Hormonal and Reproductive Factors and Risk of Myeloproliferative Neoplasms in Postmenopausal Women

Alexis D. Leal, Carrie A. Thompson, Alice H. Wang, Robert A. Vierkant, Thomas M. Habermann, Julie A. Ross, Ruben A. Mesa, Beth A. Virnig, and James R. Cerhan

Abstract

Background: Hormonal and reproductive history has been associated with risk of some hematologic malignancies, but their role in myeloproliferative neoplasms (MPN) is largely unknown.

Methods: Using a population-based cohort study, we evaluated the association of these factors with risk of MPN overall, and for essential thrombocytopenia (ET) and polycythemia vera (PV) specifically. Incident MPN cases from 1993 to 2004 were identified via linkage to Medicare. RR and 95% confidence intervals (CI) were estimated using Cox proportional hazard regression.

Results: After >250,000 person-years of follow-up, 257 cases of MPN were identified (172 ET, 64 PV). Ever use of hormone therapy (HT) was associated with an increased risk of ET (RR = 1.63; 95% CI, 1.19–2.23) but a decreased risk of PV (RR = 0.58; 95% CI, 0.34–0.98). There were no statistically significant associations of oral contraceptives or reproductive factors available are related to risk of lymphoid malignancies, with studies finding no association between risk of non–Hodgkin lymphoma (NHL) with hormone therapy (HT; refs. 2–8) and oral contraceptive (OC) use (8, 9), although other studies have shown either a reduced (10) or an increased risk of NHL associated with HT (11–13). A pooled analysis of case–control studies from the InterLymph Consortium reported no association of risk of NHL overall with OC use, but increased risk for follicular lymphoma (14); in contrast there was a decreased risk of NHL overall with HT use, particularly use close to menopause (15). Reproductive factors, including age at menarche (7, 9, 10, 16), age at menopause (5, 8, 16), age at first live birth (7, 9, 10, 16), and nulliparity (9, 16), have largely shown no association with NHL risk, which was also found in an InterLymph pooled analysis (14). Although fewer in number, studies of acute myeloid leukemia (AML) have shown no association with use of HT (17, 18), age at menarche (17), or parity (17, 19), although one study showed a weak inverse association between OC use and risk of AML (17). One study showed a weak inverse association between parity and age at first birth in chronic myelogenous leukemia (CML; ref. 19).

In this study, we evaluated the association of exogenous estrogen use and reproductive factors with risk of MPN overall and by the common MPN subtypes in a large prospective cohort of Iowa women.

Materials and Methods

Iowa Women’s Health Study (IWHS)

The IWHS is a prospective cohort study, the details of which have been previously published elsewhere (20, 21). In brief, the
IWHS consists of 41,836 randomly selected women, in the age range of 35 to 69 years, with a valid Iowa driver's license, who were enrolled in the study in 1986. Study participants completed a baseline questionnaire in 1986 and follow-up questionnaires in 1987, 1989, 1992, 1997, and 2004. The baseline questionnaire included demographics, anthropometrics, medical history, and lifestyle factors. Approximately 79% of participants responded to the 1992 questionnaire, and only data from the 1986 and 1992 questionnaires were included in this analysis. Annual linkage to a database of Iowa death certificates, supplemented by linkage to the National Death Index, was utilized to identify deaths for survey nonrespondents and those that emigrated from Iowa. This study was approved by the University of Minnesota and the Mayo Clinic Institutional Review Boards.

**Exposure assessment**

OC use, age at menarche, age at menopause, parity, number of live births, and age at first live birth were ascertainmented on the 1986 questionnaire. Quartiles of ovulatory years were determined by subtracting age at menarche and time spent pregnant from age of menopause. HT use was ascertainmented in 1992 and 1986 and summarized as ever versus never use. Several factors previously associated with MPN risk were assessed as potential confounding factors (22), including physical activity (1986), body mass index (BMI; 1992), diabetes (1986 and 1992), smoking (1986 and 1992), and aspirin use (1992).

**MPN ascertainment**

Cases of MPN were identified in the IWHS cohort via linkage to the Centers for Medicare Services (23) claims data using an established methodology (24). We acquired Medicare hospitalization data from 1986 to 2004 (MedPAR file) and outpatient and carrier files (physician and other suppliers) from 1991 to 2004 (Part B claims data were not available before 1991). We only included women in the Medicare fee for service program, as all but 87 of the IWHS participants who survived to age 65 years and were linked to Medicare data had been, for at least some period of time, enrolled in the Medicare fee-for-service program. MPN cases were identified from Medicare Part A and B claims data by using International Classification of Diseases, Ninth Revision (ICD-9) codes 238.4 (PV), 238.7 (myeloproliferative and lymphoproliferative NOS; idiopathic thrombocytopenia; myelosclerosis; myelodysplastic syndrome; panmyelosis), 289.6 (familial polycythemia), 289.89 (MF; hypercytopenia; myelosclerosis; myelodysplastic syndrome; panmyelosis), 289.0 (secondary polycythemia), and 289.9 (blood dyscrasia NOS; erythroid hyperplasia), as recommended by Ma and colleagues (25). Cases were classified if the same code was used at least twice in one year, which were not allowed to occur on the same day. We defined PV by codes 238.4 and 289.6; ET by 289.9; MF by 289.89; and unspecified MPN by 283.7 and 289.0. Women with more than one diagnosis of PV, ET, or MF were classified as the subtype that was diagnosed at the earliest date. Due to the existence of nonspecific codes that also include myelodysplastic syndromes, patients were censored if they only met nonspecific MPN criteria, but never had a documented diagnosis of PV, ET, or MF.

Women who were not enrolled in both Medicare part A and B for at least 1 month on or after January 1, 1993 (n = 3,014), who did not complete the 1992 follow-up questionnaire (n = 8,819), who had a self-reported history of cancer on the 1986 or 1992 questionnaires or were identified with cancer through 1992 by linkage to the Iowa Cancer Registry (n = 6,723), who had a history of PV, ET, or other MPN prior to age 66 (n = 42), who had less than 1 year of follow-up (n = 2,666), who had an MPN event within 1 year of follow-up (n = 170), and who had a first diagnosis date before January 1, 1993 (n = 4), were excluded from the original sample. At the end of our analysis, 27,370 women remained in the cohort and were eligible for analysis.

To decrease the likelihood of pre-enrollment prevalent subclinical disease, individuals did not contribute person-years of observation until one year after Medicare enrollment. Each woman accumulated person-years of follow-up from this date until the first occurrence of an MPN diagnosis, Medicare Part A or B disenrollment, date of death, or December 31, 2004, if none of these events occurred.

**Data analysis**

RR and 95% confidence intervals (CI) were calculated as a measure of association of reproductive factors of interest with MPN incidence using Cox proportional hazards regression (26), with age as the underlying time variable (27). Analyses were conducted for all MPN cases as well as ET and PV; there were too few MF cases to provide reliable estimates. When estimating MPN subtype risk, those with MPN not of that type were censored at time of diagnosis. Tests for trend were completed by ordering the ordinal exposure categories of intake quartiles from lowest to highest and including the resulting variable as a one degree-of-freedom linear term in the Cox regression models.

Basic Cox regression models accounted for age only, and multivariable models adjusted for subtype-specific potential confounding factors (22). Potential confounding variables included diabetes, BMI, physical activity, aspirin use, and smoking, and were coded as presented in Table 1. Heterogeneity of RRs for exposure variables between PV and ET were assessed by using a
competing risk form of Cox proportional hazards regression (28). All statistical tests were two-sided, and analyses were performed using the SAS (SAS Institute Inc.) and R software systems.

Results

At the 1992 analysis baseline, there were 27,370 eligible cancer-free women in the at-risk cohort; their mean age was 70.3 years (range, 65.0–85.6), and 99.3% were Caucasian. The median follow-up was 11 years, and the mean age at MPN diagnosis was 76.2 years (range, 66.0–88.7). The distribution of potential confounding factors between cases and non-cases is shown in Table 1.

Ever use of HT showed a weak positive association with overall risk of MPN (RR = 1.23), which was not statistically significant (Table 2). However, there was significant heterogeneity by subtype ($P = 0.00091$), with ever use of HT associated with increased risk of ET (RR = 1.63; 95% CI, 1.19–2.23) but decreased risk of PV (RR = 0.58; 95% CI, 0.34–0.98). There was no association of OC use with risk of MPN overall or by subtype.

Although there was no association of oophorectomy with overall risk of MPN, there was evidence of heterogeneity by subtype ($P = 0.0042$). Specifically, bilateral oophorectomy, compared with no oophorectomy, was associated with an increased risk of ET (RR = 1.58; 95% CI, 1.11–2.25), but decreased risk of PV (RR = 0.32; 95% CI, 0.12–2.14), although the latter was not statistically significant. There were no significant associations of unilateral oophorectomy with risk of ET or PV. There were also no associations for age at menarche, age at menopause, parity, number of live births, or age at first live birth. Quartiles of ovulatory years were not associated with overall risk of MPN. In subtype analysis, ovulatory years were associated with risk of PV (RR = 2.15 for 33.25–36.83 years; RR = 1.68 for >36.83 years; $P$ trend = 0.045), although there was no association with ET.

We next pursued multivariable modeling (Table 3). For ET, when we included both HT use and oophorectomy in the same model for risk of ET, the former slightly attenuated (RR = 1.52) although the latter showed much greater attenuation (RR = 1.33 for bilateral versus no oophorectomy) and was no longer statistically significant ($P = 0.15$). Because HT is often prescribed following oophorectomy, it is difficult to disentangle associations of each with risk of ET. However, the HT association remained (although attenuated) after subsetting to the 19,870 women who did not undergo oophorectomy (RR = 1.44; 95% CI, 0.98–2.12); we did not have sufficient data to assess oophorectomy by ever/never use of HT.

To assess the impact of potential confounding for other factors on these associations, we separately adjusted HT use and oophorectomy for diabetes, BMI, physical activity, and ever use of aspirin, all factors associated with ET risk in the IWHS (22); both HT use (RR = 1.67) and oophorectomy (RR = 1.56 for bilateral versus no oophorectomy) remained associated with risk of ET (Table 3).

For PV, inclusion of HT use (RR = 0.70; 95% CI, 0.40–1.21), oophorectomy (RR = 0.41 for bilateral versus no oophorectomy; 95% CI, 0.14–1.16), and ovulatory years (RR = 1.25 for quartile 4 versus 1; $P$ trend = 0.26) in the same model (Table 3) attenuated all associations, acknowledging the correlated nature of these three variables. When we excluded women who ever had an oophorectomy, HT (RR = 0.55; 95% CI, 0.29–1.04) and ovulatory years (RR = 1.88 for quartile 4 versus 1; $P$ trend = 0.091) were largely similar to the estimates in Table 2. To assess the impact of potential confounding, we separately adjusted each of these three exposure variables for smoking, the main factor associated with PV risk in the IWHS (22); HT use (RR = 0.59; 95% CI, 0.34–1.02) and oophorectomy (RR = 0.34 for bilateral versus no oophorectomy; 95% CI, 0.12–0.95), but not ovulatory years (RR = 1.36 for quartile 4 versus 1; $P$ trend = 0.13), remained associated with risk of PV.

Discussion

Among this cohort of over 27,000 women, we found that ever use of HT was associated with an increased risk of ET, but a decreased risk of PV. We also found that quartiles of ovulatory years were associated with an increased risk of PV, but not ET. Furthermore, we found that bilateral oophorectomy was associated with increased risk of ET and decreased risk of PV. These factors were not impacted by adjustment for other risk factors for ET or PV. These findings suggest possible distinct etiologies of these two MPN subtypes.

There are several strengths to this study, one of which is that this is the first study to these authors’ knowledge to investigate the risk of estrogen exposure on the development of MPN. Recall and selection bias were minimized due to the prospective cohort design of this study. The subtype analysis of the two most common MPN subtypes, ET and PV limits the heterogeneity inherent to classifying MPN as a single entity. Additionally, cases of MPN were identified via linkage to Medicare, which eliminates potential bias due to self-reporting of these diagnoses.

There are also limitations to this study, the first of which is that due to the ascertainment of MPN cases via linkage to Medicare claims data, cases identified were limited to those that occurred in women of age 65 and older. Cases were identified using administrative billing codes using a published, validated algorithm (25); however, we did not validate these diagnoses in this study. The heterogeneity of the diagnostic criteria used from 1986 through 2004 is an important limitation. Additionally, although it is most accurate to categorize MPN subtypes as PV, ET, primary MF, and post-PV or post-ET MF, this was not feasible utilizing the billing data available. We utilized codes for ET and PV and required at least two diagnoses within one year, as well as excluded nonspecific codes, which included myelodysplastic syndrome to increase validity. The Iowa SEER Registry was not utilized to ascertain MPN cases as these data were not collected prior to 2001, and these data are likely underreported due to diagnosis in an outpatient setting (25). Exposure ascertainment was collected via questionnaire and was all self-reported, and we did not have type of hormones used or duration or recency of use. Our cohort consists mainly of older Caucasian women who live in the Midwest and thus may not be easily generalized to other populations.

HT, oophorectomy, and ovulatory years are clinically interdependent in that women undergoing bilateral oophorectomy no longer accrue ovulatory years and may be prescribed HT as part of their ongoing medical treatment. These relationships make it difficult to disentangle associations of each with risk of ET and PV. The relative strength of association for HT in age-adjusted analyses compared with oophorectomy and ovulatory years, along with the fact that we observed slightly less attenuation of associations with HT in multivariate models than with
<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-years</th>
<th>Cases</th>
<th>RR (95% CI)*</th>
<th>P trend</th>
<th>Cases</th>
<th>RR (95% CI)*</th>
<th>P trend</th>
<th>Cases</th>
<th>RR (95% CI)*</th>
<th>P trend</th>
<th>P-heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone therapy use</td>
<td>0.11</td>
<td>126,598</td>
<td>115</td>
<td>1.00 (Reference)</td>
<td></td>
<td>65</td>
<td>1.00 (Reference)</td>
<td></td>
<td>40</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>0.068</td>
<td>210,700</td>
<td>220</td>
<td>1.00 (Reference)</td>
<td></td>
<td>148</td>
<td>1.00 (Reference)</td>
<td></td>
<td>55</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
<td>109,579</td>
<td>101</td>
<td>1.00 (Reference)</td>
<td></td>
<td>73</td>
<td>1.00 (Reference)</td>
<td></td>
<td>22</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Age at menopause</td>
<td></td>
<td>31,055</td>
<td>34</td>
<td>1.00 (Reference)</td>
<td></td>
<td>20</td>
<td>0.97 (0.59, 1.59)</td>
<td></td>
<td>7</td>
<td>1.00 (0.47, 2.58)</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>0.0095</td>
<td>190,366</td>
<td>180</td>
<td>1.00 (Reference)</td>
<td></td>
<td>111</td>
<td>1.00 (Reference)</td>
<td></td>
<td>53</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>0.95</td>
<td>22,503</td>
<td>20</td>
<td>1.00 (Reference)</td>
<td></td>
<td>11</td>
<td>1.00 (Reference)</td>
<td></td>
<td>7</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Number of live births</td>
<td>0.87</td>
<td>22,503</td>
<td>20</td>
<td>1.00 (Reference)</td>
<td></td>
<td>11</td>
<td>1.00 (Reference)</td>
<td></td>
<td>7</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Age at first live birth</td>
<td>0.16</td>
<td>237,648</td>
<td>237</td>
<td>115 (0.73, 1.82)</td>
<td></td>
<td>161</td>
<td>1.40 (0.76, 2.58)</td>
<td></td>
<td>57</td>
<td>0.82 (0.37, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Quartiles of ovulatory years</td>
<td></td>
<td>27.75</td>
<td>65,080</td>
<td>61</td>
<td>1.00 (Reference)</td>
<td></td>
<td>46</td>
<td>1.00 (Reference)</td>
<td></td>
<td>11</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>

*RR (relative risk) and 95% confidence interval (CI) from Cox model accounting for age (modeled as the time variable).
Table 3. Multivariable models for risk of essential thrombocytopenia and polycythemia vera, IWHS, 1993 to 2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>Essential thrombocytopenia (ET)</th>
<th>Polycythemia vera (PV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simultaneous adjustment model⁺</td>
<td>Confounder modelsᵇ</td>
</tr>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Hormone therapy use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>1.52 (1.09, 2.13)</td>
<td>1.67 (1.21, 2.30)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.081</td>
<td>0.0018</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Yes - unilateral</td>
<td>1.14 (0.66, 1.97)</td>
<td>1.21 (0.71, 2.08)</td>
</tr>
<tr>
<td>Yes - bilateral</td>
<td>1.33 (0.90, 1.95)</td>
<td>1.56 (1.09, 2.24)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.16</td>
<td>0.015</td>
</tr>
<tr>
<td>Quantiles of ovulatory years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1: 0 &lt; x ≤ 27.75</td>
<td>Not included</td>
<td>Not done</td>
</tr>
<tr>
<td>Q2: 27.75 &lt; x ≤ 33.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3: 33.25 &lt; x ≤ 36.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4: 36.83 &lt; x</td>
<td>1.25 (0.58, 2.73)</td>
<td>1.36 (0.63, 2.98)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.26</td>
<td>0.13</td>
</tr>
</tbody>
</table>

⁺Model adjusted for all variables in the column (i.e., hormone therapy and oophorectomy) and accounting for age.
ᵇModel adjusted for all variables in the column (i.e., hormone therapy, oophorectomy, and ovulatory years) and accounting for age.
ᶜEach variable is individually adjusted for diabetes, body mass index, physical activity, aspirin use, and accounting for age.
ᵈEach variable is individually adjusted for smoking and accounting for age.

Estrogen Exposure and Risk of MPN

Table 3 summarizes the results of multivariable models for the risk of essential thrombocytopenia and polycythemia vera, based on the International Women’s Health Study (IWHS) data from 1993 to 2004. The table includes data for hormone therapy use, oophorectomy, and quantiles of ovulatory years. Each variable is individually adjusted for smoking and accounting for age.

The role of estrogen in the pathogenesis of hematologic malignancies has not been clearly elucidated. The breast, ovaries, and uterus are all considered estrogen target organs. However, estrogen receptors are also known to be present in several other tissues including cells of lymphoid and myeloid origin (30), and studies have shown that estrogens are important in the regulation of maturation, migration, and differentiation of both lymphoid and myeloid cells (30–33). Additionally, estrogen receptors have been identified on leukemia (33, 34) and lymphoma (35) cell lines and hypermethylation of the estrogen receptor has been shown to portend a favorable outcome in AML (36). One potential mechanism for estrogen’s role in the development of hematologic malignancy lies in its action as a potent stimulator of cell proliferation via its actions in the estrogen-signaling pathway (30, 37). An additional means of tumorigenesis is that estrogens may be metabolized to quinones, which may then interact with DNA to form adducts (38). Identification and removal of these adducts may result in the production of reactive oxygen species and subsequent oxidative DNA damage (37).

Alternative, laboratory studies in JAK2VI617F mutant mice have shown that the use of selective estrogen receptor modulators may decrease MPN-associated neutrophilia, thrombocytosis, splenomegaly, and MF and blocked MPN progression by inhibiting JAK2VI617F hematopoietic stem/progenitor cell expansion (39). Additional studies are needed to further define the role of estrogen, both risk and protective, in the pathogenesis of ET and PV.

In summary, these results suggest that estrogens play different roles in the etiology of ET and PV, and replication and further mechanistic investigations are warranted.

Disclosure of Potential Conflicts of Interest

R. Mesa reports receiving commercial research support from CTI, Gilead, and Incite; has received speakers bureau honoraria from Novartis; and is a consultant/advisory board member for Ataxa. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: R.A. Mesa, J.R. Cerhan
Development of methodology: R.A. Vierkant, R.A. Mesa, J.R. Cerhan

www.aacrjournals.org    Cancer Epidemiol Biomarkers Prev; 25(1) January 2016    155

Downloaded from cebp.aacrjournals.org on June 21, 2017. © 2016 American Association for Cancer Research.
Acknowledgments

The authors wish to thank Sondra Ruebler for editorial assistance. The authors also thank Drs. Aaron Folsom and DeAnn La过错ovich, the former and current Principal Investigator of the IWHS study.

Grant Support

This work was supported by grants from the NIH [R01 CA93742 [A.R. Folsom]; K05 CA157439 (A.D. Leal)]. There are no financial disclosures to report.

Received June 5, 2015, revised October 27, 2015, accepted November 4, 2015, published OnlineFirst November 12, 2015.
Hormonal and Reproductive Factors and Risk of Myeloproliferative Neoplasms in Postmenopausal Women

Alexis D. Leal, Carrie A. Thompson, Alice H. Wang, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-15-0613

Cited articles
This article cites 39 articles, 12 of which you can access for free at:
http://cebp.aacrjournals.org/content/25/1/151.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.