SHORT COMMUNICATION

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Exogenous hormone use, reproductive history and risk of adult myeloid leukaemia

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Background: A hormonal aetiology is one explanation for the lower incidence of myeloid leukaemia in women compared with men.

Methods: In this population-based case–control study, we evaluated associations between exogenous hormone use and reproductive history and myeloid leukaemia, overall and by disease subtype.

Results: We observed a suggestive association between oral contraceptive use and acute myeloid leukaemia (odds ratio = 0.55, 95% confidence interval = 0.32–0.96). Hormone replacement therapy and reproductive factors were not associated with risk.

Conclusion: Despite the biological plausibility for a role of oestrogen in leukaemogenesis, other aetiologic factors are likely to explain the differing incidence rates in males and females.

In the United States, 14 590 incident cases and 10 370 deaths are expected to occur annually due to myeloid leukaemia (Siegel *et al*, 2013). Known risk factors for myeloid leukaemia, including ionising radiation, smoking, and prior chemotherapy, explain only a small number of cases (Deschler and Lubbert, 2006). Incidence rates are higher in men than women (4.33 per 100 000 *vs* 3.01 per 100 000; Howlader *et al*, 2012), although the reason is not known. One potential explanation is a reduction in risk due to increased levels of circulating oestrogens in women.

Reproductive and hormonal (e.g., oestrogen) factors have been implicated in solid tumours where sex differences in incidence rates occur. Few studies have focused on oestrogens in leukaemia (Traversa *et al*, 1998; Ross *et al*, 2005). Oestrogen receptors are expressed on certain haematopoietic cells and in leukaemia cells (Forsberg, 1984; Danel *et al*, 1985; Cutolo *et al*, 2001), providing biological plausibility for a potential role in leukaemia aetiology. We evaluated the association between adult myeloid leukaemia and hormones in a population-based case–control study of leukaemia.

MATERIALS AND METHODS

Study participants. Detailed information regarding case and control recruitment has been described (Ross *et al*, 2011). Briefly, eligible cases were diagnosed with acute myeloid leukaemia (AML; ICD-O-3 codes: 9840, 9861, 9866–9867, 9871–9874, 9891–9897, 9910, 9920), chronic myelogenous leukaemia (CML; 9863, 9875–9876), chronic myelomonocytic leudemia (CMML; 9945) or other myeloid leukaemias (9860, 9865, 9869, 9870, 9911) between 1 June 2005 and 30 November 2009. Cases were identified by rapid case ascertainment by the Minnesota Cancer Surveillance System (MCSS), a population-based registry in Minnesota. Cases were eligible for the study if they were a Minnesota resident, diagnosed between the ages of 20 and 79 years, and could understand English or Spanish. Proxy interviews were not conducted. Centralised pathology and cytogenetics review were conducted to classify the leukaemias into AML, CML and CMML/other myeloid subtypes. A total of 488 pathologically confirmed female cases were identified by MCSS. Ninety-one patients died soon after diagnosis and twenty-eight patients and/or physicians declined to receive information on

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the study. Of the remaining 369 women, 278 completed the study, resulting in an overall response rate of 57%. We were able to classify 250 cases by disease subtype (AML *vs* CML). The remaining 28 were not classified due to refusal of medical record release ($N=6$) or insufficient pathology information for classification ($N=22$).

Controls were identified through the Minnesota State driver's license/identification card list, which includes nearly all Minnesotans between the ages of 16 and 85 years. Controls were eligible for the study if they were alive at the time of contact, resided in Minnesota, were between the ages of 20 and 79 years, could understand English or Spanish, and had not had a prior diagnosis of myeloid leukaemia. Controls were frequency matched to cases on decile of age. Of a total of 543 eligible female population controls identified, 471 were contacted (contact rate = 87%), 112 refused participation and 359 were enrolled for an overall response rate of 66%.

This study was approved by the Institutional Review Boards of the University of Minnesota, the Mayo Clinic, the Minnesota Department of Health and participating area hospitals.

Data collection. Exposure data were collected by a self-administered questionnaire as previously described (Ross *et al*, 2011). Relevant sections for the current analysis included demographics, medication use including oral contraceptive (OC) and hormone replacement therapy (HRT), medical history, and reproductive history.

HRT was assessed by asking women if they had ever used oestrogen or oestrogen-containing pills other than OCs. Women were classified as current, former or never users, and by duration (none, <1, 1–5, >5 years). OC use was evaluated by ever/never use and duration (none, <1–5, >5 years). We also evaluated reproductive history, including age at menarche (⩽12 *vs* >12 years), age at menopause (premenopausal, <50, ⩾50 years), type of menopause (natural, surgical, other), age at first birth (nulliparous, <20, 20–24, 25–29, ⩾30), and number of live births (0, 1–2, 3–4, 5 or more).

Statistical analysis. We used unconditional logistic regression to compute crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate associations between myeloid leukaemia and categorical variables in female cases and controls. Age group (<50, 50–59, 60–69, 70+; frequency-matching variable), BMI category (normal/underweight, overweight, obese), smoking status (ever, never), income, education, and benzene exposure were evaluated as potential confounders. Variables were included in the final model if they changed the magnitude of the OR >10%. Stratified analyses were used to evaluate differences by subtype (AML ($n=171$) and CML ($n=79$)). All analyses were performed using SAS Enterprise Guide (Version 5.1, SAS Institute Inc., Cary, NC, USA) and all reported *P*-values are two-sided.

RESULTS

There were 278 female cases and 358 female controls with data available for analysis. When we compared participating and non-participating cases and controls, we found that participation rates were higher for CML cases and did not differ by year of diagnosis. The median time to completion of the interview was 70 days following diagnosis for cases. Cases and controls were equally distributed by age (Table 1). There were no significant differences in education or income by case–control status (Table 1). As expected, ever smoking and higher BMI were both associated with an increased risk of myeloid leukaemia (Table 1).

We observed a reduced risk of myeloid leukaemia associated with being premenopausal at diagnosis and an increased risk

Table 1. Selected characteristics of the study population and association with myeloid leukaemia

	Controls *N* (%)	All cases *N* (%)	OR (95% CI)	AML cases *N* (%)	OR (95% CI)	CML cases *N* (%)	OR (95% CI)
Total	358	278		171		79	
Age (years)							
<50	108 (30)	95 (34)	(Matching variable)	68 (40)	(Matching variable)	22 (28)	(Matching variable)
50–59	80 (22)	63 (23)		36 (21)		24 (30)	
60–69	100 (28)	77 (28)		47 (28)		23 (29)	
70+	70 (20)	43 (16)		20 (12)		10 (11)	
Race/ethnicity							
Non-hispanic white	339 (95)	262 (94)	Ref.	160 (94)	Ref.	74 (94)	Ref.
Other	19 (5)	16 (6)	1.09 (0.55, 2.16)	11 (6)	1.23 (0.57, 2.64)	5 (6)	1.21 (0.44, 3.33)
Smoking status							
Never	202 (57)	136 (49)	Ref.	85 (50)	Ref.	36 (46)	Ref.
Ever	152 (43)	141 (51)	1.38 (1.01, 1.89)	85 (50)	1.33 (0.92, 19.2)	43 (54)	1.59 (0.97, 2,59)
Education							
<HS	121 (34)	86 (31)	0.81 (0.55, 1.19)	49 (29)	0.71 (0.45, 1.11)	26 (33)	0.95 (0.52, 1.73)
Some post HS	115 (32)	101 (36)	Ref.	66 (39)	Ref.	26 (33)	Ref.
College graduate	122 (34)	91 (33)	0.85 (0.58, 1.24)	56 (33)	0.80 (0.52, 1.24)	27 (34)	0.98 (0.54, 1.78)
Income[a]							
⩽$40 000	152 (43)	118 (43)	1.06 (0.75, 1.51)	74 (44)	1.17 (0.77, 1.77)	28 (36)	0.72 (0.42, 1.25)
$40 000–$80 000	137 (39)	100 (38)	Ref.	57 (34)	Ref.	35 (46)	Ref.
>$80 000	62 (18)	54 (20)	1.19 (0.76, 1.87)	36 (22)	1.40 (0.84, 2.33)	14 (18)	0.88 (0.44, 1.76)

Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; HS=high school; OR = odds ration; Ref. = referent.
[a]*N* does not sum to total due to missing data (6 cases, 7 controls).

associated with 'other' type of menopause, which includes chemotherapy-induced menopause (Table 2). When we stratified by disease subtype, 'other' menopause was associated only with AML (OR = 8.14, 95% CI = 2.53, 26.2). We also observed a suggestive association between AML and longer duration of OC use (OR = 0.55, 95% CI = 0.32, 0.96 for >5 years of use *vs* never use). Age at menarche, HRT, and parity were not associated with leukaemia risk (Table 2 and Supplementary Table 1).

Because we did not have information on timing of OC use, we stratified the analysis by menopausal status as an attempt to control for latency of exposure. Interestingly, use of OC for >5 years was associated with a non-significant increased risk of AML in premenopausal women (OR = 3.97, 95% CI = 0.80, 19.6) and a decreased risk of AML in postmenopausal women (OR = 0.35, 95% CI = 0.18–0.68); however, the *P*-value for the interaction term was non-significant ($P = 0.33$).

To determine whether the strong association between 'other' type of menopause and AML was explained by therapy-related AML (t-AML; Vardiman *et al*, 2002), we repeated the analyses after exclusion of the eight cases with t-AML. The magnitude of the associations between premenopausal status (OR = 0.53, 95% CI = 0.27, 1.05) and OC use (OR = 0.64, 95% CI = 0.38, 1.08) remained the same in this subgroup analysis. We also repeated the analysis after exclusion of all women (cases and controls) who reported 'other' menopause ($N = 25$). The associations between premenopausal status (OR = 0.75, 95% CI = 0.37, 1.53) and OC use (OR = 0.75, 95% CI = 0.44, 1.29) and AML were attenuated.

DISCUSSION

We did not observe evidence for a strong association between HRT use or reproductive factors and myeloid leukaemia risk, overall or by the main leukaemia subgroups of AML and CML. We did not confirm a previous study reporting an increased risk of adult acute leukaemia in women who had filled prescriptions for OCs (Traversa *et al*, 1998). Instead, we observed a suggestive inverse association between longer duration of OC use (>5 years) and AML, although this finding should be confirmed because we cannot rule out chance as a potential explanation. Chemotherapy-induced early menopause (Brincker *et al*, 1987; Pedersen-Bjergaard

Table 2. Associations between hormone use and reproductive factors and myeloid leukaemia risk, overall and by leukaemia subtype

	Controls N[a] (%)	All Cases N[a] (%)	Adj.[b] OR (95% CI)	AML Cases N[a] (%)	Adj.[b] OR (95% CI)	CML Cases N[a] (%)	Adj.[b] OR (95% CI)
Age at menopause (years)							
<50	116 (34)	106 (39)	Ref.	59 (36)	Ref.	35 (45)	Ref.
⩾50	121 (35)	89 (33)	0.91 (0.61, 1.36)	56 (34)	1.10 (0.69, 1.78)	23 (29)	0.69 (0.37, 1.27)
Premenopausal	104 (31)	74 (28)	0.55 (0.31, 0.99)	49 (30)	0.42 (0.20, 0.88)	20 (26)	0.62 (0.25, 1.51)
Type of menopause							
Natural	157 (66)	109 (55)	Ref.	63 (54)	Ref.	31 (53)	Ref.
Hysterectomy	72 (30)	65 (33)	1.17 (0.75, 1.82)	33 (28)	1.03 (0.60, 1.77)	26 (45)	1.52 (0.78, 2.96)
Oophorectomy	5 (2.1)	2 (1.0)	0.64 (0.12, 3.47)	2 (1.7)	1.04 (0.19, 5.63)	0	—
Other[c]	4 (1.7)	21 (11)	5.08 (1.62, 15.88)	19 (16)	8.14 (2.53, 26.2)	1 (1.7)	0.66 (0.07, 6.37)
OC use							
Never	79 (23)	58 (21)	Ref.	38 (23)	Ref.	12 (15)	Ref.
Ever	272 (77)	215 (79)	0.91 (0.59, 1.39)	130 (77)	0.71 (0.43, 1.17)	66 (85)	1.30 (0.63, 2.69)
OC duration							
None	79 (23)	58 (21)	Ref.	38 (23)	Ref.	12 (15)	Ref.
⩽5 years	121 (34)	114 (42)	1.11 (0.70, 1.76)	71 (43)	0.89 (0.52, 1.52)	33 (42)	1.53 (0.71, 3.33)
>5 years	150 (43)	100 (37)	0.74 (0.47, 1.19)	58 (34)	0.55 (0.32, 0.96)	33 (42)	1.11 (0.51, 2.43)
P-trend			0.12		0.03		0.93
PMH use[d]							
Never	126 (52)	106 (54)	Ref.	66 (56)	Ref.	27 (47)	Ref.
Former	94 (39)	76 (38)	1.03 (0.67, 1.57)	42 (36)	1.16 (0.70, 1.91)	26 (45)	1.59 (0.82, 3.11)
Current	24 (10)	16 (8)	0.80 (0.39, 1.61)	10 (8)	1.13 (0.50, 2.54)	5 (9)	1.47 (0.50, 4.29)
PMH duration[d]							
None	126 (52)	106 (54)	Ref.	66 (56)	Ref.	27 (47)	Ref.
<1	17 (7)	11 (6)	0.75 (0.33, 1.71)	6 (5)	0.89 (0.33, 2.40)	5 (9)	1.56 (0.50, 4.86)
1–5	42 (17)	39 (20)	1.10 (0.64, 1.88)	22 (19)	1.38 (0.74, 2.57)	13 (22)	1.83 (0.83, 4.03)
>5	56 (23)	42 (21)	1.01 (0.61, 1.67)	24 (20)	1.12 (0.62, 2.04)	13 (22)	1.43 (0.64, 3.18)
P-trend			0.85		0.99		0.49

Abbreviations: Adj. = adjusted; AML = acute myeloid leukaemia; CI = confidence interval; CML = chronic myelogenous leukaemia; OC = oral contraceptive; OR = odds ration; PMH = postmenopausal hormone; Ref. = referent.

[a] *N*'s may not sum to total due to missing data.

[b] All models are adjusted for age group (<50, 50–59, 60–69, 70+), body mass index category (normal/underweight, overweight, obese), and smoking status (never/ever).

[c] Other includes: chemotherapy and hormone therapy, radiation.

[d] Analysis for PMH does not include premenopausal women.

and Philip, 1991; Goodwin *et al*, 1999) is the most likely explanation for the strong association between 'other' type of menopause and myeloid leukaemia. Of note, 8 out of 21 cases who reported 'other' as the cause of menopause were classified as therapy related under the WHO criteria (Vardiman *et al*, 2002).

There is biological plausibility for a role of hormones, particularly oestrogen, in leukaemia aetiology, although the expected direction of the association is not entirely clear. First, oestrogen is involved in proliferation and differentiation of normal haematopoietic cells (Kincade *et al*, 2000; Kouro *et al*, 2001; Medina *et al*, 2001). Second, binding sites for oestrogen have been reported in primary leukaemias (Danel *et al*, 1985) and leukaemia cell lines (Kauss *et al*, 2008). Finally, oestrogen receptor methylation is associated with improved AML survival (Li *et al*, 1999). Despite this evidence, we found that, with the possible exception of OC use for AML and parity for CML, hormonal and reproductive factors are not likely to have a significant aetiological role in myeloid leukaemia.

The inverse association between OC use and AML reported here is the opposite to the Traversa *et al* (1998) study, who reported a nonsignificant increased risk of acute leukaemia (i.e., including acute lymphoblastic leukaemia) in women who filled at least one prescription for OCs (OR = 1.8, 95% CI = 0.8–4.0). This difference in case populations may explain differences in findings, further, results were not stratified by leukaemia subtype. In fact, the association between CML and OC use was nonsignificantly positive, supporting potential differences by leukaemia subtype. OCs have been shown to influence lymphocytes, specifically cytotoxic lymphocytes and B cells, in a previous prospective study (Auerbach *et al*, 2002). The association between OCs and AML should be further evaluated in additional studies or pooled analyses.

There are a number of strengths associated with our study, including rapid case ascertainment for this rapidly fatal disease and absence of proxy interviews. However, there are also a number of limitations including the potential for recall bias, the lack of detail regarding the type of postmenopausal hormones and OCs used, the timing of OC and PMH use, and the reliance on self-report. Selection bias is also possible given the response rates (58% for cases and 64% for controls), although we observed no difference between cases and controls with respect to income and education. We did observe differences in participation rates by disease subtype, which is most likely explained by the lack of proxy interview. The strong association between 'other' type of menopause and AML risk suggests that women may have reported menopause related to treatment for their current leukaemia.

Overall, these data suggest that exogenous hormone use and reproductive factors are unlikely to have a significant role in the aetiology of myeloid leukaemia, and suggest that other undiscovered aetiologic factors likely explain the lower incidence of leukaemia in females.

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