been biased according to the development of disease. It is possible that participants may have had symptoms of disease before recruitment that may have changed their patterns of drinking and smoking. However, even after we censored the first 2 years of follow-up, there were no significant changes in our findings to suggest this potential bias as a major concern. Previous studies have examined either cirrhosis or gallbladder disease but not both outcomes within the same cohort. We examined the effects of alcohol use and smoking on the risks of both cirrhosis and gallbladder disease in the same study because of the putatively opposing effects of alcohol on the 2 diseases and the similar effects of smoking. The fact that these results are consistent with what has been previously described in the literature—that is, we found opposing effects of alcohol and harmful effects for smoking within the same cohort—further underlies the robust nature of the exposure and outcome ascertainment.

Our findings suggest that in women, even moderate levels of alcohol consumption increase the risk of liver cirrhosis. Smoking also substantially increases this risk. However, the joint effects of alcohol drinking and cigarette smoking are particularly hazardous, with more than multiplicative effects. For gallbladder disease, alcohol consumption reduces risk while smoking modestly increases risk, and the joint effects are proportional to their separate risks.

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Appendix Table. Relative Risks of Liver Cirrhosis and Gallbladder Disease According to Alcohol Consumption and Cigarette Smoking in 3 Sensitivity Analyses[a] as Compared with Relative Risks From the Main Analysis, United Kingdom, 1996-2005

	Liver Cirrhosis							Gallbladder Disease						
	Main Analysis RR (n = 2,105)[b]	Sens1 (n = 155)		Sens2 (n = 1,505)		Sens3 (n = 500)		Main Analysis RR (n = 23,989)	Sens1 (n = 1,686)		Sens2 (n = 17,227)		Sens3 (n = 7,601)	
		RR	95% CI	RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI	RR	95% CI
Alcohol intake, units/week[c]														
0 (never/former drinker)	1.41	1.23	0.74, 2.06	1.44	1.22, 1.69	1.40	1.07, 1.83	1.09	1.14	1.01, 1.29	1.08	1.03, 1.12	1.01	0.95, 1.07
1–2	1.00	1.00	Reference	1.00	Reference	1.00	Reference	1.00	1.00	Reference	1.00	Reference	1.00	Reference
3–6	1.24	1.73	1.04, 2.86	1.32	1.11, 1.57	1.15	0.86, 1.54	0.91	0.92	0.80, 1.05	0.92	0.88, 0.96	0.95	0.89, 1.01
7–14	1.77	1.92	1.15, 3.21	2.04	1.73, 2.40	1.94	1.47, 2.54	0.74	0.71	0.61, 0.84	0.74	0.70, 0.78	0.79	0.73, 0.85
≥15	4.10	5.38	3.02, 9.58	4.96	4.15, 5.93	3.47	2.45, 4.60	0.59	0.43	0.30, 0.62	0.61	0.56, 0.67	0.65	0.57, 0.74
Cigarette smoking														
Never smoker	1.00	1.00	Reference	1.00	Reference	1.00	Reference	1.00	1.00	Reference	1.00	Reference	1.00	Reference
Current smoker														
1–9 cigarettes/day	1.83	2.37	1.21, 4.63	2.05	1.64, 2.55	1.53	0.97, 2.42	1.12	1.01	0.79, 1.30	1.12	1.04, 1.20	1.23	1.10, 1.37
10–19 cigarettes/day	2.82	2.97	1.87, 4.71	3.06	2.63, 3.57	3.39	2.58, 4.46	1.23	1.22	1.04, 1.43	1.24	1.18, 1.31	1.32	1.21, 1.44
≥20 cigarettes/day	3.76	3.33	1.94, 5.71	3.97	3.35, 4.71	4.78	3.52, 6.49	1.29	1.41	1.16, 1.71	1.28	1.20, 1.37	1.31	1.17, 1.47
Former smoker	1.36	1.39	0.88, 2.19	1.39	1.21, 1.60	1.45	1.16, 1.81	1.10	1.06	0.94, 1.20	1.09	1.05, 1.13	1.07	1.02, 1.13

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Sens1, women who were recruited in Scotland only; Sens2, censoring of the first 2 years of follow-up; Sens3, adjustment for coffee consumption based on information from the resurvey.

[b] Number of cases.

[c] A unit was defined as 1 standard drink (i.e., 1 glass of wine, half a pint of beer, or 1 measure of spirits).