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Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study

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BACKGROUND: Previous research suggests associations of lower alcohol intake and higher tobacco consumption with increased risks of haematological malignancy. The prospective Million Women Study provides sufficient power for reliable estimates of subtype-specific associations in women.

METHODS: Approximately 1.3 million middle-aged women were recruited in the United Kingdom during 1996–2001 and followed for death, emigration and cancer registration until 2009 (mean 10.3 years per woman); potential risk factors were assessed by questionnaire. Adjusted relative risks were estimated by Cox regression.

RESULTS: During follow-up, 9162 incident cases of haematological malignancy were recorded, including 7047 lymphoid and 2072 myeloid cancers. Among predominantly moderate alcohol drinkers, higher intake was associated with lower risk of lymphoid malignancies, in particular diffuse large B-cell lymphoma (relative risk 0.85 per 10 g alcohol per day (95% confidence interval 0.75–0.96)), follicular lymphoma (0.86 (0.76–0.98)) and plasma cell neoplasms (0.86 (0.77–0.96)). Among never- and current smokers, higher cigarette consumption was associated with increased risk of Hodgkin lymphoma (1.45 per 10 cigarettes per day (1.22–1.72)), mature T-cell malignancies (1.38 (1.10–1.73)) and myeloproliferative/myelodysplastic disease (1.42 (1.31–1.55)).

CONCLUSION: These findings confirm and extend existing evidence for associations of subtypes of haematological malignancy with two common exposures in women.

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Haematological malignancies are cancers that originate from lymphoid or myeloid cells and affect blood, bone marrow and lymph nodes. The tenth revision of the International Classification of Diseases (ICD-10) groups cases primarily by clinical presentation (leukaemia, myeloma or lymphoma). In contrast, the third edition of the International Classification of Diseases for Oncology (ICD-O-3) groups haematological malignancies primarily by cell lineage (lymphoid or myeloid), and includes some myeloid neoplasms that are not coded as malignant in ICD-10 (Jaffe *et al*, 2001; Swerdlow, 2008). A hierarchical classification based on ICD-O-3 has been used in recent international collaborative studies (Morton *et al*, 2007; Sant *et al*, 2010; Turner *et al*, 2010).

Alcohol drinking and tobacco smoking are modifiable exposures that are widespread in developed countries. Both are known to be associated with risks of certain types of haematological malignancy. Several recent cohort studies have reported decreasing trends in risk of non-Hodgkin lymphoma (NHL) and/or diffuse large B-cell lymphoma (a major subtype of NHL) with increasing alcohol intake among drinkers (Lim *et al*, 2007; Allen *et al*, 2009; Kanda *et al*, 2010; Troy *et al*, 2010). Smoking is considered to be causally related to myeloid leukaemia in adults (IARC, 2002), and (comparing current with never-smokers) has been associated with increased risk of Hodgkin lymphoma, acute myeloid leukaemia and myelodysplastic syndromes in recent cohort (Fernberg *et al*, 2007; Lim *et al*, 2007; Nieters *et al*, 2008; Ma *et al*, 2009, 2010) and case–control (Kasim *et al*, 2005; Besson *et al*, 2006a) studies. However, haematological malignancies are probably heterogeneous in aetiology, and much of the evidence for subtype-specific associations remains inconclusive, perhaps reflecting inconsistent exposure classifications, or relatively small study sizes.

We examined association of subtypes of haematological malignancy with alcohol drinking and tobacco smoking in the prospective Million Women Study. To aid comparison with previous research, we report findings based on both ICD-O-3 and ICD-10. The large size of this cohort provides sufficient power to estimate risk for relatively rare subtypes.

MATERIALS AND METHODS

Definitions

The Million Women Study has been described elsewhere (Reeves *et al*, 2007). Between 1996 and 2001, with appropriate ethical approval, 1.3 million middle-aged women were recruited through breast cancer screening clinics in the United Kingdom. Participants gave written informed consent, and completed questionnaires recording personal and lifestyle characteristics (available at www.millionwomenstudy.org). By linkage to the National Health Service Central Registers, participants are followed for death, emigration and cancer registration. Each incident neoplasm is coded using the combination of a disease code from ICD-10 and a morphology

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code from either the second or the third (ICD-O-3) edition of the International Classification of Diseases for Oncology.

For this analysis, haematological neoplasms were defined by the following ICD-10 codes: C81-C96 (malignant neoplasms of lymphoid, haematopoietic and related tissue), D45 (polycythemia vera), D46 (myelodysplastic syndromes) and D47 (other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue). Women were excluded if they had been diagnosed before recruitment with any haematological neoplasm (as defined above), or cancer of any other site except non-melanoma skin cancer (all other ICD-10 C codes except C44), or *in situ* breast carcinoma (ICD-10 D05), using equivalent definitions from earlier standard coding systems where necessary. For the remaining women, observation extended from the date of recruitment to the date of death, emigration, diagnosis with any of the neoplasms listed in the exclusion criteria, or end of follow-up, whichever occurred first. Follow-up ended on 31 December 2008 for Scotland and the North West (Merseyside and Cheshire) cancer registry region, and 31 December 2009 elsewhere.

Morphology codes for incident haematological neoplasms were converted from the second to the third edition as necessary (National Cancer Institute, 2011). Where the morphology code was uninformative (80001/80003, $N=115$) or discrepant ($N=3$), it was changed to match the ICD-10 code, unless both were non-specific ($N=10$). Malignant disease was defined and classified in two different ways (Table 1). ICD-O-3 morphology codes with fifth digit 3 (malignant) and first three digits in the range 959–998 (haematological neoplasms), except 975 (histiocytic and dendritic neoplasms, $N=2$), were grouped using a classification adapted from the InterLymph hierarchical scheme for epidemiological research (Turner *et al*, 2010) and the Haemacare project (Sant *et al*, 2010). Cases were grouped primarily by cell lineage. Subtypes of mature B-cell lymphoid malignancy included plasma cell neoplasms and 'CLL/SLL' (cases coded as either chronic lymphocytic leukaemia or small lymphocytic lymphoma, now considered to be a single disease). Hodgkin lymphoma formed a separate subtype of lymphoid malignancy. Myeloid malignancies were divided into two subtypes: acute myeloid leukaemia and 'myeloproliferative/myelodysplastic disease' (myeloproliferative and myelodysplastic neoplasms, including chronic myeloid leukaemia). For comparison, cases with ICD-10 codes C81-C96 were classified as Hodgkin lymphoma (C81), NHL (C82-C85, C96), 'myeloma' (multiple myeloma, plasma cell neoplasms and malignant immunoproliferative diseases (C88, C90)) and leukaemia (C91-C95).

Statistical analysis

Relative risk was estimated by Cox regression, taking attained age as the underlying time variable, and stratifying by cancer registry region of residence at recruitment (i.e. assuming equal coefficients across strata but with a baseline hazard unique to each stratum) (StataCorp., 2009). The proportional hazards assumption was examined using Schoenfeld residuals and found acceptable. To assess the possibility that associations might reflect lifestyle changes caused by subclinical disease (reverse causation), all analyses were repeated without the first 3 years of follow-up. All statistical tests were two-sided and used the 5% significance level.

Categorical exposure measures were derived from information given on the questionnaire completed by each woman at the time of recruitment to the study, as follows: current weekly alcohol consumption (none, 0.5–<3, 3–<7, ⩾7 drinks, in units equivalent to approximately 10 g of pure alcohol); tobacco smoking (past, never, current <15 cigarettes per day, current ⩾15 cigarettes per day); socioeconomic status (within-study quintiles of the 1991 Townsend deprivation index for the census enumeration district or output area containing the woman's home address at recruitment

Table 1 Number of women diagnosed with haematological neoplasms during follow-up: cross-classification by ICD-O-3 and ICD-10

Classification	ICD-O-3	ICD-10				
Term	All specified codes have 5th digit 3 (malignant behaviour)	HL C81	NHL C82-C85 C96	MM C88, C90	Leuk C91-C95	Oth D45-D47	Total
Lymphoid malignancies	*959–973, 976, 982–983, 9940, 9948*	*287*	*4226*	*1597*	*937*	*0*	*7047*
Hodgkin lymphoma	965–966	287	0	0	0	0	287
Mature B cell	967–969 except (9675), 973, 976, 9823, 9826, 9833, 9940						
Diffuse large B cell	9678, 9679, 9680, 9684	0	1151	1	0	0	1152
Follicular lymphoma	969 except 9699	0	1027	0	0	0	1027
Plasma cell neoplasms	973	0	0	1518	0	0	1518
CLL/SLL	9670, 9823	0	133	0	787	0	920
Other/unspec. mat. B cell	9671, 9673, 9687, 9689, 9699, 976, 9826, 9833, 9940	0	368	78	30	0	476
Mature T cell	970–971, 9827, 9831, 9834, 9948	0	194	0	3	0	197
Other/unspec. lymphoid	959, 9675, 972, 9820, 983 except (9831, 9833, 9834)	0	1353	0	117	0	1470
Myeloid malignancies	*974, 984–998 except (9940, 9948)*	*0*	*8*	*0*	*831*	*1233*	*2072*
Acute myeloid leukaemia	984–993 except (9860, 9863, 9875, 9876), 9984	0	0	0	614	3	617
Myeloprolif./dysplastic dis.	974, 9863, 9875, 9876, 9945, 9946, 995–998 except 9984	0	8	0	192	1230	1430
Other/unspec. myeloid	9860	0	0	0	25	0	25
Unspecified lineage	*980*	*0*	*0*	*0*	*43*	*0*	*43*
Not haematological cancer	*800, 975, any code with 5th digit not 3*	*0*	*12*	*0*	*0*	*243*	*255*
All haematological neoplasms		287	4246	1597	1811	1476	9417

Abbreviations: CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; HL = Hodgkin lymphoma; ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision; Leuk = leukaemia; MM = myeloma (multiple myeloma, plasma cell neoplasms and malignant immunoproliferative diseases); Myeloprolif./dysplastic dis. = myeloproliferative/myelodysplastic disease (including chronic myeloid leukaemia); NHL = non-Hodgkin lymphoma; Oth = other haematological neoplasms.

(Townsend, 1988)); body mass index (<25, 25–<30, ⩾30 kg m^{-2}); height (<160, 160–<165, ⩾165 cm). The questions relevant to smoking habits were 'About how many cigarettes do you smoke on average each day, now?' and 'Are you an ex-smoker?' (yes/no). Body mass index (Reeves *et al*, 2007) and height (Green *et al*, 2011) were known to be associated with risks of haematological malignancy in this cohort.

In turn, each of the two factors of interest (alcohol and smoking) was treated as the main explanatory variable, with all the other exposure measures acting as adjustment factors. Women with missing information for the explanatory variable were excluded from that analysis; those with missing information for an adjustment factor were included as a separate category of the adjustment factor. Trends were assessed by allocating a score to each category of the explanatory variable, and fitting log-linear models to the change in hazard ratio per unit increase in score. Current non-drinkers were excluded from the alcohol trend model, and ex-smokers from the smoking trend model, because reasons for abstention might include ill-health. As an approximate correction for regression dilution bias (Macmahon *et al*, 1990), each category of drinking and smoking was scored as the mean daily intake reported at re-survey approximately 3 years after recruitment among women in that category: drinks in units of approximately 10 g pure alcohol per day (0.26, 0.75, 1.63) and smoking in multiples of 10 cigarettes per day (0, 1.10, 2.00), scoring self-reported never-smokers at recruitment as zero. Heterogeneity of trends between diagnostic groups was assessed by a χ^2 contrast test (Smith-Warner *et al*, 2006).

RESULTS

Descriptive statistics

The number of women who were eligible for these analyses was 1 319 121, after excluding 45 035 with neoplasms diagnosed before recruitment. On average, women were aged 56.6 years at recruitment, and contributed 10.3 person-years to the analyses.

The number of women diagnosed with haematological malignancies during follow-up was 9162 according to the hierarchical classification based on ICD-O-3, and 7941 according to the simple ICD-10 grouping (Table 1); the main reason for the difference was that clinical behaviour for 1230 cases of myeloproliferative/myelodysplastic disease was treated as malignant in ICD-O-3 but uncertain or unknown in ICD-10. Of the 5093 mature B-cell cases, 2679 (53%) were coded in ICD-10 as NHL, 1597 (31%) as myeloma and 817 (16%) as leukaemia.

Information on alcohol consumption at recruitment was obtained from 1 308 786 women (99%), of whom 994 030 (76%) reported ⩾0.5 drinks per week (Table 2). Among drinkers at recruitment, the mean intake reported at re-survey was 5.6 drinks per week, a moderate level by national standards (Office for National Statistics, 2003). Of the 1 241 605 women (94%) who could be classified as never, current or past smokers at recruitment, 21% (255 148) were current smokers and 28% (352 493) were past smokers. The measure of socioeconomic status was available for 1 309 534 women (99%). Height was reported by 98% of women, and both height and weight (enabling calculation of body mass index) by 95%.

Socioeconomic status, body mass index, height and age varied with alcohol and tobacco intake (Table 2). The proportion of participants with relatively low socioeconomic status was smaller for drinkers than non-drinkers, and greater for current smokers than never-smokers. On average, drinkers were slightly leaner, taller and younger than non-drinkers, and current smokers were slightly leaner, shorter and younger than never-smokers.

Alcohol

Using the ICD-O-3 classification, and taking occasional drinkers (0.5–<3 drinks per week) as the reference group, the estimated relative risk of haematological malignancy was 0.90 (95% confidence interval 0.85–0.95) for ⩾7 drinks per week (Table 3). Among drinkers, there was a statistically significant decreasing trend with increasing alcohol intake ($P_{trend}<0.001$; Table 3); the estimated relative risk for an increase of 10 g per day was 0.92 (0.89–0.96) (Figure 1). In more detail, there was a statistically significant decreasing trend for the lymphoid subgroup ($P_{trend}<0.001$) and no apparent trend for the myeloid subgroup, although the test for heterogeneity between lymphoid and myeloid trends was not statistically significant ($P_{het}=0.09$; Figure 1). Among specified subtypes of lymphoid malignancy, there was a statistically significant trend only for mature B-cell disease ($P_{trend}<0.001$), within which there were similar significant decreasing trends for diffuse large B-cell lymphoma, follicular lymphoma and plasma cell neoplasms, but not CLL/SLL; the test for heterogeneity was not statistically significant ($P_{het}=0.1$). For Hodgkin lymphoma, the risk was significantly higher in non-drinkers than in occasional drinkers (relative risk 1.70

Table 2 Characteristics of the women included in these analyses

	Alcohol		Smoking			
	Non-drinkers	Drinkers[a]	Past	Never	Current	All women
Number of women	314 756	994 030	352 493	633 964	255 148	1 319 121
Characteristics at recruitment						
% Drinkers[a]	–	–	81	76	70	76
% Current smokers	26	19	–	–	–	21
% Lower socioeconomic status[b]	45	30	33	27	48	33
Body mass index (kg m^{-2}): mean (s.d.)	27.2 (5.4)	25.9 (4.4)	26.7 (4.8)	26.2 (4.6)	25.6 (4.5)	26.2 (4.7)
Height (cm): mean (s.d.)	161.2 (6.9)	162.2 (6.7)	162.3 (6.7)	162.0 (6.7)	161.5 (6.8)	162.0 (6.7)
Age (years): mean (s.d.)	57.3 (4.9)	56.4 (4.8)	56.8 (4.9)	56.8 (4.9)	55.8 (4.5)	56.6 (4.9)
Follow-up						
Woman-years observed (1000s)	3218.0	10270.0	3622.3	6608.7	2562.9	13593.7
Number of incident cases: ICD-O–3	2469	6617	2532	4312	1797	9162
Number of incident cases: ICD-10	2152	5726	2191	3808	1487	7941

Abbreviations: ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision. [a]⩾0.5 drinks per week, in units equivalent to 10 g pure alcohol. [b]Highest within-study tertile of the 1991 Townsend deprivation index for the census enumeration district or output area of the home address.

Epidemiology

Table 3 Association of alcohol drinking with risk of haematological malignancies

	All women	Non-drinkers			0.5–<3 drinks per week		3–<7 drinks per week			⩾7 drinks per week			Trend among drinkers	
Alcohol[a]	**Cases**	**Cases**	**RR**	**95% CI**	**Cases**	**Ref**	**Cases**	**RR**	**95% CI**	**Cases**	**RR**	**95% CI**	**Cases**	P_{trend}
All haematological malignancies														
ICD-O-3 classification	9086	2469	1.05	0.99, 1.10	3364	1.00	1384	0.91	0.85, 0.96	1869	0.90	0.85, 0.95	6617	<0.001
ICD-10 classification	7878	2152	1.06	1.00, 1.12	2924	1.00	1201	0.90	0.84, 0.96	1601	0.89	0.83, 0.94	5726	<0.001
Subgroups of ICD-O-3 classification														
ICD-O-3 haematological malignancies[b]														
Lymphoid	6990	1912	1.06	1.00, 1.12	2602	1.00	1067	0.90	0.84, 0.97	1409	0.88	0.82, 0.94	5078	<0.001
Myeloid	2053	546	1.01	0.91, 1.14	745	1.00	311	0.93	0.81, 1.06	451	0.99	0.88, 1.11	1507	0.8
ICD-O-3 lymphoid malignancies														
Hodgkin lymphoma	281	108	1.70	1.27, 2.26	85	1.00	31	0.79	0.53, 1.20	57	1.06	0.76, 1.49	173	0.6
Mature B cell	5056	1344	1.01	0.94, 1.08	1925	1.00	763	0.87	0.80, 0.95	1024	0.87	0.81, 0.94	3712	<0.001
Mature T cell	196	40	0.78	0.53, 1.15	71	1.00	35	1.04	0.70, 1.57	50	1.05	0.73, 1.52	156	0.7
Other/unspecified lymphoid	1457	420	1.18	1.03, 1.34	521	1.00	238	1.00	0.85, 1.16	278	0.84	0.73, 0.98	1037	0.02
ICD-O-3 mature B-cell malignancies														
Diffuse large B-cell lymphoma	1145	331	1.07	0.93, 1.24	443	1.00	153	0.77	0.64, 0.92	218	0.82	0.69, 0.96	814	0.01
Follicular lymphoma	1021	255	0.96	0.82, 1.13	389	1.00	171	0.94	0.78, 1.13	206	0.82	0.69, 0.98	766	0.02
Plasma cell neoplasms	1506	406	1.00	0.88, 1.14	587	1.00	223	0.84	0.72, 0.98	290	0.82	0.71, 0.95	1100	0.006
CLL/SLL	911	245	1.10	0.93, 1.30	327	1.00	148	1.00	0.82, 1.22	191	0.97	0.81, 1.16	666	0.6
Other/unspecified mature B-cell	473	107	0.83	0.65, 1.06	179	1.00	68	0.84	0.64, 1.12	119	1.11	0.88, 1.40	366	0.4
ICD-O-3 myeloid malignancies[c]														
Acute myeloid leukaemia	613	165	0.99	0.81, 1.21	233	1.00	89	0.84	0.66, 1.08	126	0.89	0.71, 1.11	448	0.3
Myeloproliferative/myelodysplastic disease	1415	372	1.02	0.89, 1.17	503	1.00	220	0.98	0.83, 1.15	320	1.03	0.89, 1.19	1043	0.7
Subgroups of ICD-10 classification														
ICD-10 haematological malignancies														
Hodgkin lymphoma	281	108	1.70	1.27, 2.26	85	1.00	31	0.79	0.53, 1.20	57	1.06	0.76, 1.49	173	0.6
Non-Hodgkin lymphoma	4216	1132	1.02	0.95, 1.11	1593	1.00	652	0.89	0.82, 0.98	839	0.84	0.77, 0.92	3084	<0.001
Myeloma	1584	422	0.99	0.88, 1.13	616	1.00	231	0.83	0.72, 0.97	315	0.85	0.74, 0.98	1162	0.02
Leukaemia	1797	490	1.12	0.99, 1.26	630	1.00	287	1.01	0.87, 1.16	390	1.01	0.89, 1.15	1307	0.9

Abbreviations: Cases = number of incident cases; CI = confidence interval; CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision; P_{trend} = result of test for categorical trend per 10 g per day; Ref = referent; RR = relative risk. Myeloproliferative/myelodysplastic disease includes chronic myeloid leukaemia. [a]Reported alcohol consumption at recruitment, in units of approximately 10 g pure alcohol. RR estimates are adjusted for body mass index, height, smoking and socioeconomic status, and stratified by cancer registry region. Follow-up starts at recruitment. [b]Excludes 43 unspecified cases. [c]Excludes 25 other/unspecified cases.

(1.27–2.26); Table 3); a similar result was obtained when the first 3 years of follow-up were excluded (data not shown).

Using the ICD-10 classification, there were significant decreasing trends for NHL and myeloma separately, and little evidence of association for leukaemia or Hodgkin lymphoma, although the test for heterogeneity of trends between diagnostic groups was not statistically significant ($P_{het} = 0.06$) (Figure 1).

Excluding the first 3 years of follow-up made little difference to the trend estimates, but changed results from non-significant to significant for the tests of heterogeneity between lymphoid and myeloid malignancies ($P_{het} = 0.01$) and between mature B-cell subtypes ($P_{het} = 0.01$) (Table 5).

Smoking

Using the ICD-O-3 classification, and taking women who had never smoked as the reference group, the estimated relative risk of haematological malignancy for frequent smokers (⩾15 cigarettes per day) was 1.30 (1.20–1.40) (Table 4). There were statistically significant trends in both lymphoid (1.07 (1.03–1.12)) and myeloid (1.33 (1.24–1.42)) disease, with strong evidence of heterogeneity between these groups ($P_{het} < 0.001$) (Figure 1). There was also strong evidence of heterogeneity within lymphoid disease ($P_{het} < 0.001$), with statistically significant increasing trends for Hodgkin lymphoma (1.45 (1.22–1.72)) and mature T-cell malignancies (1.38 (1.10–1.73)) but not for mature B-cell malignancies. There was heterogeneity between subgroups of myeloid malignancy ($P_{het} = 0.001$), with a statistically significant trend for myeloproliferative/myelodysplastic disease (1.42 (1.31–1.55)) but not for acute myeloid leukaemia (1.10 (0.96–1.26)). Comparing frequent smokers with never-smokers, the estimated relative risks of Hodgkin lymphoma, mature T-cell malignancies and myeloproliferative/myelodysplastic disease were each approximately doubled (2.19 (1.56–3.09), 2.09 (1.33–3.26) and 1.98 (1.67–2.35), respectively) (Table 4).

Using the ICD-10 classification, there was strong evidence of heterogeneity between subgroups ($P_{het} < 0.001$), with statistically significant increasing trends for Hodgkin lymphoma and NHL but not for myeloma or leukaemia (Figure 1).

Excluding the first 3 years of follow-up made little difference to the trend estimates, and did not affect the conclusions of the tests for heterogeneity (Table 5).

DISCUSSION

Alcohol

In this cohort, most women who drank alcohol were moderate drinkers. Among the drinkers, greater alcohol intake was associated with significantly reduced risks of diffuse large B-cell lymphoma, follicular lymphoma and plasma cell neoplasms,

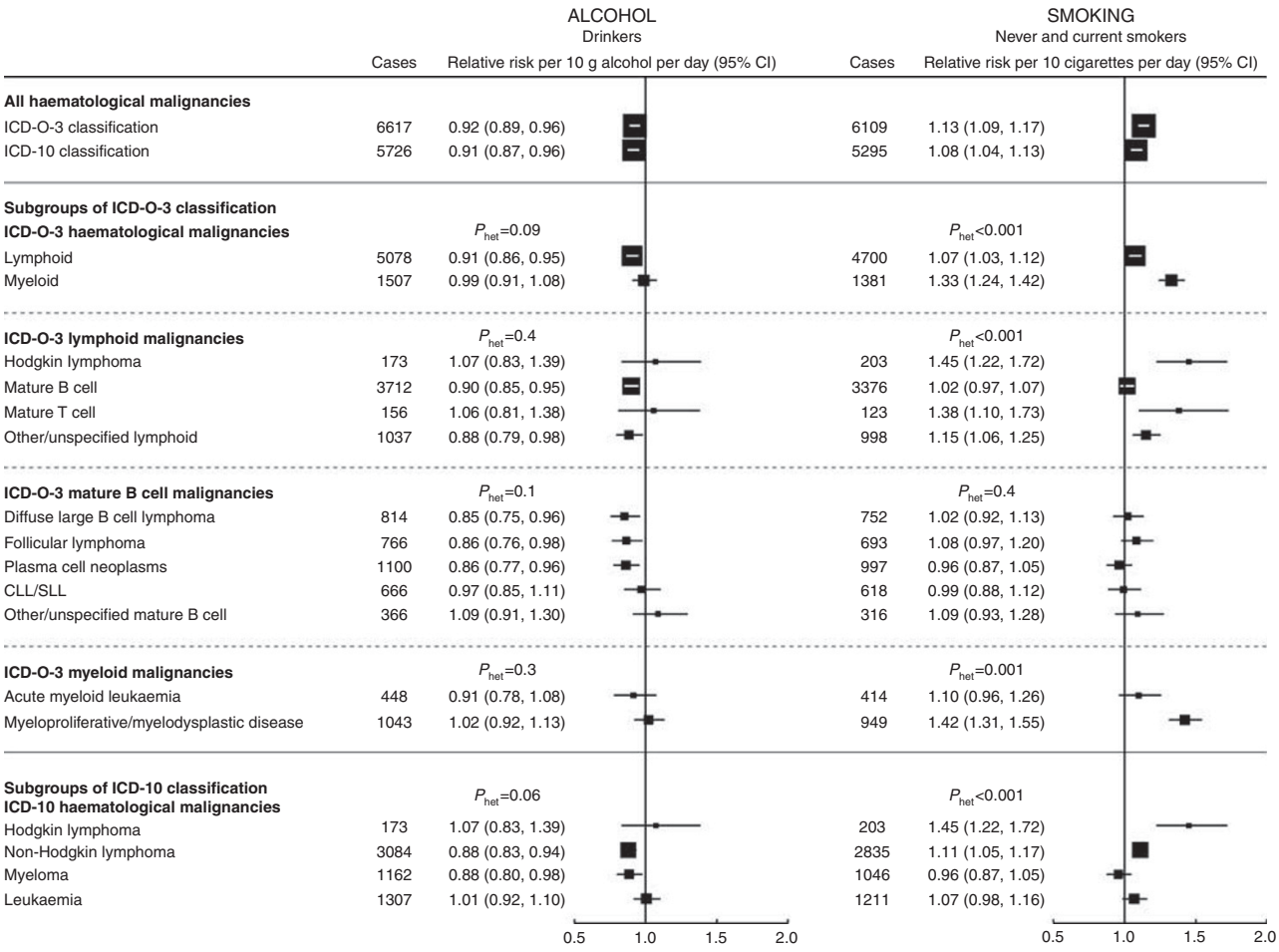

Figure 1 Association of alcohol drinking and tobacco smoking with risk of haematological malignancies. Million Women Study, United Kingdom 1996–2009. Relative risks are adjusted for body mass index, height and socioeconomic status (and for alcohol consumption and smoking where not the factor of interest) and stratified by cancer registry region. Follow-up starts at recruitment. Abbreviations: ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision; CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; Cases = number of incident cases; CI = confidence interval; P_{het} = result of χ^2 contrast test for heterogeneity of trends between subtypes. Myeloproliferative/myelodysplastic disease includes chronic myeloid leukaemia.

lymphoid and mature B-cell disease overall, but not other specified lymphoid subtypes or myeloid malignancies. Although there was no statistically significant heterogeneity between subtypes in the main analysis, significant heterogeneity between lymphoid and myeloid malignancies, and between mature B-cell subtypes, emerged when the first 3 years of follow-up were excluded. Thus some of the apparent lack of heterogeneity might be due to reverse causation. Using the ICD-10 classification, there were significant inverse associations with risks of NHL and myeloma, but not leukaemia or Hodgkin lymphoma.

Previous cohort studies have reported a statistically significant decreasing trend with greater alcohol intake among drinkers for diffuse large B-cell lymphoma (Lim *et al*, 2007; Troy *et al*, 2010), and no significant trend for Hodgkin lymphoma, follicular lymphoma, plasma cell neoplasms or any other non-Hodgkin subtype examined (Lim *et al*, 2007; Kanda *et al*, 2010; Troy *et al*, 2010), although one study found a near-significant decreasing trend for plasma cell neoplasms (Troy *et al*, 2010); comparable results from case–control studies were generally consistent with these findings (Morton *et al*, 2005b; Besson *et al*, 2006a, 2006b). In studies that estimated risks in drinkers relative to non-drinkers, similar results were obtained for lymphoid subtypes (Kanda *et al*, 2009; Chang *et al*, 2010) except for one observation of increased CLL/SLL risk in drinkers (Chang *et al*, 2010), and there was no trend in risk of acute myeloid leukaemia (Ma *et al*, 2010) or myelodysplastic syndromes (Ma *et al*, 2009). A multicentre case–control study reported lower risk of Hodgkin lymphoma in ever-regular drinkers compared with never-regular drinkers, based on 222 cases (Besson *et al*, 2006a). In our study, with 281 cases in total, the risk of Hodgkin lymphoma was estimated to be lower among current occasional drinkers (at recruitment) than in current non-drinkers, but there was no significant trend in risk with increasing intake; excluding the first 3 years of follow-up did not change either of these findings.

Using a similar ICD-10 classification, an earlier analysis of data from the Million Women Study with 7.2 years of follow-up on average (Allen *et al*, 2009) reported a statistically significant inverse association in drinkers for NHL, but not for myeloma or leukaemia; the significant association with myeloma seen in the analysis reported here probably reflects the larger number of cases accumulated over a longer follow-up period. These results are broadly consistent with comparable findings from other cohort (Chiu *et al*, 1999; Klatsky *et al*, 2009) and case–control (Gorini *et al*, 2007a,b) studies.

Our findings strengthen existing evidence for an association of greater alcohol intake with reduced risk of diffuse large B-cell lymphoma among drinkers, and demonstrate similar associations

Table 4 Association of tobacco smoking with risk of haematological malignancies

	All women	Ex-smokers			Never-smokers		<15 cigarettes per day			≥15 cigarettes per day			Trend among never- or current smokers	
Smoking[a]	**Cases**	**Cases**	**RR**	**95% CI**	**Cases**	**Ref**	**Cases**	**RR**	**95% CI**	**Cases**	**RR**	**95% CI**	**Cases**	P_{trend}
All haematological malignancies														
ICD-O-3 classification	8641	2532	1.09	1.04, 1.15	4312	1.00	896	1.13	1.05, 1.22	901	1.30	1.20, 1.40	6109	<0.001
ICD-10 classification	7486	2191	1.07	1.01, 1.13	3808	1.00	747	1.06	0.98, 1.15	740	1.19	1.10, 1.29	5295	<0.001
Subgroups of ICD-O-3 classification														
ICD-O-3 haematological malignancies[b]														
Lymphoid	6638	1938	1.06	1.01, 1.13	3394	1.00	653	1.04	0.96, 1.14	653	1.18	1.09, 1.29	4700	<0.001
Myeloid	1963	582	1.19	1.07, 1.32	902	1.00	238	1.46	1.26, 1.69	241	1.69	1.46, 1.96	1381	<0.001
ICD-O-3 lymphoid malignancies														
Hodgkin lymphoma	263	60	0.90	0.66, 1.23	122	1.00	31	1.30	0.87, 1.94	50	2.19	1.56, 3.09	203	<0.001
Mature B cell	4803	1427	1.07	1.00, 1.14	2498	1.00	452	0.98	0.89, 1.09	426	1.06	0.96, 1.18	3376	0.5
Mature T cell	184	61	1.38	0.98, 1.93	78	1.00	17	1.15	0.68, 1.95	28	2.09	1.33, 3.26	123	0.006
Other/unspecified lymphoid	1388	390	1.05	0.93, 1.19	696	1.00	153	1.20	1.01, 1.44	149	1.31	1.10, 1.58	998	0.001
ICD-O-3 mature B-cell malignancies														
Diffuse large B-cell lymphoma	1084	332	1.11	0.96, 1.27	560	1.00	99	0.97	0.78, 1.21	93	1.04	0.83, 1.30	752	0.7
Follicular lymphoma	976	283	1.07	0.92, 1.24	497	1.00	94	1.00	0.80, 1.25	102	1.22	0.98, 1.52	693	0.1
Plasma cell neoplasms	1425	428	1.08	0.96, 1.22	750	1.00	140	1.03	0.86, 1.24	107	0.91	0.74, 1.12	997	0.4
CLL/SLL	870	252	1.02	0.87, 1.19	461	1.00	84	1.00	0.79, 1.26	73	1.01	0.78, 1.29	618	0.9
Other/unspecified mature B cell	448	132	1.02	0.82, 1.27	230	1.00	35	0.79	0.55, 1.13	51	1.32	0.96, 1.80	316	0.3
ICD-O-3 myeloid malignancies[c]														
Acute myeloid leukaemia	586	172	1.08	0.89, 1.31	291	1.00	70	1.29	0.99, 1.68	53	1.08	0.80, 1.46	414	0.2
Myeloproliferative/myelodysplastic disease	1353	404	1.24	1.09, 1.41	602	1.00	163	1.52	1.27, 1.81	184	1.98	1.67, 2.35	949	<0.001
Subgroups of ICD-10 classification														
ICD-10 haematological malignancies														
Hodgkin lymphoma	263	60	0.90	0.66, 1.23	122	1.00	31	1.30	0.87, 1.94	50	2.19	1.56, 3.09	203	<0.001
Non-Hodgkin lymphoma	4011	1176	1.08	1.01, 1.16	2024	1.00	392	1.05	0.94, 1.17	419	1.26	1.14, 1.41	2835	<0.001
Myeloma	1496	450	1.08	0.96, 1.21	789	1.00	144	1.01	0.84, 1.21	113	0.92	0.75, 1.12	1046	0.3
Leukaemia	1716	505	1.06	0.95, 1.19	873	1.00	180	1.12	0.95, 1.32	158	1.11	0.93, 1.32	1211	0.1

Abbreviations: Cases = number of incident cases; CI = confidence interval; CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision; P_{trend} = result of test for categorical trend per 10 cigarettes per day; Ref = referent; RR = relative risk. Myeloproliferative/myelodysplastic disease includes chronic myeloid leukaemia. [a]Reported smoking habit at recruitment. RR estimates are adjusted for body mass index, height, alcohol consumption and socioeconomic status, and stratified by cancer registry region. Follow-up starts at recruitment. [b]Excludes 40 unspecified cases. [c]Excludes 24 other/unspecified cases.

for two further subtypes of lymphoid disease: follicular lymphoma and plasma cell neoplasms. Further work is needed to elucidate potential biological mechanisms; for example, the role of chronic inflammation (Smedby *et al*, 2008; Chang *et al*, 2010).

Smoking

We found statistically significant increasing trends in risk of Hodgkin lymphoma, mature T-cell malignancies and myeloproliferative/myelodysplastic disease with increasing current cigarette consumption relative to never-smokers (approximately double risk for women who reported smoking ⩾15 cigarettes per day), but no significant trends for mature B-cell malignancy or any of its subtypes. Tests for heterogeneity between diagnostic subgroups were highly significant. The trend estimate for acute myeloid leukaemia, although above unity, was not statistically significant. Using the ICD-10 classification, there were significant increasing trends for Hodgkin lymphoma and NHL but not for myeloma or leukaemia. Excluding the first 3 years of follow-up did not affect these conclusions.

Recent cohort studies, also comparing current smokers with never-smokers, have reported statistically significant associations for Hodgkin lymphoma (Lim *et al*, 2007; Nieters *et al*, 2008), myelodysplastic syndromes (Ma *et al*, 2009) and acute myeloid leukaemia (Fernberg *et al*, 2007; Ma *et al*, 2010), but no association for T-cell malignancies or any other non-Hodgkin subtype examined (Lim *et al*, 2007; Nieters *et al*, 2008; Troy *et al*, 2010; Lu *et al*, 2011). Results from case–control studies were similar: comparing current with never-smokers there were significant positive associations for Hodgkin lymphoma (Besson *et al*, 2006a) and acute myeloid leukaemia (Kasim *et al*, 2005), but no association for T-cell malignancies or any other non-Hodgkin subtype examined (Morton *et al*, 2005a; Besson *et al*, 2006b) except for one positive association for follicular lymphoma (Morton *et al*, 2005a); comparing ever- with never-smokers there were significant positive associations for myelodysplastic syndromes (Nisse *et al*, 2001; Strom *et al*, 2005). Trend analyses including former smokers suggested (in a cohort study) an inverse association with follicular lymphoma (Lim *et al*, 2007) and (in a case–control study) a positive association with Hodgkin lymphoma (Kanda *et al*, 2009).

Our findings support existing evidence for associations of smoking with Hodgkin lymphoma and myelodysplastic syndromes (a subset of myeloproliferative/myelodysplastic disease), and demonstrate a similar association for mature T-cell malignancies. Tobacco smoke contains benzene and other known leukaemogens, and it has been concluded that there is 'sufficient evidence in humans' that

Table 5 Association of alcohol drinking and tobacco smoking with risk of haematological malignancies: trend analysis excluding the first 3 years of follow-up

	Alcohol				Smoking			
	Trend among drinkers[a]				Trend among never- or current smokers[b]			
Excluding first 3 years of follow-up	**Cases**	**RR**	**95% CI**	P_{trend}	**Cases**	**RR**	**95% CI**	P_{trend}
All haematological malignancies								
ICD-O-3 classification	5235	0.94	0.89, 0.98	0.006	4825	1.14	1.09, 1.18	<0.001
ICD-10 classification	4528	0.92	0.87, 0.97	0.001	4170	1.07	1.03, 1.12	0.001
Subgroups of ICD-O-3 classification								
ICD-O-3 haematological malignancies[c]			$P_{het}=0.01$				$P_{het}<0.001$	
Lymphoid	4031	0.91	0.86, 0.96	<0.001	3721	1.07	1.02, 1.12	0.006
Myeloid	1177	1.04	0.95, 1.15	0.4	1082	1.36	1.26, 1.47	<0.001
ICD-O-3 lymphoid malignancies			$P_{het}=0.2$				$P_{het}<0.001$	
Hodgkin lymphoma	129	1.07	0.79, 1.44	0.7	152	1.57	1.29, 1.90	<0.001
Mature B cell	3045	0.90	0.84, 0.95	<0.001	2774	1.00	0.95, 1.06	0.9
Mature T cell	118	1.19	0.88, 1.61	0.3	88	1.34	1.02, 1.77	0.03
Other/unspecified lymphoid	739	0.88	0.78, 1.00	0.05	707	1.17	1.06, 1.30	0.002
ICD-O-3 mature B-cell malignancies			$P_{het}=0.01$				$P_{het}=0.2$	
Diffuse large B-cell lymphoma	699	0.83	0.72, 0.95	0.005	650	1.03	0.92, 1.16	0.6
Follicular lymphoma	590	0.88	0.76, 1.02	0.08	542	1.08	0.96, 1.22	0.2
Plasma cell neoplasms	901	0.83	0.74, 0.94	0.002	820	0.92	0.83, 1.02	0.1
CLL/SLL	540	0.97	0.83, 1.12	0.6	494	0.96	0.84, 1.10	0.6
Other/unspecified mature B cell	315	1.19	0.99, 1.43	0.07	268	1.10	0.93, 1.30	0.3
ICD-O-3 myeloid malignancies[c]			$P_{het}=0.4$				$P_{het}<0.001$	
Acute myeloid leukaemia	343	0.98	0.81, 1.17	0.8	311	1.07	0.91, 1.26	0.4
Myeloproliferative/myelodysplastic disease	821	1.07	0.95, 1.21	0.2	759	1.48	1.35, 1.62	<0.001
Subgroups of ICD-10 classification								
ICD-10 haematological malignancies			$P_{het}=0.06$				$P_{het}<0.001$	
Hodgkin lymphoma	129	1.07	0.79, 1.44	0.7	152	1.57	1.29, 1.90	<0.001
Non-Hodgkin lymphoma	2435	0.89	0.83, 0.96	0.001	2227	1.12	1.05, 1.18	<0.001
Myeloma	947	0.86	0.76, 0.96	0.008	856	0.92	0.83, 1.02	0.1
Leukaemia	1017	1.03	0.93, 1.14	0.6	935	1.03	0.94, 1.13	0.5

Abbreviations: Cases, number of incident cases; CI, confidence interval; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; ICD-O-3, International Classification of Diseases for Oncology 3rd edition; ICD-10, International Classification of Diseases 10th revision; P_{het} result of χ^2 contrast test for heterogeneity of trends between subtypes; Ref, referent; $P_{trend,}$ result of test for categorical trend; RR, relative risk. Myeloproliferative/myelodysplastic disease includes chronic myeloid leukaemia. [a]Relative risk per 10 g per day, adjusted for body mass index, height, smoking and socioeconomic status, and stratified by cancer registry region. [b]Relative risk per 10 cigarettes per day, adjusted for body mass index, height, alcohol consumption and socioeconomic status, and stratified by cancer registry region. [c]Excludes other/unspecified cases.

tobacco smoking causes myeloid (but not lymphoid) leukaemia (IARC, 2002). Hence, smoking is a plausible cause of myeloproliferative/myelodysplastic disease, which includes chronic myeloid leukaemia and various myeloid pre-leukaemic conditions. An association with T-cell disease has not been reported before, to our knowledge, perhaps because this is a relatively rare diagnostic group. It has been suggested that smoking might impair the T-cell-mediated immune response to Epstein–Barr virus infection, a putative causal factor for Hodgkin lymphoma (Nieters *et al*, 2008), and it is tempting to speculate that such a process might also promote T-cell malignancies.

Strengths and limitations

This very large prospective study clarifies and extends existing evidence for associations of subtypes of haematological malignancy with alcohol and tobacco consumption, using two different current classification systems. Exposures were reported by the study participants at recruitment, and follow-up for death, emigration and cancer registration was virtually complete. Estimates were mutually adjusted for alcohol and smoking, socioeconomic status, body mass index and height. Reverse causation is an unlikely explanation for the associations seen, as excluding the first 3 years of follow-up did not qualitatively change the results.

Although the analysis was stratified by cancer registry region of residence at recruitment, variation in diagnostic and coding practice remains a possible source of bias. The registries adopted ICD-O-3 during the study period, at times that differed between regions, and previous ascertainment of myeloproliferative/myelodysplastic disease is likely to have been incomplete (Office for National Statistics, 2010). Subclassification of lymphoma may sometimes have been inaccurate (Clarke *et al*, 2004, 2006) and was often imprecise. Conceivably, time to diagnosis might be associated with the factors of interest: for example, causes of mediastinal symptoms of Hodgkin lymphoma might perhaps be investigated more rapidly in smokers because of the well-known risk of lung disease in smokers. However, the strong and highly significant associations reported are unlikely to be due to coding problems, or to chance.

CONCLUSIONS

Relative risks associated with alcohol and tobacco consumption among middle-aged women in the United Kingdom were estimated for subtypes of haematological malignancy. Among predominantly moderate drinkers, greater alcohol intake was associated with reduced risk of lymphoid malignancies: in particular, diffuse large B-cell lymphoma, consistent with previous reports, and follicular lymphoma and plasma cell neoplasms (not previously reported, to our knowledge). Cigarette smoking was associated with increased risk of Hodgkin lymphoma, consistent with previous reports,

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mature T-cell malignancies (not previously reported, to our knowledge) and myeloproliferative/myelodysplastic disease (previously reported for myelodysplastic syndromes, but not for the grouping used here).

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