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.

Keywords: myeloid leukaemia; hormone replacement therapy; oral contraceptives

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, 9911), chronic myelogenous leukaemia (CML; 9863, 9875–9876), chronic myelomonocytic leukaemia (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 cytogentic 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
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 leukemia. 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 leukemia 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.

| Table 1. Selected characteristics of the study population and association with myeloid leukaemia |
|-----------------------------------------------|
| Controls | All cases | OR (95% CI) | AML cases | OR (95% CI) | CML cases | 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) | 160 (94) | 74 (94) | 36 (46) | 121 (4) |
| Other   | 19 (5)    | 16 (6)      | 11 (6)    | 5 (6)      |           | 1.21 (0.44, 3.33) |
| Smoking status |
| Never   | 202 (57)  | 136 (49)    | 85 (50)   | 36 (46)    | 121 (34)  | 86 (31)    | 49 (29)   |
| Ever    | 152 (43)  | 141 (51)    | 4.38 (1.98, 9.79) | 85 (50)   | 36 (39)   | 0.71 (0.45, 1.11) |
| Education |
| <HS     | 121 (34)  | 86 (31)     | 0.81 (0.55, 1.19) | 49 (29)   | 66 (39)   | 26 (33)    |
| Some post HS | 115 (32) | 101 (36)    | 4.29 (1.83, 9.92) | 66 (39)   | 26 (33)   | 0.95 (0.52, 1.73) |
| College graduate | 122 (34) | 91 (33)   | 0.85 (0.58, 1.24) | 56 (33)   | 27 (34)   | 0.98 (0.54, 1.78) |
| Income* |
| ≤$40,000 | 152 (43)  | 118 (43)    | 1.06 (0.75, 1.51) | 74 (44)   | 35 (46)   | 0.72 (0.42, 1.25) |
| $40,000–$80,000 | 137 (39) | 100 (38)    | 1.17 (0.77, 1.77) | 57 (34)   | 35 (46)   | 0.88 (0.44, 1.76) |
| >$80,000 | 62 (18)   | 54 (20)     | 1.40 (0.84, 2.33) | 36 (22)   | 14 (18)   |           |

Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; HS=high school; OR = odds ration; Ref. = referent.

*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

| Age at menopause (years) | Controls N (%) | All Cases N (%) | Adj. b OR (95% CI) | AML Cases N (%) | Adj. b OR (95% CI) | CML Cases N (%) | Adj. b OR (95% CI) |
|-------------------------|----------------|----------------|-------------------|----------------|-------------------|----------------|-------------------|
| <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 a                 | 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              |                |                   |                |                   |

| 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) |

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

aCases may not sum to total due to missing data.

bAll 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).

Other includes: chemotherapy and hormone therapy, radiation.

dAnalysis 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 timing of OC and PMH use, and the reliance on self-report.

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