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 10g 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.

Keywords: alcohol; smoking; lymphoma; leukaemia; plasma cell neoplasms; myelodysplastic/myeloproliferative neoplasms

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, 2003). Unfortunately, the combination of a disease code from ICD-10 and a morphology code is not always sufficient to identify the malignancy, and the specificity of some codes is limited.

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 studies (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 code from ICD-O-3.
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 (polycythaemia 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 995–998 (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 MM C88 C90 Leuk C91-C95 Oth D45-D47 Total |
| Lymphoid malignances | 959–973, 976, 982–983, 9940, 9948 | 287 | 4226 | 1597 | 937 | 0 | 7047 |
| Hodgkin lymphoma | 965–966 | 287 | 0 | 0 | 0 | 287 |
| Mature B cell | 967–969 except (9675), 973, 976, 9823, 9826, 9833, 9940 | 0 | 115 | 1 | 0 | 0 | 1152 |
| Diffuse large B cell | 9678, 9679, 9680, 9684 | 0 | 1027 | 0 | 0 | 0 | 1027 |
| Follicular lymphoma | 969 except 9699 | 0 | 0 | 1518 | 0 | 0 | 1518 |
| Plasma cell neoplasms | 973 | 0 | 133 | 0 | 787 | 0 | 920 |
| CLL/SLL | 9670, 9823 | 0 | 368 | 78 | 30 | 0 | 476 |
| Other/unspec. mat. B cell | 970–971, 9827, 9831, 9834, 9948 | 0 | 194 | 0 | 3 | 0 | 197 |
| Other/unspec. lymphoid | 959, 9675, 972, 9820, 9833 except (9831, 9833, 9834) | 0 | 1353 | 0 | 117 | 0 | 1470 |
| Myeloid malignances | 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 | 0 | 192 | 1230 | 1430 |
| Other/unspec. myeloid | 9860 | 0 | 0 | 0 | 25 | 0 | 25 |
| Unspecified lineage | 980 | 0 | 0 | 43 | 0 | 43 |
| Not haematological cancer | 800, 975, any code with 5th digit not 3 | 0 | 12 | 0 | 243 | 255 |

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 edition; 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.
Characteristics of the women included in these analyses

| Alcohol | Smoking |
|---------|---------|
| Past | Never | Current | All women |
| Non-drinkers | 31 4756 | 352 493 | 255 148 | 1 319 121 |
| Drinkers | 994 030 | 633 964 | 76 | 76 |

**Number of women**

| Characteristics at recruitment | Alcohol | Smoking |
|--------------------------------|---------|---------|
| % Drinkers | 31 4756 | 994 030 |
| % Current smokers | 26 | 19 |
| % Lower socioeconomic status | 45 | 30 |
| Body mass index (kg m\(^{-2}\); mean (s.d.)) | 27.2 (5.4) | 25.9 (4.4) |
| Height (cm; mean (s.d.)) | 161.2 (6.9) | 162.2 (6.7) |
| Age (years; mean (s.d.)) | 57.3 (6.9) | 56.4 (4.8) |

**Follow-up**

| Number of women observed (1000s) | 3218.0 | 10270.0 |
|----------------------------------|--------|--------|
| Number of incident cases: ICD-O-3 | 2679 | 6608.7 |
| Number of incident cases: ICD-10 | 2352 | 3908.0 |

Abbreviations: ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases 10th revision. *Highest within-study tertile of the 1991 Townsend deprivation index for the census enumeration district or output area of the home address.
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lymphoma (1.45 (1.22–1.72)) and mature T-cell malignancies with statistically significant increasing trends for Hodgkin disease. There was heterogeneity between subgroups of myeloid malignancy (Phet < 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 (Phet < 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.
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, 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-10 = International Classification of Diseases for Oncology 3rd edition; ICD-O-3 = International Classification of Diseases for Oncology 3rd revision; CLL/SLL = chronic lymphocytic leukaemia/small lymphocytic lymphoma; NHL = non-Hodgkin lymphoma; Myeloid/myelodysplastic disease includes chronic myeloid leukaemia.
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 leukemogens, and it has been concluded that there is ‘sufficient evidence in humans’ that

| Table 4 Association of tobacco smoking with risk of haematological malignancies |
|-----------------------------------------------|
| **Smoking** | **All women** | **Ex-smokers** | **Never-smokers** | **<15 cigarettes per day** | **≥15 cigarettes per day** |
|-----------|--------------|---------------|------------------|--------------------------|--------------------------|
| All haematological malignancies | | | | | |
| ICD-0-3 classification | 522 | 1.19 | 0.10, 1.19 | 4312 | 1.00 |
| ICD-10 classification | 2191 | 1.07 | 0.10, 1.13 | 3808 | 1.00 |

**Subgroups of ICD-0-3 classification**

| **ICD-O-3 haematological malignancies** | **Lymphoid** | **Myeloid** | **ICD-O-3 lymphoid malignancies** | **Hodgkin lymphoma** | **Mature B cell** | **Mature T cell** | **Other/unspecified lymphoid** |
|----------------------------------------|-------------|-------------|---------------------------------|-------------------|-----------------|---------------------|---------------------------|
| | | | | | | | | |
| | | | | | | | | |

**Subgroups of ICD-10 classification**

| **ICD-10 haematological malignancies** | **Hodgkin lymphoma** | **Non-Hodgkin lymphoma** | **Myeloma** | **Leukaemia** |
|----------------------------------------|-------------------|---------------------|-------------|-------------|
| | | | | |

**Abbreviations:** Cases = number of incident cases; CI = confidence interval; ICD-O-3 = International Classification of Diseases for Oncology 3rd edition; ICD-10 = International Classification of Diseases. 10th revision; P<sub>trend</sub> = result of test for categorical trend; P<sub>adj</sub> = result of test for adjusted trend; % = percentage; RR = relative risk.
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. Cigarette smoking was associated with increased risk of Hodgkin lymphoma, consistent with previous reports, and follicular lymphoma and plasma cell neoplasms (not previously reported, to our knowledge). Tobacco smoking causes myeloid (but not lymphoid) leukaemia: in particular, diffuse large B-cell lymphoma, consistent with previous reports, and follicular lymphoma 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.

**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,

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

| Subgroups of ICD-O-3 classification | Trend among drinkersa | Trend among never- or current smokersb |
|-------------------------------------|-----------------------|---------------------------------------|
| All haematological malignancies     |                       |                                       |
| ICD-O-3 classification              |                       |                                       |
| ICD-10 classification               |                       |                                       |
| Myeloid                             |                       |                                       |
| Myeloproliferative/myelodysplastic disease |       |                                       |
| Hodgkin lymphoma                    |                       |                                       |
| Mature B cell                       |                       |                                       |
| Mature T cell                       |                       |                                       |
| Other/unspecified lymphoid          |                       |                                       |
| Other/unspecified B-cell lymphoma   |                       |                                       |
| Other/unspecified mature B cell     |                       |                                       |
| Acute myeloid leukaemia             |                       |                                       |
| Myeloproliferative/myelodysplastic disease |       |                                       |

**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; RR, relative risk. Myeloproliferative/myelodysplastic disease includes chronic myeloid leukaemia.

aRelative risk per 10 g per day, adjusted for body mass index, height, smoking and socioeconomic status, and stratified by cancer registry region. 

bRelative risk per 10 cigarettes per day, adjusted for body mass index, height, alcohol consumption and socioeconomic status, and stratified by cancer registry region. 

cExcludes other/unspecified cases.
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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