Case Series

Menopausal hormone therapy and mortality among women diagnosed with ovarian cancer in the NIH-AARP Diet and Health Study

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ABSTRACT

Background: Although menopausal hormone therapy (MHT) use has been linked with an increased risk of ovarian cancer, whether pre-diagnosis MHT use affects ovarian cancer-specific mortality is unknown.
Methods: Our analysis included 395 incident epithelial ovarian cancer patients with data on pre-diagnosis MHT use from the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for MHT type and ovarian cancer-specific mortality, adjusted for tumor characteristics, treatment, and other risk factors. Effect modification by histology (serous vs. non-serous) was examined using likelihood ratio tests comparing models with and without interaction terms between MHT type and histology.
Results: Ovarian cancer-specific mortality was not associated with pre-diagnosis estrogen-only therapy (ET) (HR = 1.09, 95% CI = 0.70–1.68) or estrogen plus progestin-only therapy (EPT) (HR = 0.97, 95% CI = 0.68–1.38). Neither recency of use nor specific regimen of EPT-only (sequential vs. continuous) was related to mortality. In analyses stratified by histology, no significant association between MHT type and ovarian cancer-specific mortality was observed among serous or non-serous cases; however, a significant interaction between MHT type and histology was noted (p-heterogeneity = 0.01).
Conclusion: Our results suggest that pre-diagnosis MHT use is not related to risk of ovarian cancer-specific death.
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1. Introduction

Following publication of unfavorable results from the Women's Health Initiative (WHI) trial, including an increased risk of breast cancer associated with estrogen plus progestin therapy (EPT) (Rossouw et al., 2002), prescription of all forms of menopausal hormone therapy (MHT) in the U.S. rapidly declined (Ettinger et al., 2012). Data from the North American Association of Central Cancer Registries showed an accelerated decline in ovarian cancer incidence after the year 2002, subsequent to the publication of the WHI results (Yang et al., 2013). Ovarian cancer risk may be driven by hormone-related factors (Hunn and Rodriguez, 2012) and the presence of hormone receptors in ovarian cancer tissues suggests this malignancy is hormonally-responsive (Rao and Slotman, 1991). In a meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer, both estrogen-only therapy

(ET) and EPT increased risk of ovarian cancer overall and for the two most common histology subtypes, serous and endometrioid (Collborative Group on Epidemiological Studies of Ovarian Cancer, 2015). However, whether use of MHT prior to diagnosis affects subsequent mortality among ovarian cancer patients has not been well-described. Therefore, we examined this relationship in the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study. We further evaluated whether the association between MHT and mortality differed by hormone type (ET versus EPT) or histology (serous versus non-serous).

2. Materials and methods

2.1. Study population

The NIH-AARP Diet and Health Study has been previously described (Schatzkin et al., 2001). Briefly, the NIH-AARP cohort included 566,398 AARP members (aged 50–71 years) who completed a mailed baseline questionnaire in 1995–1996. An additional questionnaire was sent out (1996–1997) with more detailed questions on MHT use. Of the

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128,002 women who completed the 1996–1997 questionnaire, 524 women developed epithelial ovarian cancer. After excluding women who reported a bilateral oophorectomy before baseline ($n = 43$) or had missing information on oophorectomy status ($n = 4$), premenopausal women ($n = 15$) or women with unknown menopausal status ($n = 16$), borderline or non-epithelial ovarian cancer ($n = 35$), and women without information on MHT type ($n = 16$), we had 395 incident epithelial ovarian cancers in our analysis. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute and all participants gave informed consent by virtue of completing and returning the questionnaire.

2.2. Tumor characteristics and treatment information

Date of cancer diagnosis, histology, stage, grade, and first course of treatment were available from cancer registries. Histology was defined using the *International Classification of Diseases for Oncology* (ICD-O 3rd Edition) and the American Joint Committee on Cancer Staging System was used for classification of stage. Ovarian cancer cases with the following histology codes were included for analysis: serous (8441, 8460, 8461) and non-serous (endometrioid: 8380, 8382, 8383; mucinous: 8480, 8482; other epithelial: 8000, 8010, 8012, 8022, 8041, 8050, 8071, 8076, 8255, 8260, 8310, 8320).

2.3. Mortality ascertainment

Addresses for cohort members were updated periodically based on information provided by the participants and through the National Change of Address database. Vital status and causes of death were ascertained using the U.S. Social Security Administration Death Master File and the National Death Index through December 31, 2011. ICD-9 and ICD-10 codes were used to identify deaths due to ovarian cancer (ICD-9: 183; ICD-10: C56).

2.4. Menopausal hormone therapy and covariate assessment

As previously described (Lacey et al., 2007), detailed MHT information, including dates of first use and last use, total duration of use, regimen, usual dose, and name of the pill taken for the longest time was collected. Women were classified as using EPT-only if the reported dates of estrogen use and progestin use overlapped or were within 90 days of each other. Sequential EPT was defined as progestin delivered for <15 days per cycle and continuous EPT was defined as progestin delivered for ≥15 days per cycle. Women who reported using ET and EPT without overlapping dates or with unknown duration of progestin were included in a separate category. The baseline questionnaire assessed demographics, body mass index (BMI), reproductive history, oral contraceptive use, menopausal status, and smoking status, which were all considered as confounders.

2.5. Statistical analysis

Multivariable Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer-specific mortality with age as the underlying time metric. Follow-up time started at age of ovarian cancer diagnosis and ended at age of death or end of follow-up, whichever occurred first. The proportional hazards assumption was evaluated with likelihood ratio (LR) tests comparing models with and without interaction terms between MHT type and follow-up time.

We examined relationships between any MHT use and MHT type (no MHT, ET-only, EPT-only, combinations of ET and EPT) with ovarian cancer-specific mortality. Associations between recency of ET-only or EPT-only, and EPT-only regimen (sequential vs. continuous) with mortality were assessed in separate models that included indicator variables for other MHT types. Models were adjusted for stage, histology, grade,

surgery, radiotherapy, chemotherapy, years from questionnaire to diagnosis, race, parity, diabetes, age at menopause, education, and years from questionnaire to diagnosis. Analyses were repeated stratified by histology (serous vs. non-serous). We assessed effect modification by histology using LR tests comparing models with and without interaction terms between MHT type and histology. Missing data were treated as separate categories for relevant variables. All analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC).

3. Results

Our cohort consisted of 395 women diagnosed with incident epithelial ovarian cancer including 210 serous, 28 endometrioid, 20 mucinous, and 137 other cases. Women were diagnosed a median of 4.6 years (minimum < 0.1, maximum = 10.2) after the 1996–1997 questionnaire was administered. We identified 283 deaths through 2011, of which, 239 were due to ovarian cancer. Median follow-up time from ovarian cancer diagnosis to death or end of follow-up was 3.4 years (minimum < 0.1, maximum = 14.9).

Baseline characteristics of our study population according to MHT type are shown in Table 1. One hundred seventy one women (43.3%) never used MHT, while 94 (23.8%) used ET-only, 88 (22.3%) used EPT-only, and 42 (10.6%) used combinations of ET and EPT. Compared with non-MHT users, ET-only users were more likely to be younger at enrolment, normal-weight, oral contraceptive users, post-surgically menopausal, and non-diabetic; EPT-only users were more likely to be younger at enrolment, highly educated, normal-weight, former smokers, oral contraceptive users, younger when they experienced natural menopause, and non-diabetic. Years from the 1996–1997 questionnaire to ovarian cancer diagnosis did not differ according to MHT type (data not shown, Kruskal–Wallis $p = 0.33$).

3.1. Ovarian cancer-specific mortality and MHT characteristics

Compared with never use, use of any MHT was unrelated to ovarian cancer-specific mortality overall (HR = 1.00, 95% CI = 0.75–1.33) or among serous (HR = 1.12, 95% CI = 0.76–1.66) or non-serous cases (HR = 1.06, 95% CI = 0.18–2.55). We observed no significant relationship between ovarian cancer-specific mortality with ET-only use (HR = 1.09, 95% CI = 0.70–1.68), recency of ET use (former: HR = 0.80, 95% CI = 0.40–1.59; current: HR = 1.24, 95% CI = 0.77–2.01), EPT-only use (HR = 0.97, 95% CI = 0.68–1.38), regimen of EPT use (sequential: HR = 0.91, 95% CI = 0.50–1.63; continuous: HR = 1.00, 95% CI = 0.68–1.48), or recency of EPT use (former: HR = 1.08, 95% CI = 0.57–2.04; current: HR = 0.94, 95% CI = 0.64–1.38) (Table 2).

3.2. Ovarian cancer-specific mortality and MHT characteristics: stratification by histology

In analyses stratified by histology (serous versus non-serous), we did not observe significant associations among women who developed serous or non-serous tumors for any category of MHT use. Despite the lack of statistical significance in either stratum, effect estimates for MHT type were significantly heterogeneous by histology (p-heterogeneity = 0.01) (Table 2).

4. Discussion

In this study of women diagnosed with ovarian cancer, there were no significant relationships between ovarian cancer-specific death and MHT type, recency of MHT use, or EPT regimen. Although none of the relationships between MHT and ovarian cancer-specific mortality were significant within histology-defined strata, we observed significant effect modification by histology.

Three previous studies (Mascarenhas et al., 2006; Wernli et al., 2008; Hein et al., 2013), which included between 244 and 751 ovarian cancer