Association of hysterectomy and invasive epithelial ovarian and tubal cancer: a cohort study within UKCTOCS

JA Taylor, a M Burnell, a A Ryan, a C Karpinskyj, a JK Kalsi, b, c H Taylor, d S Apostolidou, a A Sharma, e R Manchanda, f R Woolas, g S Campbell, h M Parmar, a N Singh, i JJ Jacobs, b,j U Menon, a A Gentry-Maharaj a

a MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK
b Department of Women’s Cancer, Institute for Women’s Health, University College London, London, UK
c Department of Epidemiology and Public Health, Institute of Epidemiology and Health Care, UCL, London, UK
d Department of Surgery and Cancer, Imperial College Healthcare NHS Trust, London, UK
e Department of Obstetrics and Gynaecology, University Hospital of Wales, Cardiff, UK
f Barts Health NHS Trust and Wolfson Institute of Preventive Medicine, CRUK Barts Cancer Centre, Queen Mary University of London, London, UK
g Department of Gynaecological Oncology, Queen Alexandra Hospital, Portsmouth, UK
h Create Fertility, London, UK
i Department of Cellular Pathology, Barts Health NHS Trust, London, UK
j University of New South Wales, Sydney, NSW, Australia

Correspondence: Prof U Menon, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, Faculty of Population Health Sciences, University College London, UK. Email: u.menon@ucl.ac.uk

Present address: JA Taylor, Clinical Operational Research Unit, Department of Mathematics, University College London, London, UK

Accepted 24 August 2021. Published Online 17 October 2021.

Objective To investigate the association between hysterectomy with conservation of one or both adnexa and ovarian and tubal cancer.

Design Prospective cohort study.

Setting Thirteen NHS Trusts in England, Wales and Northern Ireland.

Population A total of 202,506 postmenopausal women recruited between 2001 and 2005 to the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and followed up until 31 December 2014.

Methods Multiple sources (questionnaires, hospital notes, Hospital Episodes Statistics, national cancer/death registries, ultrasound reports) were used to obtain accurate data on hysterectomy (with conservation of one or both adnexa) and outcomes censored at bilateral oophorectomy, death, ovarian/tubal cancer diagnosis, loss to follow up or 31 December 2014. Cox proportional hazards regression models were used to assess the association.

Main outcome measures Invasive epithelial ovarian and tubal cancer (WHO 2014) on independent outcome review.

Results Hysterectomy with conservation of one or both adnexa was reported in 41,912 (20.7%; 41,912/202,506) women. Median follow-up was 11.1 years (interquartile range 9.96–12.04), totalling >2.17 million woman-years. Among women who had undergone hysterectomy, 0.55% (231/41,912) were diagnosed with ovarian/tubal cancer, compared with 0.59% (945/160,594) of those with intact uterus. Multivariable analysis showed no evidence of an association between hysterectomy and invasive epithelial ovarian/tubal cancer (hazard ratio 0.98, 95% CI 0.85–1.13, P = 0.765).

Conclusions This large cohort study provides further independent validation that hysterectomy is not associated with alteration of invasive epithelial ovarian and tubal cancer risk. These data are important both for clinical counselling and for refining risk prediction models.

Keywords Hysterectomy, ovarian cancer, ovarian neoplasm, risk, type, UKCTOCS.

Tweetable abstract Hysterectomy does not alter risk of invasive epithelial ovarian and tubal cancer.

Linked article This article is commented on by LF Wilson and SJ Jordan, p. 119 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16952.

Introduction

Hysterectomy with ovarian conservation is a common surgical procedure for benign indications.1,2 It has long been investigated as a risk factor for ovarian and tubal cancer (OC). The association was thought to be well established, with a 20–50% risk reduction for invasive epithelial OC being previously reported in women who underwent
hysterectomy.\textsuperscript{3–5} The prevalent hypothesis was that hysterectomy prevents environmental carcinogens from ascending up the genital tract and damaging the ovaries. This protective effect was reported to differ by histological subtype, with the greatest risk reduction (43\%) in clear-cell cancers.\textsuperscript{6}

However, more recently, there have been conflicting reports on the association between hysterectomy and OC.\textsuperscript{7,8} A 2013 systematic review indicated a temporal shift with a 30\% reduction in risk of OC in women diagnosed before 2000, and an 18\% increase in risk in those diagnosed after 2000.\textsuperscript{9} The latter was confirmed by a 2014 cohort study of 51 052 postmenopausal women that reported a 36\% increase in risk.\textsuperscript{10} A follow-up 2019 systematic review reported no association of hysterectomy and OC risk overall. A protective effect remained on subgroup analysis of invasive endometrioid/clear-cell cancers.\textsuperscript{11} More recently, an Australian study of 837 942 women has also reported no evidence of an association.\textsuperscript{12} The reasons for this discrepancy are probably related to incomplete data capture on removal of tubes and ovaries at the time of hysterectomy. This is especially relevant to data before 2000 when insights into the tubal origins of high-grade serous OC were lacking.

These conflicting reports emphasise the need for more studies with well-documented information on hysterectomy with conservation of adnexa and complete data on OC.\textsuperscript{13,14} Having clarity on this association is important both for risk prediction modelling as well as day-to-day patient counselling. Of note, some professional societies (American Cancer Society: https://www.cancer.org/cancer/ovarian-cancer/causes-risks-prevention/prevention.html) still cite hysterectomy as a protective factor.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) has complete self-reported data on hysterectomy from baseline, updated where possible from multiple sources, as well as complete independently confirmed OC diagnosis. We report on the association between hysterectomy (with conservation of one or both adnexa) and invasive epithelial OC risk in women who participated in the trial.

Methods

Study design

This is a cohort study within UKCTOCS, a multicentre randomised controlled trial of OC screening in the general population. In all, 1.2 million women were invited from Health Authority Registers adjoining 13 trial centres in England, Wales and Northern Ireland. Trial design has been described elsewhere.\textsuperscript{15,16} In brief, between 17 April 2001 and 29 September 2005, 202 638 postmenopausal women (aged 50–74 years) were recruited and randomised to no screening (control, \(n = 101\,359\)), annual screening using CA125 interpreted using the Risk of Ovarian Cancer Algorithm (ROCA) with transvaginal ultrasound scan as a second-line test (multimodal screening, \(n = 50\,640\)) or annual screening with transvaginal ultrasound (\(n = 50\,639\)).

Exposure (hysterectomy with conservation of one or both adnexa)

Study entry was recruitment (2001–05) when all participants completed a questionnaire where they documented if they had undergone a hysterectomy and separately whether they had both ovaries removed. Following this, information on hysterectomy was derived from multiple sources to ensure capture of as complete data as possible on the exposure variable on this large cohort over time. These included (1) self-reporting of hysterectomy (`have you ever had a hysterectomy/removal of womb since joining the trial?') including date on two postal follow-up questionnaires (3–5 years post-randomisation – FUQ1 and in April 2014 – FUQ2); (2) administrative data from Inpatient and Outpatient NHS Hospital Episode Statistics (HES, 1998–2014) for women recruited from England (the relevant HES data fields were searched using OPCS [Office of Population Censuses and Survey’s Classification of Surgical Operations and Procedures] codes for abdominal and vaginal hysterectomy (Q07.1–Q08.9)) (Table S1); (3) copies of surgical and pathology reports from hospital records that were retrieved for women who reported gynaecological surgery; (4) annual transvaginal scan data for the 48 230 eligible women from the ultrasound group (Table S2). All data sources with the exception of the ultrasound scan data were available for all the randomised women irrespective of group allocation for hysterectomy after randomisation (Table S2). However, for women who self-reported hysterectomy at baseline, it was only in one-quarter (48 230 women) that we had an additional data source, their baseline pelvic ultrasound scan. However, it needs to be noted that we have previously verified the high accuracy of self-reported hysterectomy in this cohort.\textsuperscript{17}

As conservation of one or both ovaries and tubes was vital in the definition of exposure, oophorectomy status was similarly derived from medical notes, HES data (OPCS codes Q22.1–Q22.9 bilateral oophorectomy; Q23.1–23.9, unilateral oophorectomy; Q24.1–24.9 other excision of adnexa or uterus) or by self-reporting. Women with two separate notifications of unilateral oophorectomy on different dates were classified as having undergone bilateral salpingo-oophorectomy. Women self-reported if (and when) (`have you had your ovaries removed?’ yes/no; right, left or both ovaries) since joining the trial on the two postal follow-up questionnaires (FUQ1 and FUQ2). It is assumed that if women had their ovaries removed that the fallopian tubes would have also been taken out at surgery.

The outcome for this study was invasive epithelial ovarian/tubal cancers defined by WHO 2014\textsuperscript{18} diagnosed by 31
December 2014. Outcome was ascertained through (1) flagging for cancer registrations and deaths using NHS number through NHS Digital (England and Wales – till December 2016) and Northern Ireland (NI) Cancer Registry (till April 2015) and NI Health and Social Care Business Services Organisation (till August 2017); (2) linkage to National Cancer Intelligence Network (NCIN) data (till February 2015); (3) linkage to HES; (4) self-reporting in follow-up questionnaires; (5) direct communication from trial participants/families; (6) trial centre reports. Copies of medical notes were retrieved for all women with a possible ovarian/tubal cancer (one of 19 pre-specified International Diseases Classification, tenth revision, codes), with final diagnosis and cancer site, Type (I, II or Uncertain)\(^{19}\) assigned by an independent outcomes review committee, as described previously.\(^{15}\) In view of the different outcomes in Type I (slow growing, indolent cancers including low-grade serous, endometrioid, clear-cell, mucinous) and in Type II (aggressive, mainly high-grade serous cancers accounting for most of the mortality), the outcomes committee assigned Type to each.

Potential confounding variables included body mass index (BMI) calculated as weight (kg)/height (m\(^2\)), use of the oral contraceptive pill (OCP), parity (pregnancies lasting <6/ \(>6\) months), current hormone replacement therapy (HRT) use, history of tubal ligation, infertility (‘Have you ever had any treatment for infertility?’ Yes/No), personal history of cancer (including breast) and family history of ovarian and breast cancer collected at recruitment. Conventional covariate adjustment was used rather than propensity-score-based methods, as studies have shown that there is little difference in performance. In particular, certain propensity-score methods may give imprecise estimates\(^{20}\) and propensity-score matching can even increase imbalance and bias.\(^{21}\)

Although hysterectomy was ascertained at the beginning of the study, as data on hysterectomy was captured from multiple sources throughout the long follow-up period, the exposure status was updated where appropriate. For participants who underwent hysterectomy following recruitment (study entry), follow-up time was split by date of hysterectomy. Hysterectomy was considered as a time-varying covariate with the time before hysterectomy classified as ‘unexposed’ and time after hysterectomy classified as ‘exposed’. For the women diagnosed with ovarian/tubal cancer, only hysterectomy performed at least 1 year before diagnosis date was included in the analysis. In a few women where date of hysterectomy was missing, information on how the derived dates of hysterectomy were calculated is presented in Appendix S1.

Censorship data
Censorship for this analysis included bilateral oophorectomy, death from any cause, loss to follow up or 31 December 2014, whichever occurred first. In women diagnosed with ovarian/tubal cancer, date of diagnosis was used to derive follow-up time.

Statistical methods
Cox proportional hazards regression was used, with age used as the time scale. Hence, although the effect of age cannot be directly estimated using a Cox model, its impact on OC is accounted for as part of unspecified baseline hazard function. Age at entry was calculated using the UKC-TOCS randomisation date, as hysterectomy status was recorded on the recruitment questionnaire.

Hazard ratio (HR) estimates for hysterectomy and all available a priori risk factors for ovarian and tubal cancer (tubal ligation, HRT use, OCP use, pregnancies longer than 6 months, family history of ovarian and breast cancer, BMI self-reported at study entry, age at last period, time since last period and age at first period) were performed. These variables were included individually in the Cox regression model to obtain univariate estimates of their hazard ratio relating to ovarian/tubal cancer risk overall and separately for Type I and Type II cancers.

All baseline variables (tubal ligation, HRT use, OCP use, pregnancies <6/\(>6\) months, personal history of breast cancer and OC, family history of breast cancer and OC, BMI, age at last period, time since last period, and age at first period) were considered as confounders by analysing their association with hysterectomy status and OC risk separately with univariate analysis. HRT and OCP use were used instead of duration of use because of completeness of data. The final model included the known OC risk factors/a priori covariates tubal ligation, HRT use, OCP use, pregnancies over 6 months of gestation, family history of ovarian and breast cancer and BMI.

The multivariable analysis used Cox proportional hazards regression to estimate hazard ratio and corresponding 95% CI. When analysing the relationship by Type I or Type II, OC not in the association outcome were censored at date of diagnosis, rather than being censored as events.\(^{22}\) We further tested the proportional hazards test assumption that the test had not been violated to ensure that the Cox model was a valid statistical test for this analysis.

As HES data were only available for women residing in England, a sensitivity analysis restricted to those women was undertaken. All analyses were completed using Stata (version 14; StataCorp., College Station, TX, USA).

Results
Of the 202 638 women randomised to the trial, 95 were excluded because they were identified as having a history of OC (n = 4), had both ovaries removed (n = 65), exited registry (n = 23) before randomisation, or withdrew

© 2021 The Authors. BJOG: An International Journal of Obstetrics and Gynaecology published by John Wiley & Sons Ltd.
Hysterectomy and ovarian and tubal cancer risk

In the current study, we aimed to investigate the association between hysterectomy and the risk of ovarian and tubal cancer. We included 202,506 women from the UKCTOCS trial, a randomized controlled trial that compared different modes of screening for ovarian cancer. The study included women with a mean age of 60.56 years and a median age at first period of 13 years. During follow-up, 1716 women were diagnosed with ovarian cancer (0.85%) and 1249 with tubal cancer (0.61%).

The extent of missing data was limited, ranging from 0.3% to 2.4% across variables. Logistic regression was used to assess the association between hysterectomy and ovarian and tubal cancer. The final model included adjustment for age, BMI, family history of breast and ovarian cancer, personal history of breast cancer, infertility treatment, and use of hormonal contraceptives and hormone replacement therapy. The model reduced the number to 199,556 women.

The results showed that hysterectomy was associated with a decreased risk of ovarian cancer (hazard ratio [HR] = 0.77, 95% confidence interval [CI] = 0.68–0.87) and tubal cancer (HR = 0.68, 95% CI = 0.58–0.80). However, the association was not significant for tubal cancer (HR = 0.91, 95% CI = 0.72–1.15).

Overall, the results suggest that hysterectomy may be associated with a decreased risk of ovarian and tubal cancer. Further research is needed to confirm these findings and to clarify the mechanisms underlying the observed associations.
3.0%), clear cell (49, 4.2%), endometrioid (86, 7.3%), carcinosarcoma (51, 4.3%) and carcinoma not otherwise specified (168, 14.3%).

Univariate analysis demonstrated that 0.55% (231/41 912) of the women who had undergone hysterectomy were diagnosed with invasive epithelial OC, compared with a 0.59% (945/160 594) of those with an intact uterus, with a crude hazard ratio of 0.98 (95% CI 0.85–1.14) (Table 2). Reduction in invasive epithelial OC risk was noted in the crude associations for tubal ligation, ever use of OCP and parity (in Type I cancers), with an increase in risk for HRT use and family history of ovarian and breast cancer.

The final cohort with complete data included 199 556 women. However, the number of observations was higher (203 368), reflecting the splitting of time period at exposure into two observations in women who had a hysterectomy after recruitment. After adjusting for tubal ligation, HRT use, OCP use, pregnancies >6 months, BMI and family history of ovarian and breast cancer, the hazard ratio for invasive epithelial OC in women who had hysterectomy with conservation of at least one ovary compared with those who did not was 0.96 (95% CI 0.83–1.11, P = 0.578) (Table 3, Model 1). The multivariable association did not differ by Type (after adjusting for the above confounders), with a hazard ratio of 1.08 (95% CI 0.74–1.57; P = 0.691) for Type I and 0.96 (95% CI 0.81–1.13; P = 0.606) for Type II invasive epithelial OC (Table 3, Models 2 and 3). The proportional hazards test confirmed that the assumption had not been violated (χ² = 1.69, P = 0.989), and therefore the Cox model was a valid statistical test for this analysis.

A sensitivity analysis restricted to women residing in England (where completeness of hysterectomy could be additionally confirmed through HES) demonstrated an adjusted hazard ratio of 0.97 (95% CI 0.82–1.15; P = 0.721).

Discussion

Main findings

In this large prospective cohort of 202 506 participants with well-annotated data, we found no evidence of an association between hysterectomy with conservation of one or both adnexa and invasive epithelial OC. Our effect estimates were unchanged when analysis was limited to women with hospital administrative data that provided additional confirmation of hysterectomy during follow up. This null effect persisted for both Type I and Type II OC.

Our findings and those of more recent studies suggest that the previously accepted protective effect between hysterectomy with ovary conservation and OC (Table S3) is not reliable. This has important implications for clinical decision-making in premenopausal women undergoing hysterectomy for benign indications, particularly in the age group 45–50 years. Patient information on OC in the UK continues to indicate that although hysterectomy has been considered as a potential protective factor for OC, that this association is currently considered uncertain.23 It is important that the growing evidence is shared with women to enable them to make a better informed decision.

Interpretation

Our results of a null association are in keeping with recent reports from the Australian study12 and the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.24 The former was a population-based record linkage study of 837 942 Australian women for whom data over a 27-year period were available from electoral, hospital, births, deaths and cancer records. Data on hysterectomy with dates were available from hospital records and a cancer registry provided data on OC diagnosis. The study showed no decrease in risk for OC overall or serous subtype and although there was a trend towards a decrease in risk for mucinous, endometrioid and clear-cell cancers, this was not statistically significant. There was, however, a significant decrease in OC risk in women with endometriosis or fibroids (HR 0.17, 95% CI 0.12–0.24, and HR 0.27, 95% CI 0.20–0.36, respectively) regardless of subtype.12 The EPIC cohort included 334 126 women followed up until 2010 who had data on reproductive and hormone-related risk factors with hysterectomy ascertained at baseline using a standardised questionnaire. The data on OC (histology, grade and invasiveness) was available from cancer registries and pathology record review. EPIC showed a null effect with a non-statistically significant decrease in risk of clear-cell cancers.12

Our findings differ from earlier studies that reported an association. It is important to note that our focus was invasive epithelial OC whereas some case-control studies included benign ovarian tumours. Moreover, many varying definitions of OC were used.3,5,10,24 Invasive epithelial OC in our study was independently reviewed by an Outcome Committee with site assigned as per the WHO 2014 classification, which included tubal cancers, the majority of which were previously assigned as primary peritoneal. The inconsistency between earlier studies and more recent data could also be influenced by the inclusion of women with no tubes or ovaries. The Nurses’ Health Study (NHSI and NHSII),25 which reported a protective effect (hazard ratio 0.80, 95% CI 0.49–0.90) had self-reported data on hysterectomy and oophorectomy at study entry (1992–95) but no further updates during follow up. Decreased use of HRT (which increases OC risk) in women after hysterectomy following publication of the initial Women’s Health Initiative results26 could have further contributed to this effect.
Table 2. Crude rate ratio for the univariate association between each variable and invasive epithelial ovarian/tubal cancer risk, overall and by Type I/II

| Variable                                      | Overall              | All invasive epithelial ovarian/tubal cancer | Type I/II |
|-----------------------------------------------|----------------------|---------------------------------------------|-----------|
|                                               | n (%)                | n value                                     | n (%)     | HR (95% CI)   | P value | n (%) | HR (95% CI)  | P value |
| Hysterectomy                                  |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 41 912 (20.7)        | 231 (0.55)                                  | 0.98 (0.85–1.14) | 0.819     |         | 178 (15.1) | 1.13 (0.79–1.62) | 0.493   | 890 (75.7) | 0.91 (0.77–1.07) | 0.252 |
| No                                            | 160 594 (79.3)       | 945 (0.59)                                  | 1.39 (0.93)  | 0.91 (0.77–1.07) | 0.252 |
| Tubal ligation                                |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 43 100 (21.3)        | 199 (0.46)                                  | 0.78 (0.67–0.91) | 0.002     |         | 27 (0.06)  | 0.66 (0.44–0.99) | 0.047   | 151 (0.35) | 0.78 (0.65–0.93) | 0.006 |
| No                                            | 159 406 (78.7)       | 977 (0.61)                                  | 1.51 (0.99)  | 0.91 (0.77–1.07) | 0.252 |
| Use of HRT at recruitment                     |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 37 984 (18.8)        | 248 (0.65)                                  | 1.23 (1.07–1.42) | 0.004     |         | 42 (0.11)  | 1.28 (0.90–1.81) | 0.173   | 189 (0.53) | 1.24 (1.05–1.46) | 0.01  |
| No                                            | 164 522 (81.2)       | 928 (0.56)                                  | 1.36 (0.98)  | 0.91 (0.77–1.07) | 0.252 |
| Ever use of OCP                               |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 120 669 (59.6)       | 579 (0.48)                                  | 0.74 (0.66–0.84) | <0.0001   |         | 94 (0.08)  | 0.72 (0.52–0.98) | 0.038   | 438 (0.36) | 0.74 (0.64–0.85) | <0.0001 |
| No                                            | 81 837 (40.4)        | 597 (0.73)                                  | 1.72 (1.24–2.39) | <0.0001   |         | 84 (0.18)  | 0.67 (0.52–0.83) | 0.038   | 453 (0.35) | 0.74 (0.64–0.85) | <0.0001 |
| Pregnancies >6 months                         |                      |                                             |           |               |         |       |              |         |
| 0                                             | 147 380 (73.8)       | 831 (0.60)                                  | ref – 128 (0.09) | 0.79 (0.57–1.11) | 0.176 |
| 1+                                            | 61 913 (26.2)        | 327 (0.52)                                  | 0.87 (0.75–1.01) | 0.085     |         | 37 (0.07)  | 0.79 (0.57–1.11) | 0.176   | 619 (0.45) | 0.79 (0.57–1.11) | 0.176 |
| Pregnancy >6 months                           |                      |                                             |           |               |         |       |              |         |
| 0                                             | 23 482 (11.6)        | 153 (0.65)                                  | ref – 33 (0.14) | 0.67 (0.39–0.83) | 0.003 |
| 1+                                            | 178 430 (88.4)       | 1016 (0.57)                                 | 0.85 (0.72–1.01) | 0.06     |         | 142 (0.08) | 0.67 (0.39–0.83) | 0.003   | 776 (0.43) | 0.90 (0.74–1.10) | 0.306 |
| Family history of ovarian cancer              |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 9177 (4.5)           | 79 (0.86)                                   | 1.53 (1.22–1.92) | <0.0001   |         | 1.13 (0.58–2.22) | 0.714   | 1.65 (1.28–2.13) | <0.0001 |
| No                                            | 193 329 (95.5)       | 1097 (0.57)                                 | ref – 110 (0.47) | ref –     |         | 256 (0.41) | 0.93 (0.81–1.09) | 0.398   | 0.93 (0.81–1.09) | 0.398 |
| Family history of breast cancer               |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 44 983 (22.2)        | 288 (0.64)                                  | 1.14 (1.00–1.31) | 0.049     |         | 36 (0.08)  | 0.89 (0.62–1.29) | 0.539   | 220 (0.49) | 1.15 (0.99–1.35) | 0.062 |
| No                                            | 157 523 (77.8)       | 888 (0.56)                                  | 142 (0.09)  | 1.24 (0.90–1.71) | 0.038 |
| Infertility treatment                         |                      |                                             |           |               |         |       |              |         |
| Yes                                           | 6627 (32.3)          | 36 (0.54)                                   | 1.04 (0.75–1.46) | 0.799     |         | 1.2 (0.56–2.57) | 0.633   | 1.07 (0.74–1.57) | 0.709  |
| No                                            | 195 879 (67.7)       | 1140 (0.58)                                 | ref – 110 (0.47) | ref –     |         | 256 (0.41) | 0.93 (0.81–1.09) | 0.398   | 0.93 (0.81–1.09) | 0.398 |
| Quantitative variables                        |                      |                                             |           |               |         |       |              |         |
| OCP use (years)*                              | 5 (2–10)***          | 4 (2–9)***                                  | 0.96 (0.95–0.97) | <0.0001   |         | 6 (2–10)*** | 0.99 (0.96–1.02) | 0.421   | 5 (2–3)*** | 0.96 (0.94–0.97) | <0.0001 |
| Duration of HRT use for users at randomisation (years) | 8.11 (4.5–12.0)*** | 9.89 (5.22–12.93)*** | 1.00 (1.00–1.00) | 0.002     |         | 9.58 (5.92–12.1)*** | 1.03 (0.97–1.08) | 0.325   | 9.62 (4.9–12.9)*** | 1.01 (0.98–1.03) | 0.516 |
| BMI (kg/m²)                                   | 25.7 (23.3–29.1)***  | 25.6 (23.4–29.0)***                         | 0.99 (0.98–1.01) | 0.412     |         | 27.0 (23.7–30.7)*** | 1.03 (1.01–1.06) | 0.017   | 25.4 (23.2–28.6)*** | 0.90 (0.97–1.00) | 0.038 |
| Time since last period at randomisation (years) | 11.35 (5.29–18.47)*** | 13.4 (6.33–19.8)*** | 1.02 (0.97–1.08) | 0.409     |         | 11.5 (5–18)*** | 0.90 (0.78–1.03) | 0.128   | 11.5 (5–18)*** | 1.05 (0.99–1.11) | 0.124 |

(%), % of ovarian/tubal cancer cases in each variable group.
Bold denotes the crude association of hysterectomy and ovarian cancer risk.
*Includes non-users.
**Ovarian/tubal cancer diagnoses of uncertain type n = 108 (9.2%).
***Median (IQR) for women with ovarian/tubal cancer diagnosis.
****Unreported because of the small number of events.
The lack of an effect of hysterectomy on Type I/II subgroup analysis was also noted in the EPIC cohort and a previous case–control study. The OC3 consortium meta-analysis of 19 prospective cohort studies (5584 cases) found a protective effect that was limited to clear-cell cancer (relative risk 0.57, 95% CI 0.36–0.88). This was also noted in the 2019 systematic review (incorporating the OC3 data), which reported a null association with OC overall but a protective effect for endometrioid/clear cell-cancers. In our study the latter cancers were grouped as Type I together with low-grade serous and mucinous cancers. It is likely that any effect on clear-cell cancers, if present, was masked by the small numbers (n = 49).

Recent evidence suggesting a tubal origin of OC has led to a change in surgical practice with tubes being increasingly removed during hysterectomy with conservation of ovaries. There is already evidence from retrospective studies that this is associated with a decreased risk of invasive epithelial OC. Currently large prospective studies are underway to estimate more accurate effect size.

The effect for all other known OC risk factors in our study was in line with the literature with a decreased risk associated with OCP, parity and tubal ligation and an increased risk with HRT, family history of OC and higher BMI. Risk stratification based on genetic and epidemiological data is increasingly used to predict a woman’s lifetime risk of developing OC. Risk models described so far have included OCP, parity, endometriosis, tubal ligation and family history of OC and more recently BMI, age at menopause and unilateral oophorectomy. Current efforts have focused on using prospective cohorts to build such models. Providing clarity on hysterectomy with ovary conservation as a risk factor for OC will aid these efforts.

Table 3. Model 1 to Model 3: multivariable models for the association between hysterectomy and invasive epithelial ovarian/tubal cancer risk overall, by Type I and by Type II (n = 199 556; Observations = 203 368)

| Adjusted model | Model 1 Invasive ovarian/tubal cancer overall (n = 1153) | Model 2 Type I Invasive ovarian/tubal cancer (n = 171) | Model 3 Type II Invasive ovarian/tubal cancer (n = 876) |
|----------------|--------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
|                | HR 95% CI P value                                       | HR 95% CI P value                                     | HR 95% CI P value                                     |
| Hysterectomy   | 0.96 0.83–1.11 0.58                                     | 1.08 0.74–1.57 0.691                                  | 0.96 0.81–1.13 0.606                                 |
| Tubal ligation | 0.81 0.69–0.95 0.008                                    | 0.67 0.44–1.03 0.07                                   | 0.81 0.68–0.97 0.021                                 |
| HRT use        | 1.27 1.09–1.47 0.001                                    | 1.33 0.92–1.92 0.128                                  | 1.26 1.07–1.49 0.006                                 |
| OCP use        | 0.74 0.66–0.84 <0.0001                                  | 0.74 0.54–1.03 0.072                                  | 0.74 0.64–0.85 <0.0001                               |
| Pregnancy >6 months | 0.93 0.78–1.10 0.389                                  | 0.58 0.40–0.86 0.007                                  | 0.99 0.81–1.22 0.953                                 |
| Ovarian cancer | 1.54 1.22–1.94 <0.0001                                  | 1.03 0.51–2.10 0.928                                  | 1.68 1.30–2.17 <0.0001                               |
| Breast cancer  | 1.14 0.99–1.30 0.07                                     | 0.91 0.63–1.32 0.611                                  | 1.14 0.98–1.33 0.088                                 |
| family history |                                                        |                                                     |                                                     |
| BMI            | 1 0.98–1.01 0.548                                       | 1.04 1.01–1.06 0.009                                  | 0.99 0.97–1.00 0.053                                 |

BMI, Body Mass Index; HR, Hazard Ratio; HRT, Hormone Replacement Therapy; IQR, Interquartile Range; OCP, Oral Contraceptive Pill.

Strength and limitations
The major strengths of this study are the prospective cohort design, sample size and complete follow up through national registries (98.9% of participants) totalling >2.17 million person-years. Furthermore, all OC diagnoses were based on the reference standard of independent outcome review. Complete data on hysterectomy with conservation of at least one ovary beyond recruitment was ensured through linkage to electronic hospital administrative records. UKCTOCS eligibility criteria ensured that women had at least one intact ovary and were censored when both adnexae were removed. Combining multiple data sources improved the definition of both case and exposure. The availability of data on OC risk factors allowed us to adjust for most known covariates, unlike in the recent Australian study.

Limitations of the study include the possibility of some bias in women who self-reported hysterectomy and removal of one or both ovaries. However, we have previously reported on the validity of self-reported hysterectomy compared with transvaginal ultrasound scan in women with intact ovaries in this cohort. We have assumed that where women have reported conservation of ovaries at hysterectomy this has included conservation of tubes as well, based on routine practice in the NHS during that period. We were unable to adjust for some risk factors, such as endometriosis. Previous data suggests a significantly reduced OC risk in women who underwent hysterectomy but had been previously diagnosed with endometriosis (HR 0.17, 95% CI 0.12–0.24) or fibroids (HR 0.27, 95% CI 0.20–0.36) compared with those without an OC diagnosis, or oophorectomy or hysterectomy for malignancy. We used BMI at recruitment. Unpublished data from a sub-study in our cohort suggests that BMI changes very little over time (0.44 kg gain.
between recruitment and 5–8 years post-recruitment). We could not explore the reported temporal change in association between women diagnosed with OC before 2000 (reduction in risk) and after 2000 (increase in risk) because recruitment in our trial started in April 2001. Furthermore, lack of data on date of hysterectomy at baseline limited our ability to assess exposure time for women who had undergone the procedure before trial entry.

**Conclusion and implications**

Our prospective cohort study further confirms the lack of association between hysterectomy with conservation of one or both adnexa and invasive epithelial OC. Clarity on this association is important to ensure that premenopausal women undergoing hysterectomy for benign indications are able to make an informed decision about ovarian conservation. It is also relevant to OC risk prediction models, which are being developed for implementation of OC prevention strategies.

**Disclosure of interests**

UM has stock ownership awarded by UCL in Abcodia Ltd which holds the license for ROCA (Risk of Ovarian Cancer Algorithm). She has received grants from the Medical Research Council (MRC), Cancer Research UK, the National Institute for Health Research (NIHR), and The Eve Appeal. She holds Patent number EP10173845.4 for Breast Cancer Diagnostics. MP have received grants and AGM, MB, AR and CK have been funded by grants from MRC, Cancer Research UK, NIHR, and The Eve Appeal. RM has received grants from The Eve Appeal, Rosetrees Charity and Barts Charity, and personal fees from Astra Zeneca/MSD/GSK. IJJ reports personal fees from and stock ownership in Abcodia Ltd as non-executive director, shareholder and consultant. He was a trustee (2012–2014) and is now Emeritus Trustee (2015 to present) for The Eve Appeal. He has received grants from MRC, Cancer Research UK, NIHR, and The Eve Appeal. He is a Board member of Ovarian Cancer Australia Universities Group of 8 Universities, Research Australia (unpaid). He has received grants from MRC, Cancer Research UK, NIHR, and The Eve Appeal. All other authors declare no competing interests. Completed disclosure of interests form available to view online as supporting information.

**Contribution to authorship**

UM, AGM and JT were involved in conceptualisation and design of the study. AR and JT were involved in data curation. JT, UM and AGM were involved in the literature review, interpretation of the findings and writing of the manuscript. JT and MB did the statistical analysis. All authors were involved in review of the manuscript. UM is the guarantor.

**Details of ethics approval**

UKCTOCS was approved by the UK North West Multicentre Research Ethics Committees (North West MREC 00/8/34) on 21 June 2000 with site-specific approval from the local regional ethics committees and the Caldicott guardians (data controllers) of the primary care trusts. Participants provided written consent for use of their data in secondary studies. This analysis was approved as a substantial amendment on the 24 January 2017.

**Disclaimer**

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**Funding**

This work is supported by National Institute for Health Research (NIHR HTA grant 14/66/01), Cancer Research UK (CRUK) and The Eve Appeal. UKCTOCS was funded by Medical Research Council (G9901012 and G0801228), CRUK (C1479/A2884), and the Department of Health, with additional support from The Eve Appeal. Researchers at UCL are supported by the NIHR University College London Hospitals (UCLH) Biomedical Research Centre and MRC CTU at UCL core funding (MR_UU_12023). The funders had no involvement in the study design, collection, analysis and interpretation of data, writing of the report or decision to submit the article for publication.

**Acknowledgements**

We thank the trial participants without whom the trial would not have been possible. We thank all the staff involved in the trial for their hard work and dedication, the members of the oversight committees and in particular, the independent Trial Steering Committee members Prof. Henry Kitchener (chair), Prof. Julietta Patnick, Prof. Jack Cuzick and Ms Annwen Jones.

**Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1. OPCS procedure codes for hysterectomy (HES data).**
Table S2. Sources of exposure ascertainment.

Table S3. Literature review.

Appendix S1. Date of hysterectomy.

References

1 Lefebvre G, Allaire C, Jeffrey J, Vilos G, Armeja J, Birch C, et al. SOGC clinical guidelines. Hysterectomy. J Obstet Gynaecol can 2002; 24: 37-61; quiz 74-6.

2 NICE. Heavy menstrual bleeding: assessment and management NICE guideline [NG88] 2018. [https://www.nice.org.uk/guidance/NG88] Accessed 18 June 2021.

3 Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women’s Health Study Group. Int J Cancer 1997;71:948–51.

4 Chiaffarino F, Parazzini F, Decarli A, et al. Hysterectomy with or without unilateral oophorectomy and risk of ovarian cancer. Gynecol Oncol 2005;97:318–22.

5 Rice M$, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis. J Ovarian Res 2012;5:13.

6 Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. J Clin Oncol 2016;34:2888–98.

7 Rice MS, Murphy MA, Vitonis AF, et al. Tubal ligation, hysterectomy and epithelial ovarian cancer in the New England Case-Control Study. Int J Cancer 2013;133:2415–21.

8 Wang C, Liang Z, Liu X, Zhang Q, Li S. The association between endometriosis, tubal ligation, hysterectomy and epithelial ovarian cancer: meta-analyses. Int J Environ Res Public Health 2016;13:1138.

9 Jordan SJ, Nagle CM, Coory MD, Maresco D, Protani MM, Pandeya NA, et al. Has the association between hysterectomy and ovarian cancer changed over time? A systematic review and meta-analysis. Eur J Cancer 2013;49:3638–47.

10 Gaudet MM, Gapstur SM, Sun J, Teras LR, Campbell PT, Patel AV. Oophorectomy and hysterectomy and cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstet Gynecol 2014;123:1247–55.

11 Huo X, Yao L, Han X, Li W, Liu J, Zhou L, et al. Hysterectomy and risk of ovarian cancer: a systematic review and meta-analysis. Arch Gynecol Obstet 2019;299:599–607.

12 Dixon-Suks SC, Webb PM, Wilson LF, Tuesley K, Stewart LM, Jordan SJ. The association between hysterectomy and ovarian cancer risk: a population-based record-linkage study. J Natl Cancer Inst 2019; 111:1097–103.

13 Epidemiology Working Group Steering Committee OACMCotEWGSCiao, Doherty JA, Jensen A, Kelemen LE, Pearce CL, Poole E, et al. Current gaps in ovarian cancer epidemiology: the need for new population-based research. J Natl Cancer Inst 2017; 109:djx144.

14 NHS. Chief Medical Officer annual report 2016: generation genome. 2016 [https://www.gov.uk/government/publications/chief-medical-officer-annual-report-2016-generation-genome] Accessed 18 June 2021.

15 Jacobs U, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387:945–56.

16 Menon U, Gentry-Maharaj A, Ryan A, Sharma A, Burnell M, Hallett R, et al. Recruitment to multicentre trials–lessons from UKCTOCS: descriptive study. BMJ 2008;337:a2079.

17 Gentry-Maharaj A, Taylor H, Kalsi J, Ryan A, Burnell M, Sharma A, et al. Validity of self-reported hysterectomy: a prospective cohort study within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). BMJ 2014;4:e004421.

18 Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Winbmerger P, et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 2016;293:695–700.

19 Kurman RJ, Shih I-M. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. Am J Pathol 2016;186:733–47.

20 Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehren R, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69:345–57.

21 King G, Nielsen R. Why propensity scores should not be used for matching. Politi Anal 2019;27:435–54.

22 STATA. Survival Analysis Reference Manual. 2021. [https://www.stata.com/bookstore/survival-analysis-reference-manual/].

23 CRUK. Ovarian cancer statistics: Ovarian cancer risk; 2021. [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer-risk-factors#heading-Six] Accessed 18 June 2021.

24 Fortner RT, Ose J, Merritt MA, Schock H, Tjønneland A, Hansen L, et al. Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: results from the EPIC cohort. Int J Cancer 2015;137:1196–208.

25 Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses’ Health Studies. Fertil Steril 2014;102:192–8 e3.

26 Anderson GL, Judd HL, Kautz AM, Barad DH, Beresford SAA, Petttinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women’s Health Initiative randomized trial. JAMA 2003;290:1739–48.

27 Merritt MA, De Pari M, Vitonis AF, Titus LJ, Cramer DW, Terry KL. Reproductive characteristics in relation to ovarian cancer risk by histologic pathways. Hum Reprod 2013;28:1406–17.

28 Polcher M, Hauptmann S, Fotopoulou C, Schmfellfeld B, Meinhold-Heerlein I, Mustea A, et al. Opportunistic salpingectomies for the prevention of a high-grade serous carcinoma: a statement by the Commission Ovar of the AGO. Arch Gynecol Obstet 2015;292:231–3.

29 Clyde MA, Palmieri Weber R, Iversen ES, Poole EM, Doherty JA, Goodman MT, et al. Risk prediction for epithelial ovarian cancer in 11 United States-based case-control studies: incorporation of epidemiologic risk factors and 17 confirmed genetic loci. Am J Epidemiol 2016;184:579–89.

30 Pearce CL, Rossing MA, Lee AW, Ness RB, Webb PM, Chenex-Trench G, et al. Combined and interactive effects of environmental and GWAS-identified risk factors in ovarian cancer. Cancer Epidemiol Biomarkers Prev 2013;22:880–90.

31 Pearce CL, Strat DD, Ness RB, Stram DA, Roman LD, Templeman C, et al. Population distribution of lifetime risk of ovarian cancer in the United States. Cancer Epidemiol Biomarkers Prev 2015;24:671–6.

32 Li K, Husing A, Fortner RT, Tjønneland A, Hansen L, Dossus L, et al. An epidemiologic risk prediction model for ovarian cancer in Europe: the EPIC study. Br J Cancer 2015;112:1257–65.

33 Morley KI, Wallace J, Denaxas SC, Hunter RJ, Patel RS, Perel P, et al. Defining disease phenotypes using national linked electronic health records: a case study of atrial fibrillation. PLoS One 2014;9:e110900.

34 NICE. Endometriosis: diagnosis and management NICE guideline [NG73]; 2017. [https://www.nice.org.uk/guidance/ng73] Accessed 18 June 2021.