Anti-Mullerian hormone and endometrial cancer: a multi-cohort study

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Background: The Mullerian ducts are the embryological precursors of the female reproductive tract, including the uterus; anti-Mullerian hormone (AMH) has a key role in the regulation of foetal sexual differentiation. Anti-Mullerian hormone inhibits endometrial tumour growth in experimental models by stimulating apoptosis and cell cycle arrest. To date, there are no prospective epidemiologic data on circulating AMH and endometrial cancer risk.

Methods: We investigated this association among women premenopausal at blood collection in a multicohort study including participants from eight studies located in the United States, Europe, and China. We identified 329 endometrial cancer cases and 339 matched controls. Anti-Mullerian hormone concentrations in blood were quantified using an enzyme-linked immunosorbent assay. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) across tertiles and for a doubling of AMH concentrations (ORlog2). Subgroup analyses were performed by ages at blood donation and diagnosis, oral contraceptive use, and tumour characteristics.

Results: Anti-Mullerian hormone was not associated with the risk of endometrial cancer overall (ORlog2: 1.07 (0.99–1.17)), or with any of the examined subgroups.

Conclusions: Although experimental models implicate AMH in endometrial cancer growth inhibition, our findings do not support a role for circulating AMH in the aetiology of endometrial cancer.

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In early gestation, male and female embryos have both Wolffian ducts, which subsequently develop into the male genital tracts in the male fetus, and Mullerian ducts, which develop into the uterus, the fallopian tubes, and the upper vagina in female fetus (Sobel et al, 2004). The anti-Mullerian hormone (AMH), also known as the Mullerian-inhibiting substance (MIS), is secreted by the Sertoli cells of the testes and is responsible for the regression of the Mullerian ducts during foetal life in males (MacLaughlin and Donahoe, 2010). Its concentrations are very low at birth, increase significantly at puberty, remain stable thereafter until age ~25 years, and then slowly decline to be undetectable at the onset of menopause, when the ovarian follicle pool is exhausted (Dewailly et al, 2014). The clinical use of AMH is well established. In females, serum AMH is utilised for monitoring patients with ovarian granulosa cell tumours, with up to 90% of cases presenting with high AMH concentrations (Geerts et al, 2009), and AMH concentrations can be predictive of ovarian response after in vitro fertilisation treatments (Fleming et al, 2015). Further, AMH is under discussion to become a diagnostic criterion for patients with polycystic ovary syndrome (PCOS), as AMH levels are two to four times higher in women with PCOS as compared with healthy women (Garg and Tal, 2016).

Anti-Mullerian hormone activates downstream pathways notable for differentiation and growth inhibition by binding to its specific type II receptor (AMHRII), and in vitro experimental models have shown that AMH inhibits endometrial cancer growth by apoptosis and cell cycle arrest in AMHRII-positive endometrial cancer cell lines (Kim et al, 2014). Renaud et al (2005) provided the first evidence for a potential inhibitory effect of AMH in endometrial cancer, showing that AMH inhibits endometrial cancer growth by apoptosis and cell cycle arrest in AMHRII-positive endometrial cancer cell lines.

In 2012, endometrial cancer, also referred to as cancer of the corpus uteri, was predicted to be diagnosed in more than 47 000 women in the United States (Siegel et al, 2012) with more than 300 000 incident cases worldwide (Ferlay et al, 2014). Although this cancer is frequently diagnosed when still localised, ~30% of cases are diagnosed at more advanced stages (regional/distant; Howlader et al, 2017) according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Established risk factors for endometrial cancer are obesity and use of exogenous oestrogen after menopause; however, these factors can only explain about half of the endometrial cancer cases in Western countries (Arnold et al, 2015).

To date, there are no prospective epidemiologic data on the association between AMH and risk of endometrial cancer. However, given experimental data, we hypothesised that higher circulating AMH levels may confer a relative protection against the development of endometrial cancer. We investigated this hypothesis in a nested case–control study including premenopausal women from cohort studies within the Prospective Study of AMH and Gynecologic Cancer Risk.

### MATERIALS AND METHODS

#### Study population

This nested case–control study included participants from eight prospective cohort studies located in the United States, Europe, and China. The following studies contributed to this investigation: Columbia, Missouri Serum Bank (USA; Dorgan et al, 2009), the Campaign Against Cancer and Heart Disease (CLUE I/II; USA; Mc Sorley et al, 2007), the New York University Women’s Health Study (NYUWHS; USA; Clendenen et al, 2016), the European Prospective Investigation into Cancer and Nutrition (EPIC; Europe; Dossus et al, 2010), the Guernsey Cohort Study (UK; Wang et al, 2014), the Hormones and Diet in the Etiology of Breast Cancer (ORDET; Italy; Clendenen et al, 2016), the Northern Sweden Health and Disease Study (NSHDS; Sweden; Clendenen et al, 2016), and the Shanghai Women’s Health Study (SWHS; China; Dorgan et al, 2009).

In each of the cohort studies, blood samples were collected using standardised protocols. Samples were stored at ~70 °C in all studies except the Guernsey study; samples from this study were stored at ~20 °C. Detailed information on each of the contributing cohorts is provided in Table 1 and Supplementary Table 1. The study was approved by the institutional review boards of the collaborating institutions and the University of Heidelberg, Germany, and the University of Maryland, Baltimore, MD, USA. All participants provided informed consent.

#### Ascertainment of cases

Our investigation was limited to premenopausal participants, who were younger than 47 years at blood collection, as AMH concentrations decline with age and are undetectable after menopause. Cases included women diagnosed with incident, primary endometrial cancer ascertained by self-report with medical record confirmation and/or linkages to cancer registries. All cases had no history of cancer, with the possible exception of non-melanoma skin cancer, before the diagnosis of endometrial cancer and did not report prior hysterectomy. Tumour characteristics (i.e., histology, stage, and grade) were obtained from cancer registries, pathology reports, and medical records. We identified a total of 329 eligible endometrial cancer cases diagnosed after blood collection. Six of these cases were diagnosed with synchronous ovarian cancer (none of which were of granulosa tumours); these cases were excluded in sensitivity analyses.

#### Control selection

Eligible controls were premenopausal women younger than 47 years at blood collection and were cancer-free (except non-melanoma skin cancer) and not reporting prior hysterectomy at the index date of their matched case. For every cohort, except NSHDS, one control was matched to each case; NSHDS matched up to two controls per case. All studies matched cases and controls on age and date at blood collection; additional matching factors specific to each cohort included study centre, time of day at blood collection, fasting status, and menstrual cycle phase (matching factors by study provided in Supplementary Table 1). A total of 339 matched controls were identified.

### Table 1. Characteristics of samples from participating cohorts: prospective study of AMH and gynaecologic cancer risk

| Cohort       | Recruitment population                                                                 | N cases/controls |
|--------------|----------------------------------------------------------------------------------------|-----------------|
| **USA**      |                                                                                         |                 |
| Columbia     | Residents of Columbia, MO                                                               | 10/10           |
| CLUE VII     | Residents of Washington County, MD                                                     | 102/102         |
| NYUWHS       | Women attending a breast cancer screening center in New York, NY                         | 60/60           |
| **Europe**   |                                                                                         |                 |
| EPIC         | Volunteers in 10 European countries                                                    | 6/67            |
| Guernsey     | Residents of the island of Guernsey, UK                                                | 11/11           |
| ORDET        | Residents of the Varese province, Italy                                                | 18/18           |
| NSHDS        | Residents of Northern Sweden                                                           | 13/23           |
| **China**    |                                                                                         |                 |
| SWHS         | Residents of seven urban communities in Shanghai                                        | 48/48           |

Abbreviations: AMH—anti-Mullerian hormone; CLUE—Campaign against Cancer and Heart Disease; EPIC—European Prospective Investigation into Cancer and Nutrition; NSHDS—Northern Sweden Health and Disease Study; NYUWHS—New York University Women’s Health Study; ORDET—Hormones and Diet in the Aetiology of Breast Cancer; SWHS—Shanghai Women’s Health Study.
Participating cohorts contributed between 10 cases/10 controls (Columbia Serum Bank) to 102 cases/102 controls (CLUEI/II; Table 1).

**Case characteristics.** Histology data were available for 309 cases (94%). The majority of cases were diagnosed with adenocarcinoma not otherwise specified (NOS; n = 166, 54%), followed by endometrioid tumours (n = 96, 31%) and others (n = 47, 15%; e.g., serous (n = 10), mucinous (n = 6)). The majority of cases had data on stage (n = 227; 69%) and grade (n = 219; 67%) at diagnosis. Well-differentiated tumours (i.e., grade 1) were classified as 'low grade' (n = 118; 54%), whereas moderately and poorly/undifferentiated tumours (i.e., grades 2 and 3) were classified as 'high grade' (n = 101; 46%). Data on histology and grade were used to classify 82% of tumours into Type I and Type II. We classified endometrioid adenocarcinoma (ICD-O-2 codes: 8380, 8381, 8382, and 8383) with grades 1 and 2, adenocarcinoma NOS (8140), and adenocarcinoma with squamous differentiation (8560, 8570) as Type I (90%, n = 242), and endometrioid adenocarcinoma with grade 3, serous/papillary serous (8441, 8460, 8461) and mixed cell adenocarcinoma (8323) as type II tumours (Setiawan et al, 2013).

**Covariate data.** Each participating cohort provided data on covariates; these data were collected at the time of blood collection and were centrally collated and harmonised. Information on demographics, lifestyle, reproductive history, and medical history was obtained via self-report and interview (Supplementary Table 1).

**Laboratory assays – AMH.** Blood samples from each cohort were sent to a single laboratory at the Massachusetts General Hospital (Boston, MA, USA) for AMH assays. This investigation used serum or plasma samples, depending on sample availability. Anti-Mullerian hormone concentrations in paired serum and plasma samples from the same individuals are highly correlated (r ≥ 0.98; Merhi et al, 2008) and we observed no difference in the mean AMH concentrations among participants with serum or plasma in the two studies that provided samples in both matrices (CLUEI/II: P = 0.84; EPIC: P = 0.88). Further, matrix (serum or plasma) was the same for each case and her matched control. Specimens of individually matched case and control subjects were always included in the same laboratory batch, alongside blinded quality-control samples. The technicians performing the assays were blinded to the case, control, or quality-control status of the specimens. Concentrations of AMH were measured using a commercially available picoAMH enzyme-linked immunosorbent assay (ELISA; Ansh Catalog no. AL-124, Webster, TX, USA); the assay limit of detection was 0.02 ng ml⁻¹. The overall coefficient of variation for AMH based on the study blinded pooled quality-control samples was 13.9%.

**Laboratory assays – androgens and sex hormone-binding globulin.** Androgens were measured as potential confounders. Where available, we used existing data on testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), and sex hormone-binding globulin (SHBG). These data were available from previous studies for at least a subset of participants in four of the participating cohorts (CLUE, EPIC, NYUWHS, and N5HS; n = 193, 29%). Laboratory methods for these measurements are provided in Supplementary Table 1. For participants without existing data on androgens or SHBG, participating cohorts were asked to provide additional serum (or plasma) volume for these assays. Samples from 235 participants from the Columbia, EPIC, Guernsey, NYUWHS, and ORDET cohorts were centrally assayed at the laboratory of the Division of Cancer Epidemiology at the German Cancer Research Center (DKFZ; Heidelberg, Germany). Direct radioimmunoassays (Beckman-Coulter, Brea, CA, USA) were used to measure testosterone, androstenedione, and DHEAS. SHBG was measured using an immunoradiometric assay (Cis-Bio, Gif-sur-Yvette, France). The overall coefficients of variation for samples assayed at DKFZ were <22% for all androgens and 21% for SHBG.

**Statistical analyses.** Anti-Mullerian hormone concentrations were log2-transformed to normalise the distribution; this transformation also allows an estimation of the effect of a doubling of AMH (i.e., one-unit increase in log-transformed AMH corresponds to a doubling). The extreme Studentised deviate many-outlier procedure was used to identify outliers (Rosner, 1983); no outliers were identified. Tertiles of AMH were defined using the study-specific distribution in controls; P for trend was calculated using tertile medians. Given that age is a very strong determinant of AMH concentrations, cases and controls were matched on age at blood draw and in addition all models were adjusted for age. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) across tertiles of AMH concentrations and for a doubling of AMH concentrations (ORlog2).

To assess between-study heterogeneity, we used a random effects model as proposed by DerSimonian and Laird (1986); we observed no significant between-study heterogeneity. Therefore, we present results based on the pooled participant data.

We evaluated the effect of potential confounders (i.e., age at menarche (continuous, 25% missing), body mass index (BMI; continuous, 21% missing), ever use of oral contraceptives (OC; no, yes, 23% missing), total number of pregnancies (0, 1, 2, 3, ≥ 4; 27% missing), smoking status (never, past, current; 4% missing)) using multiple imputations with 10 imputed data sets and adjusted OR estimates calculated in each of the multiple-imputed data sets and pooled using Rubin’s rule (Raghunathan et al, 2010). None of the potential confounders were retained in the final models since effect estimates were not influenced by statistical adjustment (<10% change after adjustment), and statistical significance of the observed associations was not affected.

Data on circulating androgen concentrations were available for 221 cases and 207 controls (64%). Adjustments for androgens or SHBG in subjects with available data had a negligible effect on risk estimates (<10% change after adjustment), and thus these markers were not retained in the final models.

Polytomous conditional logistic regression models were used to examine heterogeneity of associations between AMH concentrations and endometrial cancer by subtype defined by tumour-related characteristics (e.g., histology and age at diagnosis). Statistical heterogeneity of associations in stratified analyses was assessed via a likelihood ratio test comparing a model allowing the association for the risk factor of interest to vary by subgroup vs one assuming the same association (Wang et al, 2016). We evaluated heterogeneity by oral contraceptive use and age at blood draw by including a multiplicative interaction term in the models and evaluating the Wald P-value.

We conducted sensitivity analyses excluding women diagnosed at ≤ 1 or ≤ 2 years after blood donation to evaluate any effect of subclinical endometrial cancer on AMH concentrations, as well as the exclusion of women with synchronous ovarian cancer. Further sensitivity analyses excluded current OC users, as AMH levels are lower in current users compared with former or never users (Dollemann et al, 2013).

Given the final sample size of 329 cases and 339 controls, this study had statistical power to detect an OR of 0.61 or 1.64 with 80% power and 95% confidence when examining tertiles. This uses the observed within-matched pair correlation of M5 levels of 0.16. The study was slightly better powered than the protocol-specified detectable effect of 0.56 or 1.80, which had anticipated 342 matched pairs but also a larger within-matched pair correlation that would have reduced power. The study was also able to detect an ORlog2 of 0.87 or 1.15 for a one-unit change in log2-transformed AMH for endometrial cancer overall based on the observed log-2 transformed AMH s.d. of 2.26. Statistical power was more limited
in small subgroups (e.g., type II disease (n = 28 cases), 80% power, 95% confidence, and minimum detectable ORlog2 of 0.65 or 1.60).

All statistical analyses were conducted using the Statistical Analyses System (SAS) software, version 9.3 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and were considered statistically significant at P < 0.05.

RESULTS

The median age at blood draw in the study population was 41.5 years, ranging from 38 years in Guernsey and CLUE to 44 years in SWHS (Table 2 and Supplementary Table 2). Relative to controls, cases had a somewhat higher median BMI (kg m\(^{-2}\); cases: 24.8; controls: 23.7), a higher percentage was nulliparous (cases: 25%; controls: 20%), and a lower percentage reported ever OC use (cases: 46%; controls: 56%). The median age at diagnosis was 54 years and a median of 12 years elapsed between blood draw and diagnosis. As expected, AMH was inversely correlated with age at blood collection (Spearman: \(r_{\text{cases}} = -0.50, r_{\text{controls}} = -0.43\), both \(P < 0.01\)). Weak correlations were observed between androgens and SHBG and AMH (Spearman: \(r_{\text{cases}} = -0.27\) (SHBG) to 0.19 (testosterone), \(r_{\text{controls}} = -0.03\) (DHEAS) to 0.15 (testosterone)).

We observed no significant association between AMH and risk of endometrial cancer overall (ORlog2 = 1.07 [0.99–1.17]), and results from the pooled individual-level data were similar to those from the meta-analysis (ORlog2, meta-analysis = 1.05 [0.97–1.15]; \(P_{\text{heterogeneity}} = 0.46\); Figure 1). Similarly, we observed no association comparing extreme tertiles (OR \(T_3\) vs. \(T_1\) = 1.29 [0.82–2.03]; Table 3).

Results did not significantly differ by disease subtype (e.g., by histology, \(P_{\text{histology}} = 0.86\), endometrioid, OR \(T_3\) vs. \(T_1\) = 1.12 [0.49–2.57], \(P_{\text{trend}} = 0.46\); adenoacarcinoma, NOS, OR \(T_3\) vs. \(T_1\) = 1.47 [0.78–2.75], \(P_{\text{trend}} = 0.08\); Table 3), age at blood donation (\(P_{\text{age}} = 0.13\), or ever OC use (\(P_{\text{age}} = 0.85\)). In analyses stratified by cancer-related characteristics, we observed no heterogeneity by age at diagnosis (\(P_{\text{age}} = 0.77\), time between blood donation and diagnosis (\(P_{\text{age}} = 0.81\)), tumour grade (\(P_{\text{grade}} = 0.68\)), stage (\(P_{\text{stage}} = 0.53\), or Type I/II classification (\(P_{\text{stage}} = 0.70\)).

Results were similar when restricting analyses to women not using oral contraceptives at blood collection (\(n = 291\) sets; OR \(T_3\) vs. \(T_1\) = 1.19 [0.73–1.93], \(P_{\text{trend}} = 0.15\); ORlog2 = 1.06 [0.98–1.16]), or to women diagnosed more than 1 year after blood draw (\(n = 323\) sets) or 2 years after blood draw (\(n = 315\) sets; data not shown). Exclusion of the six cases with synchronous ovarian cancer did not have an impact on the observed effect estimates.

DISCUSSION

We conducted a world-wide collaborative investigation, including eight prospective cohort studies, and present the first data on pre-diagnosis AMH concentrations and subsequent risk of endometrial cancer. We observed no association between AMH concentrations and risk of endometrial cancer overall, or in analyses stratified by age at blood draw, oral contraceptive use, or cancer-related characteristics.

To date, evidence for an involvement of AMH in the development of endometrial cancer risk comes from experimental models (reviewed in Kim et al. (2014)). Experimental data have shown that AMH inhibits growth of human endometrial cancer cell lines that express the AMHRII by causing cell cycle arrest in the G1 phase and inducing apoptosis. Anti-Mullerian hormone regulates the proteins p107 and p130, responsible for G1-to-S phase transition and cell cycle exit, respectively, as well as the transcription factor E2F1, which leads to decreased cell division (Renaud et al., 2005). It should be noted that the concentrations used in these experimental models were reported to be double the dose required to induce Mullerian duct regression in culture (Renaud et al., 2005). Similar inhibitory effects have been observed in experimental models of endometrial stromal cells (Wang et al., 2009) and of endometriosis (reviewed in Kim et al. (2014); Signorel et al. (2014)). In terms of epidemiologic data, prior studies have noted lower AMH concentrations among women with endometriosis, although findings to date are somewhat inconsistent.
Prospective Study of AMH and Gynecologic Cancer Risk.

cohort and overall association in pooled analysis and meta-analysis:

Figure 1. ORs (95% CI) for a doubling of AMH concentrations by study

time to diagnosis

Table 3. ORs (95% CI) by age at blood draw, oral contraceptive use, and cancer-related information across tertiles and for
doubling of circulating AMH concentrations: prospective study of AMH and gynecologic cancer risk

| All women                                      | Cases/controls | Tertile 1 | Tertile 2 | Tertile 3 | \( P_{\text{rand}} \) | \( P_{\text{het}} \) | OR doubling | \( P \) |
|------------------------------------------------|----------------|-----------|-----------|-----------|----------------|----------------|-------------|--------|
| By age at blood draw                           |                |           |           |           |                 |                |             |        |
| <40 Years                                      | 109/113        | ref.      | 3.20 [1.78–6.80] | 1.97 [0.76–5.12] | 0.42           | 0.13           | 1.10 [0.94–1.30] | 0.24   |
| >40 Years                                      | 220/226        | ref.      | 0.98 [0.60–1.58] | 1.36 [0.79–2.35] | 0.10           |                | 1.07 [0.97–1.18] | 0.16   |
| By oral contraceptive use                      |                |           |           |           |                 |                |             |        |
| Ever                                           | 82/84          | ref.      | 1.40 [0.59–3.31] | 1.30 [0.55–3.06] | 0.24           | 0.85           | 1.11 [0.93–1.33] | 0.25   |
| Never                                          | 80/80          | ref.      | 1.27 [0.50–3.19] | 1.34 [0.52–3.46] | 0.34           |                | 1.05 [0.89–1.25] | 0.53   |
| Age at diagnosis                               |                |           |           |           |                 |                |             |        |
| ≤55 Years                                      | 198/203        | ref.      | 1.20 [0.68–2.11] | 1.32 [0.75–2.33] | 0.07           | 0.77           | 1.09 [0.98–1.20] | 0.10   |
| >55 Years                                      | 131/136        | ref.      | 1.49 [0.82–2.70] | 1.15 [0.53–2.47] | 0.67           |                | 1.05 [0.90–1.22] | 0.54   |
| Time to diagnosis                              |                |           |           |           |                 |                |             |        |
| ≤10 Years                                      | 118/120        | ref.      | 1.03 [0.51–2.08] | 1.40 [0.68–2.87] | 0.18           | 0.81           | 1.07 [0.96–1.20] | 0.22   |
| >10 Years                                      | 211/219        | ref.      | 1.49 [0.89–2.50] | 1.25 [0.70–2.23] | 0.24           |                | 1.08 [0.96–1.21] | 0.22   |
| Histology                                      |                |           |           |           |                 |                |             |        |
| Endometrioid                                   | 96/97          | ref.      | 1.03 [0.50–2.13] | 1.12 [0.49–2.57] | 0.46           | 0.86           | 1.05 [0.88–1.27] | 0.59   |
| Adenocarcinoma, NOS                            | 166/173        | ref.      | 1.07 [0.58–1.98] | 1.47 [0.78–2.75] | 0.08           |                | 1.10 [0.99–1.23] | 0.07   |
| Other                                          | 47/49          | ref.      | 3.43 [1.09–10.61] | 1.54 [0.34–6.95] | 0.67           |                | 1.05 [0.86–1.29] | 0.64   |
| Grade                                          |                |           |           |           |                 |                |             |        |
| Low grade (1)                                  | 118/120        | ref.      | 1.40 [0.71–2.75] | 1.30 [0.62–2.73] | 0.59           | 0.68           | 1.04 [0.91–1.19] | 0.56   |
| High grade (≥1)                                | 101/102        | ref.      | 1.27 [0.61–2.67] | 1.01 [0.41–2.50] | 0.33           |                | 1.08 [0.92–1.27] | 0.32   |
| Stage                                          |                |           |           |           |                 |                |             |        |
| Low stage (I, II)                              | 203/210        | ref.      | 1.22 [0.74–2.02] | 1.29 [0.71–2.34] | 0.38           | 0.53           | 1.06 [0.95–1.28] | 0.29   |
| High stage (>II)                               | 24/25          | ref.      | 2.57 [0.57–11.54] | 0.76 [0.15–3.69] | 0.83           |                | 1.00 [0.76–1.31] | 0.99   |
| Type I/I                                       |                |           |           |           |                 |                |             |        |
| I                                              | 242/249        | ref.      | 1.12 [0.69–2.10] | 1.39 [0.84–2.31] | 0.07           | 0.70           | 1.09 [1.00–1.20] | 0.06   |
| II                                             | 28/30          | ref.      | 1.37 [0.84–2.26] | 0.94 [0.64–1.57] | 0.51           |                | 1.02 [0.76–1.37] | 0.90   |

Abbreviations: AMH = anti-Mullerian hormone; CI = confidence interval; NOS = not otherwise specified; OR = odds ratio. All models are adjusted for age at blood draw; \( P_{\text{het}} \) based on tertile medians. Study-specific tertile cutpoints for AMH (ng ml\(^{-1}\)). Columbia: \( 1.19/1.19–3.72/\geq 3.7 \); CLUE III: \( 0.635/0.635–2.315/\geq 2.315 \); NYUWHS: \( 0.505/0.505–1.575/\geq 1.575 \); EPIC: \( 0.440/0.440–1.660/\geq 1.660 \); NSHDS: \( 0.600/0.600–1.685/\geq 1.685 \); SWHS: \( 0.250/0.250–0.740/\geq 0.740 \).
granulosa cell tumours, which would have caused elevated AMH concentrations. Exclusion of the six cases with synchronous ovarian cancer did not have an impact on the observed effect estimates. Samples utilised in this study were from established biorepositories, and have been in storage for up to decades. However, no association between storage time and AMH concentrations was observed in our previous cross-sectional study (Jung et al., 2017). Finally, the median age at diagnosis in this study was 54 years; this is younger than the median age at diagnosis in the population at large (e.g., median age at diagnosis in the United States: 62 years) (Howlader et al., 2017). It is plausible that the results observed here for endometrial cancer with younger age at diagnosis are not generalisable to women with later disease onset.

Anti-Mullerian hormone has been proposed as a potential treatment for endometrial cancers (Kim et al., 2014). However, although experimental models demonstrate an inhibiting effect of AMH on endometrial cancer growth, our findings in premenopausal women do not support a role for circulating AMH concentrations in the aetiology of endometrial cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The authors assume full responsibility for analyses and interpretation of these data.

DATA SHARING

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

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