Body size in relation to incidence of subtypes of haematological malignancy in the prospective Million Women Study

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Background: Greater adiposity and height have been associated with increased risk of haematological malignancies. Associations for disease subtypes are uncertain.

Methods: A cohort of 1.3 million middle-aged UK women was recruited in 1996–2001 and followed for 10 years on average. Potential risk factors were assessed by questionnaire. Death, emigration, and incident cancer were ascertained by linkage to national registers. Adjusted relative risks were estimated by Cox regression.

Results: During follow-up, 9162 participants were diagnosed with lymphatic or haematopoietic cancers. Each $10 \, kg \, m^{-2}$ increase in body mass index was associated with relative risk of 1.20 (95% confidence interval: 1.13–1.28) for lymphoid and 1.37 (1.22–1.53) for myeloid malignancy ($P = 0.06$ for heterogeneity); similarly, Hodgkin lymphoma 1.64 (1.21–2.21), diffuse large B-cell lymphoma 1.36 (1.17–1.58), plasma cell neoplasms 1.21 (1.06–1.39), acute myeloid leukaemia 1.47 (1.19–1.81), and myeloproliferative/myelodysplastic syndromes 1.32 (1.15–1.52). Each 10 cm increase in height was associated with relative risk of 1.21 (1.16–1.27) for lymphoid and 1.11 (1.02–1.21) for myeloid malignancy ($P = 0.07$ for heterogeneity); similarly, mature T-cell malignancies 1.36 (1.03–1.79), diffuse large B-cell lymphoma 1.28 (1.14–1.43), follicular lymphoma 1.28 (1.13–1.44), plasma cell neoplasms 1.12 (1.01–1.24), chronic lymphocytic leukaemia/small lymphocytic lymphoma 1.23 (1.08–1.40), and acute myeloid leukaemia 1.22 (1.04–1.42). There was no significant heterogeneity between subtypes.

Conclusion: In middle-aged women, greater body mass index and height were associated with modestly increased risks of many subtypes of haematological malignancy.

Although previous studies have reported associations of haematological cancer with adiposity (Renehan *et al*, 2008) and height (Gunnell *et al*, 2001; Engeland *et al*, 2007; Green *et al*, 2011), associations with specific disease subtypes are not yet well-established. Traditionally, epidemiological studies have used broad categories defined mainly by clinical features: Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), leukaemia, and multiple myeloma. A new classification, introduced by the World Health Organisation (WHO) in 2001, divides haematological malignancies into lymphoid and myeloid neoplasms, and then more specifically according to cell lineage, so that each disease entity is defined by

morphological, immunophenotypic, and genetic features (IARC, 2008). In this report, we describe associations of adiposity and height with risks of subtypes of haematological malignancy in women, using both traditional and updated disease classifications.

MATERIALS AND METHODS

Between 1996 and 2001, 1.3 million middle-aged women were recruited to the Million Women Study through the United

Kingdom national breast cancer screening programme. Ethics approval for the study was given by the Multi-Centre Research Ethics Committee for Anglia and Oxford, and all participants provided written consent. Details of the study design have been published elsewhere (Reeves *et al*, 2007). Briefly, participants completed a questionnaire regarding personal, lifestyle, and health factors (www.millionwomenstudy.org), and are followed up for cancer diagnosis, emigration, and death, by linkage to National Health Service Central Registers. Each cancer registration is coded according to the International Classification of Disease 10th revision (ICD-10), with a morphology code from either the 2nd (ICD-O-2) or the 3rd edition (ICD-O-3) of the International Classification of Diseases for Oncology; for this study, ICD-O-2 morphology codes were converted to ICD-O-3 (SEER, 2001). All participants were asked to report their current height and weight at recruitment. In addition, a sample of study participants who responded to a study questionnaire during 2006–2007 were asked in 2006–2009 to have their height and weight measured by their family doctor (Armstrong *et al*, 2011; Green *et al*, 2011).

Registrations with the following ICD-10 topography codes were examined: C81-96 (malignant neoplasms of lymphoid, haemato-poietic, and related tissue), D45 (polycythaemia vera), D46 (myelodysplastic syndromes), and D47 (other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic, and related tissue). Those with ICD-O-3 code in the range M-959 to M-998 and behaviour code 3 were eligible for the study. Histiocytic and dendritic neoplasms (M-975) were excluded.

Haematological cancer diagnoses were classified in two ways. First, to allow comparison with older studies, we used broad disease categories based on ICD-10: Hodgkin lymphoma (C81), NHL (C82–85, C96), leukaemia (C91–95), and 'myeloma' (multiple myeloma and (other) malignant plasma cell neoplasms (C90) combined with malignant immunoproliferative diseases (C88)) (Ferlay *et al*, 2010). Secondly, we used a hierarchical classification adapted from the InterLymph and HAEMACARE projects, based on ICD-O-3 (Table 1) (Sant *et al*, 2010; Turner *et al*, 2010).

Lymphoid subtypes include plasma cell neoplasms (predominantly multiple myeloma), and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL, combining subgroups of ICD-10 categories 'leukaemia' and 'NHL' that are now considered to be the same disease). Myeloid cases are grouped as acute myeloid leukaemia and myeloproliferative/myelodysplastic neoplasms (myeloproliferative neoplasms and myelodysplastic syndromes, including chronic myeloid leukaemia); case numbers were insufficient for further subdivision. Details of the correspondence between the two classifications for haematological neoplasms in this cohort are reported elsewhere (Kroll *et al*, 2012).

Adiposity was assessed using body mass index (weight in kilograms divided by the square of height in metres). Following the WHO criteria, 'overweight' was defined as $25–29.9 \, kg \, m^{-2}$ and 'obese' as $30 \, kg \, m^{-2}$ or more (WHO, 1995). We excluded recruits who reported that they had been previously diagnosed with cancer, defined as *in situ* breast carcinoma or any malignancy except non-melanoma skin cancer (ICD-10 D05 or any ICD-10 C code except C44). For the remaining women, observation extended from the date of recruitment to the date of the earliest of four possible outcomes: cancer diagnosis, emigration, death, or end of follow-up. Follow-up ended on 31 December 2008 for Scotland and the North West (Merseyside and Cheshire) cancer registry region, and 31 December 2009 elsewhere.

Adjusted relative risks (RRs) of haematological cancer were estimated by Cox regression, using attained age as the underlying time variable, with stratification by cancer registry region of residence at recruitment. Exposure categories were derived from information reported on the recruitment questionnaire: body mass index, height, socioeconomic status (quintiles of the Townsend deprivation index of residence at recruitment), alcohol consumption (none, 0.5–<3, 3–<7, and ≥7 units per week), and smoking status (never, past, and current). Body mass index and height were treated in turn as the main explanatory variable, adjusting for all the other factors. Trends were assessed by allocating a score to each category of the explanatory variable (the mean measurement among sampled participants within the

Table 1. Number of women diagnosed with haematological malignancy during follow-up: ICD-O-3 classification (Million Women Study, United Kingdom 1996–2009)

Subgroup	Subtype	ICD-O-3 morphology (all with behaviour code 3, malignant)	Cases
Lymphoid malignancies			
Hodgkin lymphoma	Hodgkin lymphoma	9650–9667	287
Mature B cell	Diffuse large B cell	9678–9684	1152
	Follicular lymphoma	9690–9698	1027
	Plasma cell neoplasms	9731–9734	1518
	CLL/SLL	9670, 9823	920
	Other	9671, 9673, 9687, 9689, 9699, 9760–9762, 9764, 9826, 9833, 9940	476
Mature T cell	Mature T cell	9700–9719, 9827, 9831, 9834, 9948	197
Other/unspecified	Precursor cell	9727–9729, 9835–9837	74
	Unspecified	9590, 9591, 9596, 9675, 9820, 9832	1396
Myeloid malignancies			
Acute myeloid leukaemia	Acute myeloid leukaemia	9840, 9861, 9866–9874, 9891–9910, 9930, 9931, 9984	617
Myeloproliferative/dysplastic[a]	Myeloproliferative/dysplastic	9740–9742, 9863, 9875, 9876, 9945, 9946, 9950, 9960–9964, 9980–9983, 9985–9989	1430
Unspecified	Unspecified	9860	25
Unspecified lineage			
Unspecified	Unspecified	9800, 9801, 9805	43
Total			9162

Abbreviations: CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; ICD-O-3 = International Classification of Diseases for Oncology 3rd edition.
Excludes women with previous cancer. Includes women with missing data on body mass index and height. Excludes histiocytic/dendritic neoplasms (9750–9758).
[a]Myeloproliferative/myelodysplastic neoplasms include chronic myeloid leukaemia.

category), and fitting log-linear models to the change in hazard ratio per unit increase in score. Heterogeneity of trends between diagnostic groups was assessed by a χ^2 contrast test (Smith-Warner et al, 2006). The proportional hazards assumption was examined using Schoenfeld residuals, and found acceptable. To investigate the possibility that associations might be influenced by changes in body size caused by subclinical disease (reverse causation), all analyses were repeated excluding the first 3 years of follow-up. All statistical tests were two-sided and used the 5% significance level.

RESULTS

Descriptive statistics. Of the 1 364 156 women potentially eligible for this analysis, we excluded 45 035 who reported prior cancer at recruitment. Of the remaining women, we excluded 21 499 with missing height data, leaving 1 297 622 for the height analyses, and a further 47 725 with missing weight data, leaving 1 249 897 for the body mass index analyses. At recruitment, 95% were aged 50–65 years. The mean age at recruitment was 56.6 years, and the mean follow-up period was 10.3 years. Some characteristics of the cohort are summarised in Table 2 for each category of body mass index and height. Women with higher body mass index tended to be of lower socioeconomic status, and were less likely to be current smokers or frequent alcohol drinkers; taller women tended to be of higher socioeconomic status, were slightly younger on average, and were less likely to be current smokers but more likely to be frequent alcohol drinkers. Other characteristics have been reported elsewhere (Reeves et al, 2007; Green et al, 2011).

Before exclusions for missing height and weight data, the number of haematological cancers diagnosed during follow-up was 9162 according to the ICD-O-3 classification, or 7929 in ICD-10; these numbers differ because many cases included in the ICD-O-3 myeloproliferative/myelodysplastic group are not treated as malignant in ICD-10 (Kroll et al, 2012). Table 1 reports numbers of cases by ICD-O-3 subtype: 77% were lymphoid and 23% were myeloid. Among lymphoid malignancies, the most frequent subgroup was mature B cell (72%); the 'other/unspecified' category (21%) included a small proportion of precursor-cell cases, but otherwise contained unspecified lymphoid cases. Among mature B-cell malignancies, the most frequent subtypes were plasma cell neoplasms (30%), diffuse large B-cell lymphoma (23%), follicular lymphoma (20%), and CLL/SLL (18%); the 'other' category (9%) included marginal zone and mantle cell lymphomas, and immunoproliferative diseases. Among myeloid malignancies, the most frequent subgroups were myeloproliferative/myelodysplastic neoplasms (69%) and acute myeloid leukaemia (30%). Overall, the proportion of cases assigned to unspecified subtypes was 16%.

Relative risks for categories of body mass index and height are given in Tables 3 and 4. Estimated trends in risk per $10 \, \mathrm{kg \, m^{-2}}$ increase in body mass index, and per 10 cm increase in height, are shown in Figure 1.

Body mass index. Classifying by ICD-O-3, the risk of haematological malignancy among obese women (over $30 \, \mathrm{kg \, m^{-2}}$) was 1.25 (95% confidence interval 1.18–1.33) relative to the reference group (under $25 \, \mathrm{kg \, m^{-2}}$). Overall, the relative risk for an increase of $10 \, \mathrm{kg \, m^{-2}}$ (trend) was 1.24 (1.18–1.31); $P_{trend} < 0.001$. There were increasing trends for both lymphoid (1.20 (1.13–1.28); $P_{trend} < 0.001$) and myeloid (1.37 (1.22–1.53); $P_{trend} < 0.001$) malignancies, and a test for heterogeneity between the two groups was not statistically significant ($P_{het} = 0.06$). There was no significant heterogeneity between trends for lymphoid subgroups ($P_{het} = 0.1$); there were significant trends for Hodgkin lymphoma (1.64 (1.21–2.21); $P_{trend} = 0.001$) and mature B-cell neoplasms (1.16 (1.08–1.25); $P_{trend} < 0.001$). Similarly, there was no significant heterogeneity between trends for mature B-cell subtypes ($P_{het} = 0.07$); there were significant trends for diffuse large B-cell lymphoma (1.36 (1.17–1.58); $P_{trend} < 0.001$) and plasma cell neoplasms (1.21 (1.06–1.39); $P_{trend} = 0.005$). Among the myeloid subgroups, there were significant increases for both acute myeloid leukaemia (1.47 (1.19–1.81); $P_{trend} < 0.001$) and myeloproliferative/myelodysplastic neoplasms (1.32 (1.15–1.52); $P_{trend} < 0.001$), with no significant heterogeneity ($P_{het} = 0.4$).

Table 2. Characteristics of the study population, by categories of self-reported body mass index and height (Million Women Study, United Kingdom 1996–2009)

Self-reported at recruitment	Body-mass index (kg m^{-2})			Height (cm)		
	<25	25–29	30+	<160	160–164	165+
Number of women	578 091	447 348	224 458	430 424	388 678	478 520
Characteristics at recruitment						
Drinkers[a] (%)	80	77	67	73	77	79
Current smokers (%)	23	19	17	23	20	19
Lower socioeconomic status[b] (%)	29	34	42	38	32	30
Age (years): mean (s.d.)	56.4 (4.9)	56.9 (4.9)	56.7 (4.8)	56.7 (4.9)	56.7 (4.9)	56.5 (4.8)
Follow-up						
Woman-years observed (1000s)	5991.2	4610.8	2285.5	4422.8	4008.1	4942.1
Number of incident cases: ICDO-3	3676	3213	1757	2710	2674	3597
Number of incident cases: ICD-10	3191	2780	1522	2318	2323	3143
Measurements of sampled women						
Mean (s.d.)	23.9 (2.7)	28.6 (2.9)	34.5 (4.7)	154.7 (3.8)	160.4 (2.9)	167.0 (4.2)
Sample size	2006	1227	445	1083	1135	1543

Abbreviations: ICDO-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] Within-study tertile of the 1991 Townsend deprivation index for the census enumeration district or output area containing the woman's home address at recruitment.

Body mass index (kg m^{-2})^a	<25		25–29			30+			All women^b	
	Cases	Ref.	Cases	RR	95% CI	Cases	RR	95% CI	Cases	P_{trend}
All haematological malignancies										
ICD-O-3 classification	3676	1.00	3213	1.12	1.07, 1.17	1757	1.25	1.18, 1.33	8646	<0.001
ICD-10 classification	3191	1.00	2780	1.11	1.06, 1.17	1522	1.25	1.17, 1.33	7493	<0.001
Subgroups of ICD-O-3 classification										
ICD-O-3 haematological malignancies^c										
Lymphoid	2857	1.00	2464	1.10	1.04, 1.16	1332	1.21	1.14, 1.30	6653	<0.001
Myeloid	801	1.00	737	1.18	1.07, 1.31	414	1.38	1.22, 1.56	1952	<0.001
ICD-O-3 lymphoid malignancies										
Hodgkin lymphoma	95	1.00	110	1.49	1.13, 1.97	62	1.66	1.20, 2.31	267	0.001
Mature B cell	2087	1.00	1770	1.07	1.01, 1.14	945	1.17	1.08, 1.27	4802	<0.001
Mature T cell	85	1.00	62	0.95	0.69, 1.33	39	1.28	0.87, 1.88	186	0.3
Other/unspecified lymphoid	590	1.00	522	1.15	1.02, 1.30	286	1.28	1.11, 1.48	1398	<0.001
ICD-O-3 subtypes of mature B-cell malignancy										
Diffuse large B-cell lymphoma	439	1.00	413	1.18	1.03, 1.35	236	1.37	1.17, 1.62	1088	<0.001
Follicular lymphoma	459	1.00	326	0.92	0.80, 1.06	180	1.04	0.87, 1.24	965	0.9
Plasma cell neoplasms	600	1.00	538	1.12	1.00, 1.26	289	1.22	1.06, 1.41	1427	0.005
CLL/SLL	386	1.00	323	1.07	0.92, 1.24	164	1.13	0.93, 1.36	873	0.2
Other mature B cell	203	1.00	170	1.05	0.86, 1.29	76	0.97	0.74, 1.27	449	0.9
ICD-O-3 myeloid malignancies^d										
Acute myeloid leukaemia	232	1.00	212	1.17	0.97, 1.41	134	1.51	1.21, 1.87	578	<0.001
Myeloproliferative/dysplastic	562	1.00	512	1.17	1.04, 1.32	277	1.33	1.15, 1.55	1351	<0.001
Subgroups of ICD-10 classification										
ICD-10 haematological malignancies										
Hodgkin lymphoma	95	1.00	110	1.49	1.13, 1.97	62	1.66	1.20, 2.31	267	0.001
NHL	1744	1.00	1459	1.07	1.00, 1.15	815	1.22	1.12, 1.33	4018	<0.001
Myeloma	643	1.00	563	1.09	0.98, 1.23	297	1.17	1.02, 1.35	1503	0.02
Leukaemia	709	1.00	648	1.18	1.06, 1.31	348	1.31	1.15, 1.50	1705	<0.001

Table 3. Association of body mass index with risk of haematological malignancies (Million Women Study, United Kingdom 1996–2009)

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; NHL = non-Hodgkin lymphoma; P_{trend} = result of test for trend; Ref. = referent; RR = relative risk. Follow-up starts at recruitment. RR estimates are adjusted for height, alcohol consumption, smoking and socioeconomic status, and stratified by cancer registry region.
^{a}Self-reported body mass index at recruitment.
^{b}Excludes women who did not report their height or weight. Estimated trend using mean measured body mass index within each category.
^{c}Excludes 41 unspecified cases.
^{d}Excludes 23 unspecified cases. Myeloproliferative/myelodysplastic neoplasms include chronic myeloid leukaemia.

Using the ICD-10 classification, there were increases for all groups: Hodgkin lymphoma (1.64 (1.21–2.21); $P_{trend} = 0.001$), NHL (1.21 (1.11–1.31); $P_{trend} < 0.001$), myeloma (1.17 (1.02–1.33); $P_{trend} = 0.02$), and leukaemia (1.31 (1.16–1.48); $P_{trend} < 0.001$). The test for heterogeneity between trends was not significant ($P_{het} = 0.2$).

Excluding the first 3 years of follow-up did not appreciably change the trend estimates (see Table 5); the association between adiposity and myeloma using ICD-10 became non-significant ($P_{trend} = 0.08$).

Height. Using the ICD-O-3 classification, the risk of haematological malignancy for taller women (over 165 cm) relative to the reference group (under 160 cm) was 1.24 (1.18–1.31), and the overall trend per 10 cm increase in height was 1.19 (1.15–1.24); $P_{trend} < 0.001$. There were increasing trends for both lymphoid (1.21 (1.16–1.27); $P_{trend} < 0.001$) and myeloid (1.11 (1.02–1.21); $P_{trend} = 0.02$) malignancies, and the test for heterogeneity between the trends for these two groups was not significant ($P_{het} = 0.07$). There was no significant heterogeneity among trends for the lymphoid malignancies: there were significant increases for mature

B-cell neoplasms (1.21 (1.15–1.28); $P_{trend} < 0.001$) and mature T-cell neoplasms (1.36 (1.03–1.79); $P_{trend} = 0.03$), with a borderline significant increase for Hodgkin lymphoma (1.25 (1.00–1.57); $P_{trend} = 0.05$). There were significant increases for all malignant B-cell subtypes, with no significant heterogeneity: diffuse large B-cell lymphoma (1.28 (1.14–1.43); $P_{trend} < 0.001$), follicular lymphoma (1.28 (1.13–1.44); $P_{trend} < 0.001$), plasma cell neoplasms (1.12 (1.01–1.24); $P_{trend} = 0.03$), and CLL/SLL (1.23 (1.08–1.40); $P_{trend} = 0.001$). There was no statistically significant heterogeneity among the myeloid subgroups, with a significant increase for acute myeloid leukaemia (1.22 (1.04–1.42); $P_{trend} = 0.01$) but not for myeloproliferative/myelodysplastic neoplasms.

Using the ICD-10 classification, there were increases for NHL (1.23 (1.16–1.31); $P_{trend} < 0.001$), myeloma (1.12 (1.01–1.23); $P_{trend} = 0.03$), and leukaemia (1.26 (1.15–1.38); $P_{trend} < 0.001$), and a borderline significant increase for Hodgkin lymphoma (1.25 (1.00–1.57); $P = 0.05$). The test for heterogeneity of trends was not significant ($P_{het} = 0.3$).

When the first 3 years of follow-up were excluded, the trend estimates did not appreciably change (see Table 5). The test for

Table 4. Association of height with risk of haematological malignancies (Million Women Study, United Kingdom 1996–2009)

Height (cm)[a]	<160 Cases	Ref.	160–164 Cases	RR	95% CI	165+ Cases	RR	95% CI	All women[b] Cases	P_{trend}
All haematological malignancies										
ICD-O-3 classification	2710	1.00	2674	1.11	1.05, 1.17	3597	1.24	1.18, 1.31	8981	<0.001
ICD-10 classification	2318	1.00	2323	1.13	1.07, 1.20	3143	1.28	1.21, 1.35	7784	<0.001
Subgroups of ICD-O-3 classification										
ICD-O-3 haematological malignancies[c]										
Lymphoid	2050	1.00	2066	1.13	1.07, 1.21	2788	1.27	1.20, 1.35	6904	<0.001
Myeloid	651	1.00	595	1.03	0.92, 1.15	788	1.13	1.02, 1.26	2034	0.02
ICD-O-3 lymphoid malignancies										
Hodgkin lymphoma	90	1.00	79	1.06	0.78, 1.44	113	1.31	0.99, 1.73	282	0.05
Mature B cell	1491	1.00	1478	1.11	1.03, 1.20	2017	1.26	1.18, 1.35	4986	<0.001
Mature T cell	44	1.00	73	1.87	1.29, 2.72	75	1.60	1.09, 2.33	192	0.03
Other/unspecified lymphoid	425	1.00	436	1.15	1.01, 1.32	583	1.27	1.12, 1.44	1444	<0.001
ICD-O-3 subtypes of mature B-cell malignancy										
Diffuse large B-cell lymphoma	327	1.00	344	1.20	1.03, 1.40	460	1.36	1.18, 1.58	1131	<0.001
Follicular lymphoma	282	1.00	303	1.19	1.01, 1.40	420	1.36	1.17, 1.58	1005	<0.001
Plasma cell neoplasms	470	1.00	433	1.03	0.91, 1.18	576	1.15	1.01, 1.30	1479	0.03
CLL/SLL	269	1.00	259	1.07	0.90, 1.27	375	1.29	1.10, 1.51	903	0.001
Other mature B cell	143	1.00	139	1.08	0.85, 1.36	186	1.19	0.96, 1.49	468	0.1
ICD-O-3 myeloid malignancies[d]										
Acute myeloid leukaemia	191	1.00	165	0.99	0.80, 1.22	249	1.26	1.04, 1.52	605	0.01
Myeloproliferative/dysplastic	450	1.00	423	1.05	0.92, 1.20	531	1.09	0.96, 1.24	1404	0.2
Subgroups of ICD-10 classification										
ICD-10 haematological malignancies										
Hodgkin lymphoma	90	1.00	79	1.06	0.78, 1.44	113	1.31	0.99, 1.73	282	0.05
NHL	1206	1.00	1273	1.19	1.10, 1.29	1686	1.31	1.21, 1.41	4165	<0.001
Myeloma	495	1.00	455	1.03	0.90, 1.17	608	1.14	1.01, 1.29	1558	0.03
Leukaemia	527	1.00	516	1.11	0.98, 1.25	736	1.32	1.18, 1.48	1779	<0.001

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; NHL = non-Hodgkin lymphoma; P_{trend} = result of test for trend; Ref. = referent; RR = relative risk Follow-up starts at recruitment. RR estimates are adjusted for body mass index, alcohol consumption, smoking and socioeconomic status, and stratified by cancer registry region.
[a]Self-reported height at recruitment.
[b]Excludes women who did not report their height. Estimated trend using mean measured height within each category.
[c]Excludes 43 unspecified cases.
[d]Excludes 25 unspecified cases. Myeloproliferative/myelodysplastic neoplasms include chronic myeloid leukaemia.

heterogeneity between the lymphoid and myeloid groups moved from marginally non-significant ($P_{het} = 0.07$) to marginally significant ($P_{het} = 0.03$), the trend for 'other mature B-cell malignancies' became marginally significant ($P_{trend} = 0.04$), and the trends for myeloid and mature T-cell malignancies and acute myeloid leukaemia became non-significant.

DISCUSSION

In this cohort of middle-aged women, greater adiposity and height were associated with increased risk of haematological cancer. For both measures, there were statistically significant associations with most of the disease subtypes analysed, using a detailed classification based on ICD-O-3. The overall increases in risk were not very large: for example, 25% for obese women compared with normal/underweight, and 24% for women over 165 cm compared with under 160 cm. We found no statistically significant heterogeneity

between trends for subtypes within diagnostic groups, implying that chance cannot be ruled out as an explanation of the apparent differences in trend. However, the associations are very unlikely to have occurred by chance, as 16 of the 28 trend tests were significant with $P \leqslant 0.001$. Reverse causation is improbable, because the trend estimates did not appreciably change when the first 3 years of follow-up were excluded (although some trends became non-significant, presumably due to smaller numbers of cases). Consistent results were obtained using a broader ICD-10 classification.

Body mass index. Our findings are consistent with meta-analyses of previous prospective studies using disease categories compatible with our ICD-O-3 classification, which reported positive associations with body mass index for diffuse large B-cell lymphoma, acute myeloid leukaemia, and chronic myeloid leukaemia (a type of myeloproliferative neoplasm), but not for follicular lymphoma or CLL/SLL (Larsson and Wolk, 2008, 2011), and with comparable case–control studies (Cerhan et al, 2005; Chang et al, 2005; Kasim

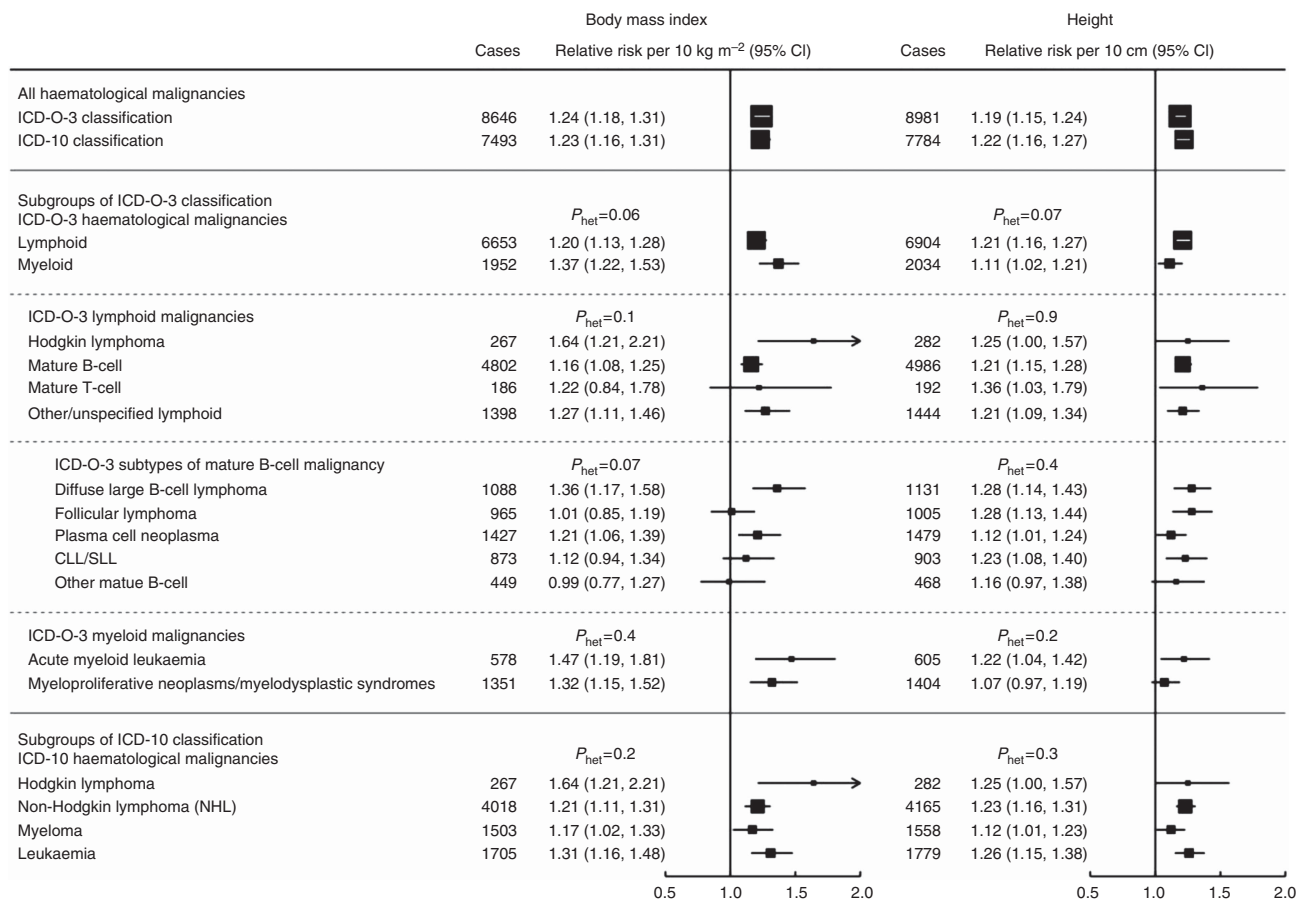|	Cases	Body mass index Relative risk per 10 kg m^{-2} (95% CI)		Cases	Height Relative risk per 10 cm (95% CI)	
All haematological malignancies						
ICD-O-3 classification	8646	1.24 (1.18, 1.31)		8981	1.19 (1.15, 1.24)	
ICD-10 classification	7493	1.23 (1.16, 1.31)		7784	1.22 (1.16, 1.27)	
Subgroups of ICD-O-3 classification						
ICD-O-3 haematological malignancies		P_{het}=0.06			P_{het}=0.07	
Lymphoid	6653	1.20 (1.13, 1.28)		6904	1.21 (1.16, 1.27)	
Myeloid	1952	1.37 (1.22, 1.53)		2034	1.11 (1.02, 1.21)	
ICD-O-3 lymphoid malignancies		P_{het}=0.1			P_{het}=0.9	
Hodgkin lymphoma	267	1.64 (1.21, 2.21)		282	1.25 (1.00, 1.57)	
Mature B-cell	4802	1.16 (1.08, 1.25)		4986	1.21 (1.15, 1.28)	
Mature T-cell	186	1.22 (0.84, 1.78)		192	1.36 (1.03, 1.79)	
Other/unspecified lymphoid	1398	1.27 (1.11, 1.46)		1444	1.21 (1.09, 1.34)	
ICD-O-3 subtypes of mature B-cell malignancy		P_{het}=0.07			P_{het}=0.4	
Diffuse large B-cell lymphoma	1088	1.36 (1.17, 1.58)		1131	1.28 (1.14, 1.43)	
Follicular lymphoma	965	1.01 (0.85, 1.19)		1005	1.28 (1.13, 1.44)	
Plasma cell neoplasma	1427	1.21 (1.06, 1.39)		1479	1.12 (1.01, 1.24)	
CLL/SLL	873	1.12 (0.94, 1.34)		903	1.23 (1.08, 1.40)	
Other matue B-cell	449	0.99 (0.77, 1.27)		468	1.16 (0.97, 1.38)	
ICD-O-3 myeloid malignancies		P_{het}=0.4			P_{het}=0.2	
Acute myeloid leukaemia	578	1.47 (1.19, 1.81)		605	1.22 (1.04, 1.42)	
Myeloproliferative neoplasms/myelodysplastic syndromes	1351	1.32 (1.15, 1.52)		1404	1.07 (0.97, 1.19)	
Subgroups of ICD-10 classification						
ICD-10 haematological malignancies		P_{het}=0.2			P_{het}=0.3	
Hodgkin lymphoma	267	1.64 (1.21, 2.21)		282	1.25 (1.00, 1.57)	
Non-Hodgkin lymphoma (NHL)	4018	1.21 (1.11, 1.31)		4165	1.23 (1.16, 1.31)	
Myeloma	1503	1.17 (1.02, 1.33)		1558	1.12 (1.01, 1.23)	
Leukaemia	1705	1.31 (1.16, 1.48)		1779	1.26 (1.15, 1.38)	

Figure 1. Associations of body mass index and height with risk of haematological malignancies. Million Women Study, United Kingdom 1996–2009. Follow-up starts at recruitment. Relative risks are adjusted for alcohol intake, smoking, and socioeconomic status (and for body mass index and height where not the factor of interest) and stratified by cancer registry region. 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 test for heterogeneity of trends within groups. Myeloproliferative neoplasms/myelodysplastic syndromes include chronic myeloid leukaemia.

et al, 2005; Pan *et al*, 2005; Willett *et al*, 2008). A small meta-analysis of five prospective studies of Hodgkin lymphoma reported an increase in the relative risk of disease for obese but not for overweight individuals (Larsson and Wolk, 2011); in contrast, we found increased risk in both overweight and obese women, probably reflecting greater statistical power. Our results are also consistent with the few previous studies of diagnostic groups not included in the meta-analyses: individual cohort studies reported positive associations with plasma cell neoplasms (Engeland *et al*, 2007; Troy *et al*, 2010) and myelodysplastic syndromes (Ma *et al*, 2009), but not mature T-cell malignancies (Lim *et al*, 2007). Using the ICD-10 classification, our results for NHL, myeloma, and leukaemia are consistent with an earlier report from the same cohort with only 5.4 years of follow-up (Reeves *et al*, 2007), and with meta-analyses that included it (Renehan *et al*, 2008; Wallin and Larsson, 2011).

Although heterogeneity tests were non-significant, the association with adiposity appeared to be much weaker for follicular lymphoma than for the more aggressive subtypes such as Hodgkin and diffuse large B-cell lymphoma. Conceivably, this might reflect differential delay in diagnosis associated with obesity: early-stage follicular lymphoma often has no obvious symptoms, and obesity would make enlarged peripheral lymph nodes more difficult to detect.

Height. A recent meta-analysis of prospective studies reported a positive association of greater height with all-cancer risk in both sexes, which remained after exclusion of the Million Women Study (Green *et al*, 2011). To our knowledge, there has been no meta-analysis of the association for haematological cancer specifically.

Using ICD-O-3, we found increased risks of both lymphoid and myeloid cancer, and of many subtypes. Positive associations have been previously reported for lymphoproliferative and myeloproliferative malignancies both separately and combined (Engeland *et al*, 2007), and for Hodgkin lymphoma (Engeland *et al*, 2007), diffuse large B-cell lymphoma (Troy *et al*, 2010), follicular lymphoma (Cerhan *et al*, 2005; Britton *et al*, 2008), plasma cell neoplasms (Engeland *et al*, 2007), CLL/SLL (Lu *et al*, 2009; Troy *et al*, 2010), and acute myeloid leukaemia (Engeland *et al*, 2007). One study analysed mature T-cell disease but found no significant association (Lim *et al*, 2007). Except for Hodgkin lymphoma (which was on the borderline of significance), we found statistically significant associations for all these subtypes.

Using ICD-10, our results for NHL, myeloma and leukaemia are consistent with a report from this cohort after 9 years of follow-up, although the association was then marginally non-significant for multiple myeloma (Green *et al*, 2011). Perhaps reflecting lower statistical power, previous studies using comparable classifications reported no association for NHL (Cerhan *et al*, 2002), and only marginally significant association for leukaemia (Ross *et al*, 2004).

Table 5. Associations of body mass index and height with risk of haematological malignancies, excluding the first 3 years of follow-up (Million Women Study, United Kingdom 1996–2009)

	Body mass index (per 10 kg m^{-2})				Height (per 10 cm)			
	Cases	RR	95% CI	P_{trend}	Cases	RR	95% CI	P_{trend}
All haematological malignancies								
ICD-O-3 classification	6836	1.25	1.17, 1.33	<0.001	7104	1.18	1.13, 1.24	<0.001
ICD-10 classification	5913	1.24	1.16, 1.33	<0.001	6149	1.21	1.15, 1.27	<0.001
Subgroups of ICD-O-3 classification								
ICD-O-3 haematological malignancies[a]		$P_{het}=0.5$				$P_{het}=0.03$		
Lymphoid	5267	1.23	1.15, 1.32	<0.001	5474	1.21	1.15, 1.27	<0.001
Myeloid	1534	1.29	1.13, 1.47	<0.001	1595	1.07	0.97, 1.18	0.2
ICD-O-3 lymphoid malignancies		$P_{het}=0.06$				$P_{het}=0.9$		
Hodgkin lymphoma	201	1.69	1.19, 2.39	0.003	213	1.21	0.93, 1.57	0.2
Mature B cell	3934	1.17	1.08, 1.27	<0.001	4094	1.21	1.14, 1.29	<0.001
Mature T cell	135	1.25	0.80, 1.94	0.3	140	1.30	0.94, 1.81	0.1
Other/unspecified lymphoid	997	1.41	1.20, 1.65	<0.001	1027	1.18	1.05, 1.33	0.006
ICD-O-3 subtypes of mature B-cell malignancy		$P_{het}=0.1$				$P_{het}=0.6$		
Diffuse large B-cell lymphoma	931	1.40	1.19, 1.65	<0.001	969	1.25	1.11, 1.42	<0.001
Follicular lymphoma	752	1.03	0.85, 1.24	0.8	786	1.25	1.09, 1.44	0.001
Plasma cell neoplasms	1166	1.18	1.02, 1.37	0.03	1211	1.13	1.01, 1.26	0.04
CLL/SLL	703	1.11	0.92, 1.35	0.3	730	1.26	1.10, 1.46	0.001
Other mature B cell	382	1.02	0.78, 1.34	0.9	398	1.22	1.01, 1.48	0.04
ICD-O-3 myeloid malignancies[b]		$P_{het}>0.9$				$P_{het}=0.4$		
Acute myeloid leukaemia	451	1.29	1.01, 1.63	0.04	470	1.14	0.96, 1.36	0.1
Myeloproliferative/myelodysplastic	1068	1.29	1.10, 1.50	0.002	1108	1.04	0.93, 1.17	0.5
Subgroups of ICD-10 classification								
ICD-10 haematological malignancies		$P_{het}=0.2$				$P_{het}=0.5$		
Hodgkin lymphoma	201	1.69	1.19, 2.39	0.003	213	1.21	0.93, 1.57	0.2
NHL	3159	1.26	1.15, 1.38	<0.001	3277	1.22	1.14, 1.31	<0.001
Myeloma	1222	1.14	0.98, 1.32	0.08	1269	1.12	1.01, 1.25	0.03
Leukaemia	1331	1.25	1.09, 1.44	0.002	1390	1.25	1.13, 1.38	<0.001

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; NHL = non-Hodgkin lymphoma; P_{het} = result of test for heterogeneity of trends within groups; P_{trend} = result of test for trend; RR = relative risk. Follow-up starts 3 years after recruitment. RR estimates (trend using mean measurements within categories) are adjusted for height or body mass index (as appropriate), alcohol consumption, smoking and socioeconomic status, and stratified by cancer registry region.
[a]Excludes 35 (body mass index) or 35 (height) unspecified cases.
[b]Excludes 15 (body mass index) or 17 (height) unspecified cases. Myeloproliferative/myelodysplastic neoplasms include chronic myeloid leukaemia.

Potential mechanisms. The means by which obesity might play a role in carcinogenesis are gradually being elucidated. It is generally accepted that obesity provokes a state of chronic inflammation resulting in metabolic dysfunction and impaired immunity (Gregor and Hotamisligil, 2011). Adipocytes and infiltrating macrophages result in abnormal cytokine production, including increased synthesis of tumour necrosis factor-α (TNF-α), which activates proinflammatory signalling pathways. Increased levels of TNF-α promote activation of nuclear factor-κB, which can promote B-lymphocyte survival and proliferation (Ben-Neriah and Karin, 2011). Furthermore, a pooled analysis from the InterLymph consortium reported an association with a common polymorphism of TNF ($TNF - 308G \rightarrow A$) and risk of NHL, particularly diffuse large B-cell lymphoma (Rothman et al, 2006).

It is now recognised that adipose tissue is metabolically active, releasing adipokines (peptide hormones such as leptin) that help to regulate energy homeostasis. Leptin is a potent pro-inflammatory cytokine that modulates immune function, supports haematopoiesis and promotes B-cell survival (Tilg and Moschen, 2006;

Claycombe et al, 2008; Lam et al, 2010). Polymorphisms of the leptin gene and its receptor are associated with the obese phenotype, and have been shown to be associated with susceptibility to NHL (Skibola et al, 2004; Willett et al, 2005).

Less is known about potential mechanisms by which height might contribute to cancer risk. Although height is largely genetically determined, in western populations approximately 20% of variation is due to environmental factors (Silventoinen, 2003). Hormonal determinants of height may play a role in cancer risk. These include the growth hormone cascade, which is a major regulator of postnatal growth (Rosenfeld and Hwa, 2009). Insulin-like growth factor-1 levels are strongly correlated with childhood skeletal growth and there may be some relationship to levels in early life and later cancer risk (Pollak et al, 2004). Whether this process could promote the development of haematological cancers is unknown.

Strengths and weaknesses. This prospective study is based on a very large cohort of women followed for 10 years on average,

yielding adequate power to investigate relatively rare subtypes of haematological malignancy. Reverse causation is unlikely to explain our findings, as excluding the first 3 years of follow-up did not qualitatively change the results.

Height and weight measurements were self-reported by study participants at recruitment. Some investigators have found that self-reported measurements tend to over-estimate height and under-estimate weight and BMI, particularly in women (Gorber et al, 2007). However, in our cohort, there was good agreement between self-reported and measured height and BMI for the subset of participants for whom direct measurements were available (Pearson's correlation 0.91 and 0.92 respectively) (Cairns et al, 2011). Measured height and weight data were used to score the categories in the trend analyses reported here, thus allowing for measurement error in the self-reported data.

Disease outcomes were derived from routine cancer registration data. It has been suggested that cancer registration for haematological malignancies in the United Kingdom might sometimes be incomplete or imprecise (NICE, 2003). Problems include the complexity of disease classification and coding, and the wide variety of factors involved in the diagnostic evaluation of haematological cancer, which often requires histology, immunophenotyping, and genetic studies (Smith et al, 2010). Imprecise diagnostic registration probably explains the non-trivial proportion of vaguely–defined cancers observed in our study (16%). Conversion from ICD-O-2 to ICD-O-3 (using a standard coding table) might have introduced some misclassification: in a study from the United States, computer conversion of histology codes was found to be somewhat imprecise in comparison with ICD-O-3 coding determined directly from pathology reports, although there was a good general level of agreement (84–89% for diffuse large B-cell lymphoma and follicular lymphoma) (Clarke et al, 2006). Finally, case ascertainment for some types of myeloproliferative/myelodysplastic disorder is likely to have been incomplete before the introduction of the 2001 WHO classification, because cancer registration was not compulsory for these diseases when their malignant nature was not fully recognised (NICE, 2003; Phekoo et al, 2006). However, there is no reason to believe that the registration problems would be differential for height or adiposity, so they are unlikely to have affected the associations reported here.

CONCLUSION

In this very large cohort of middle-aged women in the United Kingdom, greater adiposity and height were associated with modest increases in risk for many specific subtypes of haematological cancer, including both lymphoid and myeloid neoplasms. There was no statistically significant variation between trends for different subtypes within disease groups.

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