National Institute for Health and Care Excellence

Final

Menopause (update)

[F] Ovarian cancer

NICE guideline NG23

Evidence reviews underpinning recommendations 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point) and statements related to ovarian cancer in tables 1 and 2 as well as the associated absolute number tables in the NICE guideline

May 2024

Final

This evidence review was developed by NICE

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ISBN: 978-1-4731-6564-9

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Ovarian cancer

Review question

What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

Introduction

The MHRA (based on evidence from observational studies) advises that: long-term use of oestrogen-only or combined HRT may be associated with a small increased risk of ovarian cancer, which returns to baseline a few years after stopping treatment. This evidence review aimed to quantify that risk and to determine whether it was related to other factors such as the duration of use, recency of use, age at use and mode of administration.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women, non-binary and trans people with menopause (including perimenopause and post-menopause)

Intervention	HRT*
	• Oestrogen-only
	• Combined oestrogen and progestogen
	  ○ Sequential combined
	  ○ Continuous combined
	  ○ Any combined
	* Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.

Comparison	• Placebo treatment • No HRT
Outcome	**Critical** • Incidence of ovarian cancer (includes borderline tumours) • Mortality from ovarian cancer **Important** • None

HRT: hormone replacement therapy

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Eighteen studies were included in this review. One randomised controlled trial (RCT) (Anderson 2003) and 17 observational studies (Baandrup 2022; Beral 2007; Bethea 2017; Bryk 2021; CGESOC 2015; Danforth 2007; Felix 2015; Folsom 2004; Hildebrand 2010; Koskela-Niska 2013; Lacey 2002; Morch 2009; Rodriguez 2001; Schneider 2009; Simin 2020; Trabert 2012 and Tsilidis 2011). One observational study (CGESOC 2015) was an individual participant data meta-analysis of 17 prospective cohort studies of which 9 are included separately in this review due to additional reporting of subgroups (Beral 2007; Felix 2015; Folsom 2004; Hildebrand 2010; Lacey 2002; Morch 2009; Rodriguez 2001; Trabert 2012 and Tsilidis 2011).

The studies compared oestrogen-only or oestrogen plus progestogen, to either no hormone replacement therapy, or to placebo.

The studies were from Denmark, Finland, Puerto Rico, Sweden, United Kingdom, the United States. The individual participant data meta-analysis included studies from Europe and North America.

Some studies did not specify the duration of HRT use, and this is described throughout the report as unknown duration where applicable.

The included studies are summarised in Table 2.

See the literature search strategy in Appendix B and study selection flow chart in aAppendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Anderson 2003 (Women's Health Initiative) RCT United States	N=16608 Women aged 50-79 Mean age (SD), years: NR Age at screening: **Oestrogen + Progestogen, n (%):** 50-59: 2839 (33.4) 60-69: 3853	• Oestrogen + progestogen	Placebo	• Ovarian cancer incidence, by histological type • Unknown duration of use, follow-up time 5.6 years	

Study	Population	Intervention	Comparison	Outcomes	Comments
	(45.3) 70-79: 1814 (21.3) **Placebo, n (%):** 50-59: 2683 (33.1) 60-69: 3657 (45.1) 70-79: 1762 (21.8) No hysterectomy				
Baandrup 2022 Observational study Denmark	N=3776 Mean age (SD), years: NR Women aged 50 or older at diagnosis Age at diagnosis: **HRT users – n (%):** 50-59: 314 (19) 60-69: 634 (38.4) 70-79: 516 (31.2) ≥80: 189 (11.4) **No hormone replacement therapy:** 50-59: 498 (23.5) 60-69: 623 (29.3) 70-79: 637 (30.0) ≥80: 365 (17.2) No information on hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Mortality from ovarian cancer	Cohort population covered in Morch 2009; however additional survival outcomes included Cohort included in CGESOC but not mortality data
Beral 2007 Observational study	N=948576 Age at entry, years - mean (SD):	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence, by duration, by,	Cohort included in CGESOC – additional

Study	Population	Intervention	Comparison	Outcomes	Comments
United Kingdom	**No hormone replacement therapy**: 57.9 (4.9) **Past users of HRT**: 57 (4.3) **Current users of HRT**: 56.1 (4.1) Less than 33% with hysterectomy	○ Sequential ○ Continuous		constituent, by mode of administration • Mortality from ovarian cancer	outcomes in this publication
Bethea 2017 Observational study United States	N=86 Mean age total population (SD), years: 37.8 (10.3) Age at diagnosis of cancer - n (%): <40: 12 (10.45) 40-49: 29 (25.2) 50-59: 41 (35.7) ≥60: 33 (28.7) Age per arm not reported. Analysis of those taking HRT in women over age 45 only Black ethnicity No information on hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence	
Bryk 2021 Observational study Finland	N=1634 Women aged 55 or older Mean (SD), years: NR	• Oestrogen-only • Oestrogen + progestogen ○ Sequential ○ Continuous	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	

Study	Population	Intervention	Comparison	Outcomes	Comments
	No information on hysterectomy				
CGESOC 2015 Meta-analysis of 17 prospective observational studies using individual participant data Europe and North America	K=17 prospective studies Women aged 55 or older Mean age at diagnosis, years: 65.1 (SD: NR) N=52827 No hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence, by histological type • Median duration of HRT use = 6 years	
Danforth 2007 Observational study United States	N=42615 Age at diagnosis, years – mean (SD: NR): **No hormone replacement therapy**: 61 **Past users** (any HRT): 64 **Current user oestrogen-only**: 62 **Current user oestrogen + progestogen**: 58 2% of oestrogen + progestogen had a hysterectomy 47% of oestrogen-only had a hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	Cohort included in CGESOC – additional outcomes in this publication
Felix 2015 Observational study	N=395 Women aged 50-71	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Mortality from ovarian cancer	Cohort included in CGESOC – additional outcomes in

Study	Population	Intervention	Comparison	Outcomes	Comments
United States	Mean age (SD): NR No information on hysterectomy, or previous ovarian cancer	○ Continuous ○ Sequential			this publication
Folsom 2004 Observational study United States	N=31234 Women aged 55-69 Mean age (SD): NR 47% current users had a hysterectomy	• Oestrogen-only	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	Cohort included in CGESOC – additional outcomes in this publication
Hildebrand 2010 Observational study United States	N=54436 **Average age at study entry, years (SD not reported):** Never: 62.6 Current oestrogen-only: 61.4 Former oestrogen-only: 66.1 Current oestrogen + progestin: 57.5 Former oestrogen + progestin: 59.2 96.5% current oestrogen-only had a hysterectomy. No hysterectomy in current oestrogen +	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	Cohort included in CGESOC – additional outcomes in this publication

Study	Population	Intervention	Comparison	Outcomes	Comments
	progestin users				
Koskela-Niska 2013 Observational study Finland	N=15283 Women aged 50 or older Mean age (SD): NR 6% of cases, and 8% of controls had a hysterectomy	• Oestrogen-only • Oestrogen + progestogen ○ Continuous ○ Sequential	No hormone replacement therapy	• Ovarian cancer incidence by duration of use, by histological type	
Lacey 2002 Observational study United States	N=44241 Women with mean age 56.6 years SD not reported Some hysterectomy – proportions not given	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	Cohort included in CGESOC – additional outcomes in this publication
Morch 2009 Observational study Denmark	N=857877 Women aged 50 or older Age years, mean (SD): Never users: 62.5 (8.8) Oestrogen-only: 63.5 (7.9) Oestrogen plus progestogen: 60.6 (6.8) 50.9% oestrogen-only had a hysterectomy 3.5% oestrogen + progestin had hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by route of administration, by constituent	Cohort included in CGESOC, additional subgroups in publication

Study	Population	Intervention	Comparison	Outcomes	Comments
Rodriguez 2001 Observational study United States and Puerto Rico	N=211581 Women who were post-menopausal Mean age (SD): NR No hysterectomy	• Oestrogen-only	No hormone replacement therapy	• Mortality by ovarian cancer by duration of use	Cohort included in CGESOC – additional outcomes in this publication
Schneider 2009 Observational study United Kingdom	N=602 Age, years (SD): 51.3 (6.1) No information on hysterectomy	• Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by constituent	No information on whether women had bilateral oophorectomy
Simin 2020 Observational study Sweden	N=1155496 Women aged 40 or older Mean (SD): NR No hysterectomy	• Oestrogen-only • Oestrogen + progestogen	No hormone replacement therapy	• Ovarian cancer incidence by age at first use	
Trabert 2012 Observational study United States	N=92601 Women mean age 62.3 years, SD: NR 72.3% oestrogen-only had a hysterectomy 2.6% oestrogen + progestin had a hysterectomy	• Oestrogen-only • Oestrogen + progestogen ○ Any combined ○ Continuous ○ Sequential	No hormone replacement therapy	• Ovarian cancer incidence by duration of use	Cohort included in CGESOC, additional subgroups in publication
Tsildis 2011 Observational study Europe	N=126920 Age, years - mean (SD): Never users: 59 (6.2)	• Oestrogen-only • Oestrogen + progestogen ○ Continuous ○ Sequential	No hormone replacement therapy	• Ovarian cancer incidence by constituent	Cohort included in CGESOC, additional subgroups in publication

Study	Population	Intervention	Comparison	Outcomes	Comments
	Oestrogen-only: 56.9 (5.1) Oestrogen + progestin: 54.5 (4.8) 36.7% oestrogen-only had hysterectomy 4.2% oestrogen plus progestin had a hysterectomy				

CGESOC: Collaborative Group on Epidemiological Studies of Ovarian; NR: not reported; SD: standard deviation

See the full evidence tables in Appendix D and the forest plots in Appendix E.

Summary of the evidence

For this review outcomes have been judged for clinical importance based on statistical significance. Please see Supplement 1 for further details.

Comparison 1: Oestrogen + progestogen, any combined, versus no HRT

Evidence for the overall incidence of ovarian cancer came from 1 meta-analysis of observational studies, and 1 other observational study. High quality evidence showed an increased risk in ovarian cancer with oestrogen plus progestogen use when compared to no HRT use. One observational study was exclusively in a population of black women, and this showed no important difference between groups, however the evidence was very low quality with concerns regarding imprecision, risk of bias, and indirectness.

Duration of HRT use

Across the 5 observational studies that provided data for current users by years of use, very low to moderate quality evidence showed an increased risk of ovarian cancer with longer duration of use. There was no difference between groups if use was between 1 to 4 years.

Age at first use

Evidence from 1 observational study showed that there was an important harm with oestrogen plus progestogen use on the risk of ovarian cancer if the age at first use was over 60, but no difference if less than 60. The evidence was rated very low to low quality due to concerns around bias and some imprecision.

Constituent

Three observational studies provided evidence on the risk of ovarian cancer for the different progestogenic constituents. The evidence showed that there were no important differences for any of the progestogenic constituents. Most of the evidence was very low to low quality, with some of moderate quality. All of the evidence was downgraded for imprecision, and some for risk of bias.

Mode of administration

Across 2 studies, evidence showed an increased risk of epithelial and non-epithelial types of ovarian cancer in users of oral preparations when compared to non-users, but no important difference in transdermal preparations. The evidence was rated very low to low quality with concerns around risk of bias and imprecision.

Histological type

Evidence from 1 meta-analysis of observational studies provided data on the risk of ovarian cancer by histological type, for users of 5 to 9 years of use. Moderate to high quality evidence showed an important harm for oestrogen and progestogen use over non-users, for the serous and endometrioid types of ovarian cancer, but no differences for clear-cell or mucinous.

Mortality

Across 2 observational studies, some of the evidence showed an important harm for current users of oestrogen plus progestogen on mortality from ovarian cancer, but some showed no important difference. There was evidence from 1 observational study on survival from ovarian cancer, which showed no important differences between oestrogen plus progestogen and no HRT. The evidence ranged from very low to moderate quality with concerns over risk of bias, some inconsistency and imprecision.

Comparison 2 and comparison 3: Continuous oestrogen and progestogen versus no-HRT; Sequential oestrogen and progestogen versus no-HRT

Incidence

Across 6 observational studies, there was evidence on the overall risk of ovarian cancer with continuous and sequential regimens. The data was in line with that for any combined regimens that showed an increase in risk of ovarian cancer with HRT use compared to non-users, for both continuous and sequential regimens. There was evidence available for risk by duration of use which showed an increased risk in ovarian cancer for sequential regimens, but not for continuous regimens. However, this was only seen in the evidence from one study for less than 10 years duration, but not from evidence from another study at less than 1 years duration or 1 to 5 years duration, and not more than 10 years duration. There was also evidence by histological type for users of 5 to 9 years of use. For the continuous regimens there was no important difference between groups for any of the subtypes, but an increase in risk for serous and endometrioid subtypes with sequential regimens. Most of the evidence was of very low to low quality, with some of moderate quality. The evidence was downgraded from risk of bias and imprecision.

Mortality

Very low quality evidence from 1 observational study showed no important difference for mortality for either continuous combined or sequential combined when compared to no HRT. There were concerns for bias and imprecision.

Comparison 4: Oestrogen plus progestogen versus placebo

One randomised controlled trial compared oestrogen plus progestogen to placebo. All of the evidence showed no important difference between HRT and placebo on ovarian cancer overall, or for individual subtypes. All the evidence was of low quality and downgraded for imprecision.

Comparison 5: Oestrogen-only versus no HRT

Evidence for the overall incidence of ovarian cancer came from 1 individual participant data meta-analysis of observational studies, and 1 other observational study. High quality evidence showed an increased risk in ovarian cancer with oestrogen-only HRT use when compared to no HRT. One observational study was exclusively in a population of black

women, and very low-quality evidence showed no important difference between groups, however there were concerns regarding imprecision, bias and indirectness.

Duration of HRT use

Across the 6 observational studies that provided data on the incidence of ovarian cancer for current users by years of use, very low to moderate quality evidence showed an increased risk of ovarian cancer with longer duration of use. The exception was 1 study that showed a reduced risk with oestrogen-only HRT use of 1 to 4 years, but 4 other observational studies showed no important difference with 1 to 4 years of use.

Recency of HRT user

Evidence from 2 observational studies provided data on the incidence of ovarian cancer for past users of oestrogen-only HRT, however time since last use was unknown. The evidence showed that past users of duration less than 5 years and also more than 5 years had no difference in risk compared to the no HRT group. The evidence was of very low quality due to concerns are bias and imprecision.

Age at first use

Evidence from 1 observational study showed that there was an important benefit with oestrogen-only HRT use on the risk of ovarian cancer if the age at first use was less than 60, 60 to 69 or over 70. The evidence was of low quality due to concerns around bias.

Constituent

Evidence from 2 observational studies showed an important harm for equine oestrogen on the risk of ovarian cancer, compared to the no HRT group. The evidence was of low quality, with concerns around bias. Very low-quality evidence showed no important difference for oestradiol compared to no HRT with concerns around bias, inconsistency, and imprecision.

Mode of administration

Evidence from 3 studies provided data for oestrogen-only HRT and mode of administration on the risk of epithelial type of ovarian cancer. The evidence showed that there was an increased risk with oral administration, but no difference for transdermal administration. The evidence was of very low to low quality due to concerns around risk of bias and imprecision. Low quality evidence from 1 study showed a reduced risk of non-epithelial type of ovarian cancer in oestrogen users of both oral and transdermal routes of administration. The evidence was downgraded due to concerns around bias.

Histological type

Evidence from 2 studies provided data on the risk of ovarian cancer by histological type, for users of 5 to 9 years of use. The evidence showed an important harm for oestrogen users compared to no HRT, for the serous and endometrioid types of ovarian cancer, but no differences for clear cell. There was heterogeneity for mucinous types with 1 meta-analysis of observation study showing no important difference, but 1 other observational study showing an important benefit. The evidence ranged from very low to high with concerns around bias, imprecision, and inconsistency.

Mortality

Across 4 observational studies, some of the evidence showed an important harm for oestrogen-only HRT use on mortality from ovarian cancer or survival from ovarian cancer, whereas some of the evidence showed no difference between users of HRT and no HRT. The evidence ranged from very low to moderate with concerns over risk of bias, some inconsistency and imprecision.

See Appendix F for full GRADE tables and Appendix L for absolute risk tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee chose incidence of ovarian cancer and mortality from ovarian cancer as the critical outcomes for this review. They agreed that the risks regarding incidence of ovarian cancer following HRT are not well understood. They hoped to find evidence that would clarify the risks so that women can make an informed choice when deciding whether HRT is right for them. They chose mortality from ovarian cancer as a critical outcome as they discussed that incidence of different types of ovarian cancer might differ, but it was important to know whether this still had an impact on mortality.

The quality of the evidence

The quality of the evidence was assessed with GRADE. The evidence ranged from high to very low quality, with most of the concerns around imprecision around the effect estimate for most outcomes, and also risk of bias for most outcomes. Reasons for downgrading due to bias were mainly around not controlling for most of the important confounders. There were also some concerns around deviations from the intended intervention, as prescription registries or women's self-reporting may indicate the use of HRT, but it cannot be fully confirmed that they took the HRT. There were also some concerns relating to inconsistencies where some studies showed different directions of effect that could not be explained by subgroup analysis.

Benefits and harms

Overall, when considering the evidence, the committee agreed that most suggested an increase in the risk of ovarian cancer for current users of oestrogen-only and oestrogen plus progestogen/progesterone combined preparations, when compared to no HRT use. They discussed that the evidence for the risk in past users of HRT was not informative as the time since last use was not available. Nevertheless, the committee agreed that the available evidence was useful for making recommendations on the risk of ovarian cancer in current HRT users.

Combined HRT

RCT

The committee discussed that most of the evidence came from observational studies, but there was data from the Women's Health Initiative randomised trial that showed there was an increased risk of ovarian cancer for combined users of HRT compared to placebo, but that the risk increase was not statistically significant. The committee discussed that the RCT evidence provided information on the risk of ovarian cancer by histological type, but there was limited information on different durations of use. Since the data from the RCT was collected at the end of the intervention period, they discussed that the evidence from the RCT data could be relevant to current users who had used combined HRT for the duration of the trial, which was 5.6 years. They discussed that RCT evidence is not subject to risk of bias by residual confounding and therefore this data would be robust in relation to this. However, they also noted that that the baseline risk of ovarian cancer in the population is low and that a larger sample size would be required to detect any changes in the risk.

Observational evidence

The committee discussed the observational evidence, which overall showed an increased risk of ovarian cancer in HRT users when compared to women not using HRT. They discussed that although the evidence came from observational studies that are subject to risk of bias by confounding, the sample size of most of the studies was large, which they agreed was necessary considering the low baseline rate of ovarian cancer. They also considered that the data from the observational studies provided further information related subgroups (see below) that was specified in the protocol. The committee agreed this detail was useful for making informed decisions when considering HRT use for menopausal symptoms.

Duration of use

The committee discussed the evidence from observational studies that suggested that there was no difference in the risk of ovarian cancer below 5 years of combined HRT use, but an increase in the risk when duration of use was over 5 years. However, looking at the test for subgroup differences there was not a statistically significant difference in the risk of ovarian cancer depending on the duration of use. The committee discussed that the risk was likely too small to detect in the evidence when split up in subgroups due to smaller sample sizes, and therefore could not comment on the differences in risk, if any, for combined HRT use depending on duration of use.

Types of ovarian cancer

The committee discussed the different types of ovarian cancer. They noted that the most common types of ovarian cancers were epithelial, of which high grade serous and then endometroid are the most common. They discussed that the cells of origin for epithelial and non-epithelial ovarian cancers are different. They also discussed the differences in prognosis between the different histological types of epithelial ovarian cancers. The committee discussed the observational evidence that was stratified by subtypes of ovarian cancer for 5-9 years of combined HRT use. They noted that there was an increased incidence of the

serous and endometrioid subtypes of ovarian cancer, but not for the less common mucinous or clear-cell subtypes. They discussed the quality of the evidence, in particular the imprecision of the evidence for mucinous and clear-cell ovarian cancer and agreed that the wide confidence intervals reflected the rare incidence of these subtypes. Overall, the evidence suggested no difference between combined HRT and non-HRT users for ovarian cancer incidence in these subtypes, as the confidence intervals were too wide. Therefore, the committee agreed that a recommendation by subtypes would not be beneficial.

Constituent

The committee discussed the evidence for progestogenic constituents of the oestrogen plus progesterone combined HRT. They discussed that the evidence showed no difference between HRT users and non-users for all progestogenic constituents. The committee noted that there were concerns around imprecision for all of the evidence, and that this would be due to the smaller sample size in the subgroups. They discussed that the evidence did not support a recommendation specific to a progestogenic constituent and made a research recommendation related to this (see appendix K in evidence review D).

Regimen

The evidence suggested an increased risk in ovarian cancer with oestrogen plus progestogen use when compared to no HRT use, which remained the same for both sequential and continuous combined regimens. The committee discussed that since the evidence suggested no difference in risk for either regimen, a recommendation specific to either continuous or sequential was not necessary.

Mode of administration

The committee discussed that there was evidence stratified by mode of administration for both epithelial and non-epithelial types. For both types the evidence showed that there was an increased risk in oral HRT, but not for transdermal HRT when compared to no HRT. However, as they were part of subgroup analysis, the committee looked at the test for subgroup differences which showed no statistically significant difference between oral or transdermal modes of administration. They agreed that they could not use the evidence to inform recommendations on the risk of ovarian cancer with combined HRT depending on the mode of administration.

Interpretation of RCT and observational evidence

The committee discussed that there was some evidence which suggested no difference in the risk of ovarian cancer between combined HRT users and non-users, which came from RCTs, and some evidence from observational studies that suggested an increased risk. They discussed that since the baseline risk of ovarian cancer is low, studies would require large sample sizes to be able to detect differences and that and differences not detected in the evidence could be due to smaller sample sizes. They agreed that it was important to highlight that there was a very slight increase in the risk but to also highlight that the baseline risk in those under 60 was low.

Oestrogen-only HRT

Observational evidence

The committee discussed that there was only evidence from observational studies for oestrogen-only HRT, and no RCT evidence. They discussed that most of the evidence suggested that there was an increased risk in ovarian cancer in those using oestrogen-only HRT when compared to non-users. As with the evidence for combined HRT, the committee

discussed the potential limitations with observational studies, in that there would be a risk of bias by residual confounding.

Duration of use

The committee had a similar discussion for oestrogen-only HRT as with combined HRT, as the observational evidence for oestrogen-only also showed no difference in the risk of ovarian cancer in HRT users when duration was up to 4 years of use, but an increased risk of ovarian cancer when use was 5 years or more. They also noted that one study showed a reduction in the risk of ovarian cancer when duration was 1 to 4 years, but they were cautious with this result as the meta-analysis of 4 studies showed no difference in the risk. The committee looked at the test for subgroup differences and noted that the differences in the evidence by duration of use was significant. The committee concluded from this that they were able to support a recommendation that the risk of ovarian cancer with oestrogen-only HRT use was specific to durations of 5 years of more and agreed to include this in the recommendation.

Constituent

The committee then looked at the subgroup analysis for constituent types. They discussed that the evidence showed an increased risk of ovarian cancer incidence in those using equine oestrogen-only HRT, compared to non-users, and an increased risk in oestradiol users although for oestradiol the result was not statistically significant. The committee agreed that as this was in line with the evidence for overall incidence they would not make separate recommendations for the specific oestrogen constituents.

Mode of administration

The committee discussed the evidence for risk of ovarian cancer with oestrogen-only HRT by different routes of administration. The evidence for epithelial, one of the most common types, showed an increased risk with both oral and transdermal modes of administration although transdermal did not reach statistical significance. Regardless, the committee felt it was important to highlight in the recommendations that the risk of ovarian cancer with oestrogen-only is present in oral and transdermal preparations, as they recognised there was an assumption in current practice that transdermal preparations may be safer. They agreed it was important to present any risks where they might be present.

Absolute risk

The committee agreed that it was important to discuss the increased risks in absolute terms. They discussed that the information presented in this way would allow those who currently take HRT, or are considering taking HRT, to understand their risk of ovarian cancer if they did not take HRT. They discussed that although there was an overall increased risk, the absolute risks to the individual were small, because ovarian cancer is rare. They discussed that although statistically significant, when presenting the figures over women per 1000, there seemed to be no change due to the low background incidence. The committee discussed the poor prognosis of ovarian cancer, and agreed that although it was a rare cancer, it should be an individual choice to weigh the risks against any benefits for the treatment of troublesome menopausal symptoms.

Mortality from ovarian cancer and survival

The committee then looked at the evidence on mortality from ovarian cancer. Although there was some evidence suggesting no difference, the committee noted that for both oestrogen-only and combined oestrogen and progesterone there was an increased risk of mortality in current users, which was not seen in past users of HRT. The committee discussed that ovarian cancer has a poor prognosis and so incidence of ovarian cancer is more closely

linked to mortality. Although the evidence suggests a small risk in mortality in current users of HRT, the committee agreed that the absolute excess risk remains small, and therefore agreed not to make a recommendation.

Minority groups

One study, based on a population of black women, suggested that there was no difference in the incidence of ovarian cancer when taking any combined HRT compared to no HRT. The committee discussed that although the evidence was not statistically significant (in that, it showed no difference), it seemed to be in line with the direction of effect of the other evidence for overall incidence of ovarian cancer. However, the committee were unable to confidently make a conclusion specific to black people because the study was based on a small sample size. Therefore, the committee agreed that a research recommendation was necessary to encourage inclusivity in the study population in future research and studies (see Appendix K in evidence review C).

Despite a lack of evidence relating to transgender men and non-binary people the committee agreed that the evidence was generalisable to those who have never taken gender affirming hormone therapy but were uncertain about transgender people who have taken gender affirming hormone therapy in the past and no evidence was identified for this group. They therefore made a research recommendation (Appendix K of evidence report C).

Other factors the committee took into account

Whilst it is unclear how HRT might affect long term health outcomes (such as breast and endometrial cancer, CVD, and stroke) in trans men and non-binary people who have previously taken as gender affirming hormone therapy because evidence is lacking, the committee agreed that it is important to improve access to services for them. They therefore recommended that it should be ensured that they can discuss their menopause symptoms with a healthcare professional with expertise in menopause. The discussion of this is described in further detail in ‘the committee’s discussion and interpretation of the evidence’ section of evidence review C.

Cost effectiveness and resource use

No previous economic evidence was identified for this topic.

The recommendations made for this review topic centre around the risk of ovarian cancer in HRT. Whilst recommendations in this area will potentially lead to people being better informed about use of HRT, it is unclear how such information will change treatment decisions and how these will impact upon overall resource use. It would however be unethical to prevent such information being discussed with patients even if it did lead to an increase in resource use through changes in treatment decisions.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point) and statements related to ovarian cancer in tables 1 and 2 as well as the associated absolute number tables in the NICE guideline. It also supports an overarching recommendation related to trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past (recommendation 1.5.32 – see evidence review C).

Additionally, there are overarching research recommendations related to all health outcomes addressed in this guideline update (including endometrial cancer), for:

- trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past

- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

References – included studies

Anderson 2003

Anderson, Garnet L, Judd, Howard L, Kaunitz, Andrew M et al. (2003) Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 290(13): 1739-48

Baandrup 2022

Baandrup, Louise, Galanakis, Michael, Hannibal, Charlotte G et al. (2022) Long-term survival of nonlocalized epithelial ovarian cancer among women using menopausal hormone therapy prior to diagnosis: The extreme study. International journal of cancer 151(9): 1512-1522

Beral 2007

Beral, Valerie, Million Women Study, Collaborators, Bull, Diana et al. (2007) Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet (London, England) 369(9574): 1703-10

Bethea 2017

Bethea, Traci N, Palmer, Julie R, Adams-Campbell, Lucile L et al. (2017) A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women. Cancer causes & control : CCC 28(5): 385-391

Bryk 2021

Bryk, Saara, Katuwal, Sushmita, Haltia, Ulla-Maija et al. (2021) Parity, menopausal hormone therapy, and risk of ovarian granulosa cell tumor - A population-based case-control study. Gynecologic oncology 163(3): 593-597

CGESOC 2015

Collaborative Group On Epidemiological Studies Of Ovarian, Cancer, Beral, V, Gaitskell, K et al. (2015) Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet (London, England) 385(9980): 1835-42

Danforth 2007

Danforth, K N, Tworoger, S S, Hecht, J L et al. (2007) A prospective study of postmenopausal hormone use and ovarian cancer risk. British journal of cancer 96(1): 151-6

Felix 2015

Felix, Ashley S, Bunch, Kristen, Yang, Hannah P et al. (2015) Menopausal hormone therapy and mortality among women diagnosed with ovarian cancer in the NIH-AARP Diet and Health Study. Gynecologic oncology reports 13: 13-7

Folsom 2004

Folsom, A.R.; Anderson, J.P.; Ross, J.A. (2004) Estrogen replacement therapy and ovarian cancer. Epidemiology 15(1): 100-104

Hildebrand 2010

Hildebrand, Janet S, Gapstur, Susan M, Feigelson, Heather Spencer et al. (2010) Postmenopausal hormone use and incident ovarian cancer: Associations differ by regimen. International journal of cancer 127(12): 2928-35

Koskela-Niska 2013

Koskela-Niska, Virpi, Pukkala, Eero, Lyytinen, Heli et al. (2013) Effect of various forms of postmenopausal hormone therapy on the risk of ovarian cancer--a population-based case control study from Finland. International journal of cancer 133(7): 1680-8

Lacey 2002

Lacey, James V Jr, Mink, Pamela J, Lubin, Jay H et al. (2002) Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA 288(3): 334-41

Morch 2009

Morch, Lina Steinrud, Lokkegaard, Ellen, Andreasen, Anne Helms et al. (2009) Hormone therapy and ovarian cancer. JAMA 302(3): 298-305

Rodriguez 2001

Rodriguez, C, Patel, A V, Calle, E E et al. (2001) Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. JAMA 285(11): 1460-5

Schneider 2009

Schneider, C; Jick, S S; Meier, C R (2009) Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations. Climacteric: the journal of the International Menopause Society 12(6): 514-24

Simin 2020

Simin, Johanna, Tamimi, Rulla M, Callens, Steven et al. (2020) Menopausal hormone therapy treatment options and ovarian cancer risk: A Swedish prospective population-based matched-cohort study. International journal of cancer 147(1): 33-44

Trabert 2012

Trabert, B, Wentzensen, N, Yang, H P et al. (2012) Ovarian cancer and menopausal hormone therapy in the NIH-AARP diet and health study. British journal of cancer 107(7): 1181-7

Tsilidis

Tsilidis, Konstantinos K, Allen, Naomi E, Key, Timothy J et al. (2011) Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. Cancer causes & control: CCC 22(8): 1075-84

Appendices

Appendix A Review protocols

Review protocol for review question: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?

ID	Field	Content
0.	PROSPERO registration number	CRD42022362409
1.	Review title	Effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?
3.	Objective	To identify the effects, if any, of HRT on developing ovarian cancer
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • INAHTA • HTA via CRD • PsycInfo Searches will be restricted by: • Date (no restriction) • English language only • Human studies only

		• RCTs, Systematic Reviews and Cohort Studies Conference abstracts will be excluded from the search results The full search will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	Menopause
6.	Population	Women, non-binary and trans people with menopause (including perimenopause and post-menopause)
7.	Intervention/Exposure/Test	• HRT* ○ Oestrogen-only ○ Combined oestrogen and progestogen - Sequential combined - Continuous combined - Any combined * Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.
8.	Comparator/Reference standard/Confounding factors	• Placebo treatment • No HRT
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs • Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies. Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
10.	Other exclusion criteria	• People with premature ovarian insufficiency • People with early menopause (aged 40 to 44) • People with bilateral oophorectomy

		If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness. Observational studies will need to adjust for confounders Relevant confounders may include BMI, smoking, age at menopause, family history of ovarian cancer, contraceptive pill use, history of IVF, breastfeeding, number of children, inherited genetic conditions/cancers
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	Incidence of ovarian cancer (includes borderline tumours) Mortality from ovarian cancer
13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials • ROBINS-I for non-randomised, controlled/cohort studies.

		• Tierney 2015 checklist for individual participant data meta-analyses of randomised controlled trials (Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. (2015) Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLoS Med 12(7): e1001855) The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance Validated scales/continuous outcomes: published MIDs where available All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.
17.	Analysis of sub-groups	Evidence will be stratified (in 2 layers) by:

		• Recency of HRT use (current users, < 5 years, 5-9 years, ≥ 10 years since last use) by duration of HRT use (<1 year, 1-4 years, 5-9 years, 10-14 years, ≥ 15 years) Additional stratification will be done only for a single specified duration and recency of HRT use (for example: only current HRT users with 5 to 14 years of use) and will only be possible if evidence is reported in this way. Evidence will be stratified by: • Age at first use (45-50 years, 50-59 years, 60-69 years, >69 years) • Time since menopause at first use (<1 year, 1-4 years, 5-9 years, >10 years) • Constituent (equine oestrogen, oestradiol) • Mode of administration (oral, transdermal) • Progestogenic constituent (for combined HRT only: (Levo)norgestrel, Norethisterone acetate, Medroxyprogesterone acetate, Micronised progesterone, any synthetic progestin) • Length of cycle (for sequential combined HRT only: Sequential long cycle [3 monthly], Sequential 30-day cycle) • Oral contraceptive use • Family history of ovarian cancer (family history, no family history) • Personal history of ovarian cancer (personal history, no personal history) • For high risk of ovarian cancer (BRCA1/2 positive, BRCA1/2 negative) • By surgical menopause (surgical menopause, no surgical menopause) • BMI (<18.5, 18.5 to 24.9, ≥25) • By factors identified in the equalities section of the scope: o Ethnicity (White British, Asian/Asian British, Black/African/Caribbean/Black British, Mixed/Multiple ethnic groups) o Disability (disability, no disability) o Socioeconomic group (deprived, non-deprived) o Non-binary and trans people Where evidence is stratified or sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	27th September 2022			
22.	Anticipated completion date	23rd August 2023			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☑
		Piloting of the study selection process		☐	☑
		Formal screening of search results against eligibility criteria		☐	☑
		Data extraction		☐	☑
		Risk of bias (quality) assessment		☐	☑
		Data analysis		☐	☑
24.	Named contact	5a. Named contact Guideline development team NGA 5b Named contact e-mail			

		menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
25.	Review team members	Senior Systematic Reviewer Systematic Reviewer
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362409
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Ovarian cancer; hormone replacement therapy	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	X	Ongoing
		X	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.

Appendix B Literature search strategies

Literature search strategies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?

There was a combined literature search strategies for review questions:

C What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

D What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

E What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing endometrial cancer?

F What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?

G What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing dementia?

H What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

I What are the effects of hormone replacement therapy taken by women, non-binary and trans people with early menopause (aged 40 to 44) on all-cause mortality and developing:

- **venous thromboembolism**
- **cardiovascular disease**
- **type 2 diabetes**
- **breast cancer**
- **endometrial cancer**
- **ovarian cancer**
- **osteoporosis**
- **dementia**
- **loss of muscle mass and strength?**

Clinical searches

Database: Ovid MEDLINE(R) ALL <1946 to September 30, 2022>

Date of last search: 03/10/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	56226
3	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
4	("change of life" or life change?).ti,ab.	3175
5	or/1-4	117224
6	exp Hormone Replacement Therapy/	26181
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Estrogens/	97369

#	Searches	
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	8328
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
14	or/6-13	300800
15	5 and 14	38439
16	exp Breast Neoplasms/	331829
17	exp "Neoplasms, Ductal, Lobular, and Medullary"/	45099
18	exp breast/ and exp neoplasms/	31705
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	412638
20	exp uterine neoplasms/	143954
21	Endometrial Hyperplasia/	3751
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	71639
23	exp Ovarian Neoplasms/	92941
24	Fallopian Tube Neoplasms/	3090
25	Peritoneal Neoplasms/	16848
26	Pelvic Neoplasms/	7356
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	134115
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	18696
29	exp Dementia/	195885
30	(amentia* or dementia* or lewy body).ti,ab.	131539
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	172723
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	212540
33	Death/ or exp Mortality/	438343
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	2676396
35	exp Cardiovascular Diseases/	2652417
36	exp Stroke/	164004
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	265024
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	391497
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	237740
40	(stroke or strokes).ti,ab.	293720
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	177232
42	TIA.ti,ab.	9584
43	(myocardial adj2 infarct*).ti,ab.	215115
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	85723
45	atrial flutter*.ti,ab.	6330
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	150990
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	23385
48	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/	98814
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	110885
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201

#	Searches	
52	exp Bone Remodeling/ or Bone Density/	118506
53	exp radius fractures/ or spinal fractures/ or hip fractures/	45889
54	(osteoporo* or osteop?en*).ti,ab.	91147
55	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	136427
56	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	76474
57	exp Muscle Strength/ or Muscle Contraction/ or Muscle, Skeletal/ or Muscle weakness/	275399
58	exp Muscular Atrophy/	20100
59	(sarcop?en* or dynap?eni*).ti,ab.	12753
60	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	89183
61	exp Diabetes Mellitus, Type 2/	162254
62	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	178683
63	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	3367
64	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1079
65	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	11970
66	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	52630
67	or/16-66	7071734
68	15 and 67	24780
69	animals/ not humans/	5018518
70	exp Animals, Laboratory/	944064
71	exp Animal Experimentation/	10221
72	exp Models, Animal/	633340
73	exp Rodentia/	3486788
74	(rat or rats or mouse or mice).ti.	1413148
75	or/69-74	6058843
76	68 not 75	22173
77	limit 76 to english language	19974
78	Climacteric/	4935
79	Menopause/ or Perimenopause/ or Postmenopause/	56226
80	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
81	("change of life" or life change?).ti,ab.	3175
82	or/78-81	117224
83	exp Hormone Replacement Therapy/	26181
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
86	exp *Estrogens/	97369
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
89	((combin* or sequen* or continu*) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	6337
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
91	or/83-90	300359
92	82 and 91	38419
93	animals/ not humans/	5018518
94	exp Animals, Laboratory/	944064
95	exp Animal Experimentation/	10221
96	exp Models, Animal/	633340
97	exp Rodentia/	3486788
98	(rat or rats or mouse or mice).ti.	1413148
99	or/93-98	6058843
100	92 not 99	34708

#	Searches	
101	limit 100 to english language	30818
102	randomized controlled trial.pt.	578276
103	controlled clinical trial.pt.	95066
104	pragmatic clinical trial.pt.	2153
105	randomi#ed.ab.	690521
106	placebo.ab.	232230
107	randomly.ab.	392671
108	Clinical Trials as topic.sh.	200427
109	trial.ti.	271569
110	or/102-109	1520899
111	COMPARATIVE STUDIES/	1911627
112	FOLLOW-UP STUDIES/	687669
113	TIME FACTORS/	1228326
114	reviewed.tw.	604810
115	prospective$.tw.	826138
116	retrospective$.tw.	951729
117	baseline.tw.	681295
118	cohort.tw.	716940
119	case series.tw.	96297
120	or/111-119	5840666
121	COHORT STUDIES/	319704
122	FOLLOW-UP STUDIES/	687669
123	LONGITUDINAL STUDIES/	160686
124	PROSPECTIVE STUDIES/	640096
125	RETROSPECTIVE STUDIES/	1062925
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	990520
127	(incidence? adj (stud* or research or analys*)).tw.	2167
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	8189
129	(prospective* adj method*).tw.	492
130	(retrospective* adj design*).tw.	2556
131	Case-Control Studies/	323880
132	"nested case control".ti,ab.	10276
133	or/121-132	2937576
134	110 or 120 or 133	7274173
135	101 and 134	16133
136	77 or 135	25292

Database: Embase <1974 to 2022 September 30>

Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
9	exp *estrogen/	126164
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068

#	Searches	
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
14	or/6-13	401114
15	5 and 14	58995
16	exp breast tumor/	610160
17	exp medullary carcinoma/	11738
18	exp breast/ and exp neoplasm/	81181
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	580028
20	exp uterus cancer/	178703
21	endometrium hyperplasia/	8475
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	94083
23	exp ovary tumor/	165879
24	uterine tube tumor/	1128
25	exp peritoneum tumor/	32297
26	exp pelvis tumor/	8687
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	189064
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	26375
29	exp dementia/	414481
30	(amentia* or dementia* or lewy body).ti,ab.	188972
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	233156
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	296024
33	death/ or fatality/ or exp mortality/	1565750
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	3638723
35	exp cardiovascular disease/	4653676
36	exp cerebrovascular accident/	278318
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	395575
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	582395
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	388936
40	(stroke or strokes).ti,ab.	467280
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	248980
42	TIA.ti,ab.	21167
43	(myocardial adj2 infarct*).ti,ab.	308381
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	151993
45	atrial flutter*.ti,ab.	10322
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	225615
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	38407
48	pulmonary embolism/ or lung embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or vein thrombosis/ or upper extremity deep vein thrombosis/	238572
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	173070
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963

#	Searches	
53	(osteoporo* or osteop?en*).ti,ab.	139235
54	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	184524
55	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	105447
56	muscle strength/ or muscle contraction/ or skeletal muscle/ or muscle weakness/	298183
57	exp muscle atrophy/	53010
58	(sarcop?en* or dynap?eni*).ti,ab.	19831
59	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	123477
60	diabetes mellitus/ or non insulin dependent diabetes mellitus/	903538
61	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	274466
62	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	4587
63	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1729
64	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	13941
65	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	87957
66	or/16-65	10247056
67	15 and 66	41567
68	animal/ not human/	1164743
69	nonhuman/	7043049
70	exp Animal Experiment/	2901019
71	exp Experimental Animal/	776639
72	animal model/	1589792
73	exp Rodent/	3873528
74	(rat or rats or mouse or mice).ti.	1563613
75	or/68-74	9201242
76	67 not 75	35048
77	limit 76 to english language	30447
78	climacterium/ or "menopause and climacterium"/	8994
79	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
80	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
81	("change of life" or life change?).tw.	4281
82	or/78-81	184584
83	exp hormone substitution/	61182
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
86	exp *estrogen/	126164
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
89	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
91	or/83-90	401114
92	82 and 91	58995
93	animal/ not human/	1164743
94	nonhuman/	7043049
95	exp Animal Experiment/	2901019
96	exp Experimental Animal/	776639
97	animal model/	1589792
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242

#	Searches	
101	92 not 100	50424
102	limit 101 to english language	43215
103	random*.ti,ab.	1840480
104	factorial*.ti,ab.	44821
105	(crossover* or cross over*).ti,ab.	120165
106	((doubl* or singl*) adj blind*).ti,ab.	261774
107	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1196283
108	crossover procedure/	71600
109	single blind procedure/	47754
110	randomized controlled trial/	730322
111	double blind procedure/	199308
112	or/103-111	2737481
113	CONTROLLED STUDY/	9111478
114	TREATMENT OUTCOME/	935485
115	MAJOR CLINICAL STUDY/	4618747
116	CLINICAL TRIAL/	1046476
117	reviewed.tw.	873307
118	baseline.tw.	1157267
119	(compare$ or compara$).tw.	7021464
120	or/113-119	16140633
121	COHORT ANALYSIS/	901841
122	FOLLOW UP/	1902143
123	LONGITUDINAL STUDY/	179050
124	PROSPECTIVE STUDY/	798586
125	RETROSPECTIVE STUDIES/	1035839
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	1497898
127	(incidence? adj (stud* or research or analys*)).tw.	2924
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	10476
129	(prospective* adj method*).tw.	1417
130	(retrospective* adj design*).tw.	4171
131	case control study/	193429
132	"nested case control".ti,ab.	13700
133	or/121-132	4296161
134	112 or 120 or 133	17894341
135	102 and 134	30379
136	77 or 135	39104
137	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5322870
138	136 not 137	30760

Database: APA PsycInfo <1806 to September Week 4 2022>

Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938
4	or/1-3	15066
5	hormone therapy/	2262
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *estrogens/	5657
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482

#	Searches	
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
11	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
12	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
13	or/5-12	24383
14	4 and 13	2373
15	breast neoplasms/	11017
16	Breast/ and exp neoplasms/	300
17	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	15213
18	uterus/ and exp neoplasms/	43
19	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	457
20	ovaries/ and exp neoplasms/	444
21	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	1347
22	((epithelial or germ cell) adj5 ovar*).ti,ab.	58
23	exp dementia/ or exp alzheimer's disease/	87977
24	(amentia* or dementia* or lewy body).ti,ab.	72463
25	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	67104
26	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	120339
27	exp "death and dying"/	45080
28	(death or dying or die* or dead or mortality or fatal*).ti,ab.	218375
29	exp Cardiovascular Disorders/ or Cerebrovascular Accidents/	68930
30	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	14620
31	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	16319
32	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	6390
33	(stroke or strokes).ti,ab,mh.	38668
34	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	14812
35	TIA.ti,ab.	993
36	(myocardial adj2 infarct*).ti,ab.	4538
37	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	1391
38	atrial flutter*.ti,ab.	27
39	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	4960
40	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).mp.	709
41	embolisms/ or thromboses/	1323
42	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	1179
43	osteoporosis/	1165
44	bones/ and (accidents/ or injuries/ or falls/)	117
45	(osteoporo* or osteop?en*).ti,ab.	2275
46	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab,mh.	2050
47	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab,mh.	1936
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357

#	Searches	
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *estrogens/	5657
73	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
75	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
76	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
77	or/69-76	24383
78	68 and 77	2373
79	animal.po.	432218
80	(rat or rats or mouse or mice).ti.	123700
81	79 or 80	436853
82	78 not 81	1974
83	limit 82 to english language	1898
84	clinical trial.md.	34832
85	clinical trial.md.	34832
86	Clinical trials/	12104
87	Randomized controlled trials/	913
88	Randomized clinical trials/	383
89	assign*.ti,ab.	106838
90	allocat*.ti,ab.	35101
91	crossover*.ti,ab.	8375
92	cross over*.ti,ab.	3251
93	((doubl* or singl*) adj blind*).ti,ab.	28070
94	factorial*.ti,ab.	21909
95	placebo*.ti,ab.	42984
96	random*.ti,ab.	229145
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0

#	Searches	
101	followup study.md.	86839
102	TREATMENT OUTCOMES/	38539
103	treatment outcome.md.	22898
104	CLINICAL TRIALS/	12104
105	clinical trial.md.	34832
106	reviewed.tw.	93954
107	prospective$.tw.	78083
108	retrospective$.tw.	50502
109	baseline.tw.	133530
110	cohort.tw.	81269
111	case series.tw.	4679
112	(compare$ or compara$).tw.	719207
113	or/100-112	1088229
114	COHORT ANALYSIS/	1643
115	LONGITUDINAL STUDIES/ or longitudinal study.md.	188660
116	FOLLOWUP STUDIES/ or followup study.md.	87168
117	PROSPECTIVE STUDIES/ or prospective study.md.	49600
118	RETROSPECTIVE STUDIES/ or retrospective study.md.	34340
119	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	141639
120	(incidence? adj (stud* or research or analys*)).tw.	614
121	(longitudinal* adj1 (survey* or evaluat*)).tw.	5386
122	(prospective* adj method*).tw.	156
123	(retrospective* adj design*).tw.	489
124	or/114-123	307794
125	99 or 113 or 124	1485971
126	83 and 125	1056
127	64 or 126	1411

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 10 of 12, October 2022

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124

#	Searches	
20	#19 in Cochrane Reviews	56

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 10 of 12, October 2022

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56
21	#19 in Trials	8053

Database: Epistemonikos

Date of last search: 27/07/2022

#	Searches	
1	(menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes")	
2	((hormone AND (replac* OR therap* OR substitut*)) OR HRT OR HT OR MHT OR ERT OR EPRT OR SEPRT OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR ((combin* OR sequen* OR continu* OR plus) AND (progest* OR gestagen* OR gestogen* OR medroxyprogesterone* OR norgestrel* OR drospirenone* OR norethisterone* OR dydrogesterone* OR levonorgestrel*)) OR (("body identical*" OR bio-identical* OR bioidentical*) AND hormon*))	
3	1 AND 2	7537

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994

#	Searches	
8	MeSH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES	191
9	((hormon* AND (replac* or therap* or substitut*)))	1577
10	((HRT or HT or MHT or ERT or EPRT or SEPRT))	435
11	MeSH DESCRIPTOR Estrogens EXPLODE ALL TREES	136
12	((oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*))	670
13	(((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)))	291
14	((("body identical*" or bio-identical* or bioidentical*) AND hormon*))	3
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2314
16	#7 AND #15	473
17	(#7 AND #15) IN HTA	71

Database: INAHTA

Date of last search: 03/10/2022

#	Searches	
1	"Climacteric"[mh] or "Menopause"[mh] or "Perimenopause"[mh] or "Postmenopause"[mh]	56
2	(menopau* or postmenopau* or perimenopau* or climacteri*)	158
3	("change of life" or "life change" or "life changes")	1
4	#3 OR #2 OR #1	162
5	"Hormone Replacement Therapy"[mhe]	31
6	(hormon* AND (replac* or therap* or substitut*))	161
7	(HRT or HT or MHT or ERT or EPRT or SEPRT)	33
8	"Estrogens"[mhe]	7
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*)	83
10	((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*))	16
11	(("body identical*" or bio-identical* or bioidentical*) AND hormon*)	1
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	232
13	#12 AND #4	73
14	Limit to English Language	57

Economic searches

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504

#	Searches	
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352
55	26 and 54	849

Database: Embase <1974 to 2022 July 27>

Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270
8	letter.pt. or letter/	1241876

#	Searches	
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982

#	Searches	
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13

#	Searches	
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN HTA FROM 2012 TO 2022	42

Database: INAHTA

Date of last search: 28/07/2022

#	Searches	
1	"Climacteric"[mh]	2
2	"Menopause"[mh]	28
3	"Perimenopause"[mh]	1
4	"Postmenopause"[mh]	31
5	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
6	("change of life" or "life change" or "life changes")	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	163
8	Limit to English Language	134

Database: EED

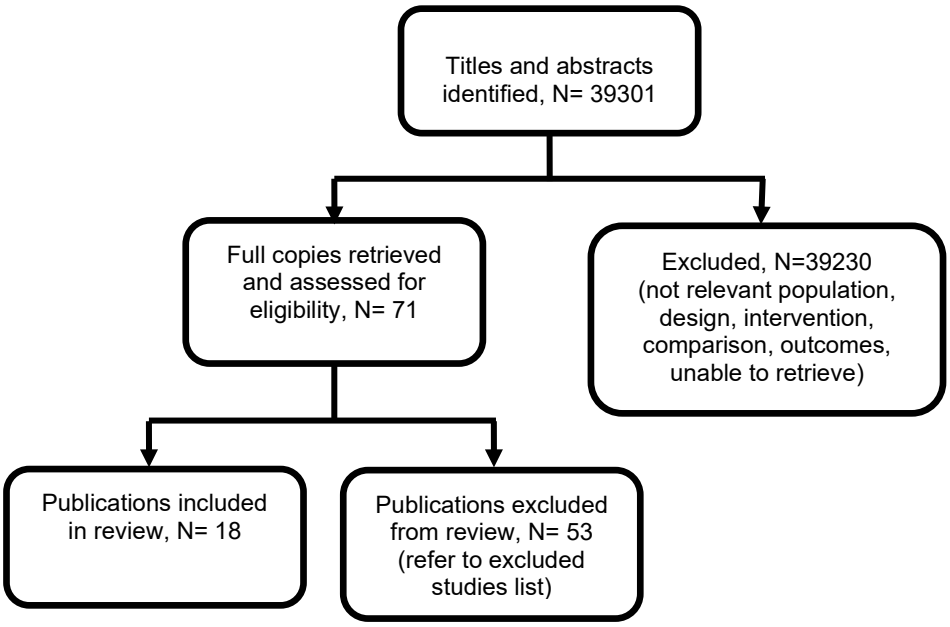
Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN NHSEED FROM 2012 TO 2022	33

Appendix C Effectiveness evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

Anderson, 2003

Bibliographic Reference	Anderson, Garnet L; Judd, Howard L; Kaunitz, Andrew M; Barad, David H; Beresford, Shirley A A; Pettinger, Mary; Liu, James; McNeeley, S Gene; Lopez, Ana Maria; Women's Health Initiative, Investigators; Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial.; JAMA; 2003; vol. 290 (no. 13); 1739-48

Study details

Country/ies where study was carried out	United States
Study type	Randomised controlled trial (RCT)
Study dates	September 1993 to October 1998
Inclusion criteria	• Women aged 50 to 79 • postmenopausal • provided written informed consent • women who had not had a hysterectomy.
Exclusion criteria	• Preexisting conditions that contraindicated use of hormones • health conditions where survival was predicted less than 3 years • health conditions that were considered likely to be poor adherers to the study protocol.
Patient characteristics	Mean (SD) – not reported for patient characteristics **Age at screening:** Estrogen + Progestin, n (%): 50-59: 2839 (33.4) 60-69: 3853 (45.3) 70-79: 1814 (21.3)

	Placebo, n (%): 50-59: 2683 (33.1) 60-69: 3657 (45.1) 70-79: 1762 (21.8)
	Ethnicity Estrogen + Progestin, n (%): White: 7140 (83.9) Black: 549 (6.5) Hispanic: 472 (5.5) American Indian: 26 (0.3) Asian/Pacific Islander: 194 (2.3) Unknown: 125 (1.5)
	Placebo, n (%): White: 6805 (84) Black: 575 (7.1) Hispanic: 416 (5.1) American Indian: 30 (0.4) Asian/Pacific Islander: 169 (2.1) Unknown: 107 (1.3)
	Body mass index: Estrogen + Progestin, n (%): <25: 2579 (30.3) 25-29: 2992 (35.2) ≥30: 2899 (34.1) Unknown: 36 (0.4)
	Placebo, n (%): <25: 2479 (30.6) 25-29: 2834 (35.0) ≥30: 2737 (33.8) Unknown: 52 (0.6)
	Smoking: Estrogen + Progestin, n (%): Never: 4178 (49.1) Past: 3362 (39.5)

	Current: 880 (10.3) Unknown: 86 (1.0) Placebo, n (%): Never: 3999 (49.3) Past: 3157 (39) Current: 838 (10.3) Unknown: 108 (1.3) **History of ovarian cancer:** Estrogen + Progestin: No: 99.1 % Placebo: No: 99.2 % **Female relatives with ovarian cancer** Estrogen + Progestin, n (%): None: 7704 (90.6) ≥1: 186 (2.2) Unknown: 616 (7.2) Placebo, n (%): None: 7332 (90.5) ≥1: 172 (2.1) Unknown: 598 (7.4) **Age at menopause, years** Estrogen + Progestin, n (%): <40: 195 (2.3) 40-44: 677 (8.0) 45-49: 1943 (22.8) 50-54: 3629 (42.7) ≥55: 1235 (14.5) Unknown: 827 (9.7) Placebo, n (%): <40: 189 (2.3) 40-44: 632 (7.8) 45-49: 1996 (24.6) 50-54: 3506 (43.3)

	≥55: 1186 (14.6) Unknown: 593 (7.3) **Parity** Estrogen + Progestin, n (%) Never pregnant: 856 (10.1) 1: 690 (8.1) 2: 1908 (22.4) 3: 2020 (23.7) 4: 1416 (16.6) ≥5: 1575 (18.5) Unknown: 41 (0.5) Placebo, n (%) Never pregnant: 832 (10.3) 1: 661 (8.2) 2: 1708 (21.1) 3: 1952 (24.1) 4: 1412 (17.4) ≥5: 1500 (18.5) Unknown: 37 (0.5) **Oral contraceptive use** Estrogen + Progestin, n (%) Ever: 4811 (56.6) Never: 3695 (43.4) Placebo, n (%) Ever: 4655 (57.5) Never: 3447 (42.5)
Intervention(s)/control	Intervention: Estrogen + progesterone (progestin) 0.625mg/d of conjugated equine estrogen plus 2.5 mg/d or medroxyprogesterone acetate - administered in a single tablet Control: Placebo - administered in a single tablet
Duration of follow-up	Average follow-up time 5.6 years

Sample size	N=16608 Estrogen + Progestin, n=8506 Placebo, n=8102

Outcomes

Invasive ovarian cancer incidence

Outcome	**Estrogen and Progestin, N = 8506**	**Placebo, N = 8102**
Overall No of events	n = 20; % = 0.04	n = 12; % = 0.03
Serous papillary No of events	n = 11	n = 7
Adenocarcinoma No of events	n = 4	n = 3
Clear cell No of events	n = 2	n = 1
Endometrioid No of events	n = 2	n = 0
Embryonal No of events	n = 1	n = 0
Mixed mullerian No of events	n = 0	n = 1

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was random and concealed and no baseline differences to suggest a problem)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants were blinded to the intervention. Some staff aware of assignment, but there were no deviations from the interventions)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for all those randomised)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Outcome assessors were blinded to the intervention and measurement of the outcome was appropriate and used standard cancer classification codes)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported as specified)*
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable

Baandrup, 2022

Bibliographic Reference	Baandrup, Louise; Galanakis, Michael; Hannibal, Charlotte G; Dehlendorff, Christian; Hertzum-Larsen, Rasmus; Morch, Lina S; Kjaer, Susanne K; Long-term survival of nonlocalized epithelial ovarian cancer among women using menopausal hormone therapy prior to diagnosis: The extreme study.; International journal of cancer; 2022; vol. 151 (no. 9); 1512-1522

Study details

Country/ies where study was carried out	Denmark

Study type	Retrospective cohort study
Study dates	2008-2014
Inclusion criteria	• Women with epithelial ovarian or fallopian tube cancer • cases from the Danish Cancer Registry and/or Pathology Registry • only women with FIGO stage 3 or 4 disease, or at least regional disease • 50 years or older • year of diagnosis between 2000 to 2014 • women had at least 5 years of potential MHT registration in the Prescription Registry prior to diagnosis.
Exclusion criteria	Previous cancer (except nonmelanoma skin cancer)
Patient characteristics	Mean – SD – not reported for patient characteristics **Age at diagnosis, years – n (%)** HRT users: 50-59: 314 (19) 60-69: 634 (38.4) 70-79: 516 (31.2) ≥80: 189 (11.4) No hormone replacement therapy: 50-59: 498 (23.5) 60-69: 623 (29.3) 70-79: 637 (30.0) ≥80: 365 (17.2)
Intervention(s)/control	Intervention: • Estrogen hormone replacement therapy • Estrogen plus progesterone (progestin) hormone replacement therapy Control: • No hormone replacement therapy (non-users) Recent use defined as 2 or more prescriptions within <5 years from date of diagnosis. Past use define as 2 more more prescriptions, but no prescriptions during the recent period.

	Non-users were defined as less than 2 prescriptions before diagnosis of cancer.
Duration of follow-up	Median follow-up time 13.1 (Q1-Q3: 8.9 to 16.6) years for users. 12.1 (Q1-Q3: 8.0 to 15.8) years for nonusers.
Sample size	N=3776 HRT users: 1653 No hormone replacement therapy: 2123
Other information	Cohort population is covered in Morch 2009; however, this publication provides survival outcomes not reported in Morch 2009. Adjusted for age, year of diagnosis, comorbidity, histology and income. Comorbidities included chronic obstructive pulmonary disease, diabetes mellitus type 1 and 2, cerebrovascular disease, congestive heart disease, atrial fibrillation and ischaemic heart disease.

Estrogen only - Survival from ovarian cancer

Outcome	5-year survival - HRT users vs Non-users	10-year survival - HRT users vs Non-users
Duration of use: 2 or fewer years Relative risk/95% CI	0.98 (0.72 to 1.34)	1.07 (0.71 to 1.61)
Duration of use: 3-4 years Relative risk/95% CI	1.43 (1.01 to 2.02)	1.09 (0.59 to 2.02)
Duration of use: 5 or more years Relative risk/95% CI	1.22 (0.96 to 1.55)	1.24 (0.88 to 1.75)
Recent use: <5 years since last use Relative risk/95% CI	1.17 (0.96 to 1.42)	1.22 (0.92 to 1.61)
Previous use: 5 years or more since last use Relative risk/95% CI	1.15 (0.8 to 1.66)	0.9 (0.52 to 1.55)

Estrogen plus progestin - Survival from ovarian cancer

Outcome	5-year survival - HRT users vs non-users	10-year survival - HRT users vs non-users
Duration of use: 2 or fewer years Relative risk/95% CI	0.8 (0.57 to 1.12)	0.87 (0.55 to 1.37)
Duration of use: 3-4 years Relative risk/95% CI	1.14 (0.85 to 1.53)	1.38 (0.91 to 2.08)
Duration of use: 5 or more years Relative risk/95% CI	1.01 (0.84 to 1.21)	0.82 (0.61 to 1.1)
Recent use: <5 years since last use Relative risk/95% CI	0.96 (0.81 to 1.14)	0.88 (0.67 to 1.16)
Previous use: 5 years or more since last use Relative risk/95% CI	1.1 (0.85 to 1.43)	1.05 (0.73 to 1.49)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis has been adjusted for some but not all appropriate confounders – no adjustments for reproductive history confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Participants were selected into the study based on cancer diagnosis, however no risk of selection bias because participants were not selected based on the intervention)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on the intervention taken from prescription registries which were recorded before the outcome was known)*

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(There is limited information on adherence to the intervention to appropriately judge bias. Participants may have redeemed prescriptions, however, information on whether they took the medication is not available)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data is available to for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(It is possible for those recording reason of death to have been aware of the intervention, however it is unlikely that this would have influenced assessment of the outcome)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Beral, 2007

Bibliographic Reference	Beral, Valerie; Million Women Study, Collaborators; Bull, Diana; Green, Jane; Reeves, Gillian; Ovarian cancer and hormone replacement therapy in the Million Women Study.; Lancet (London, England); 2007; vol. 369 (no. 9574); 1703-10

Study details

Country/ies where study was carried out	United Kingdom
Study type	Prospective cohort study
Study dates	1996-2001 (last date of follow up 31st December 2005)
Inclusion criteria	Non specified

Exclusion criteria	• If they had any type of cancer except non-melanoma skin cancer registered before recruitment • bilateral oophorectomy • not postmenopausal at the time of last contact • if use of HRT or hysterectomy status was unknown.
Patient characteristics	**Age at entry, years - mean (SD):** Never users: 57.9 (4.9) Past users of HRT: 57 (4.3) Current users of HRT: 56.1 (4.1) **Parity - mean (SD):** Never users: 2.1 (1.3) Past users of HRT: 2.2 (1.2) Current users of HRT: 2.1 (1.2) **Past use of oral contraceptives - n (%):** Never users: 223316 (47.4) Past users of HRT: 115935 (62.6) Current users of HRT: 188452 (66.2) **Hysterectomy - n (%):** Never users: 61470 (13) Past users of HRT: 38004 (20.4) Current users of HRT: 81978 (28.6)
Intervention(s)/control	Intervention: • Oestrogen-only HRT • Oestrogen + progestogen HRT (sequential or combined regimen) Control: • No HRT
Duration of follow-up	Cancer incidence: 8 years Death: 9 years
Sample size	N= 948576

	Never users, n=474682 Past users, n=186751 Current users, n=287143
Other information	Cohort has been included in CGESOC, therefore only additional subgroup analyses have been extracted. Of current users who developed ovarian cancer, the estimated duration of HRT at the time of diagnosis was 7.7 years overall: 9.2 for oestrogen-only, and 6.9 for oestrogen + progestogen.

Outcomes

Oestrogen-only

Outcome	**HRT users vs Never users**
Ovarian cancer incidence - By constituent - equine oestrogen Relative risk/95% CI	1.38 (1.1 to 1.73)
Ovarian cancer incidence - By constituent - oestradiol Relative risk/95% CI	1.33 (1.07 to 1.64)
Ovarian cancer incidence - By mode of administration - oral Relative risk/95% CI	1.37 (1.12 to 1.68)
Ovarian cancer incidence - By mode of administration - transdermal Relative risk/95% CI	1.28 (0.99 to 1.64)
Ovarian cancer incidence - By duration <5 years Relative risk/95% CI	0.89 (0.64 to 1.25)
Ovarian cancer incidence - By duration 5 or more years Relative risk/95% CI	1.53 (1.27 to 1.84)
Mortality from ovarian cancer – current user (approximately 6.9 years follow-up) Relative risk/95% CI	1.48 (1.2 to 1.81)

Oestrogen + progestogen

Outcome	HRT users vs Never users
Ovarian cancer incidence - By constituent - levo (norgestrel) Relative risk/95% CI	1.13 (0.95 to 1.33)
Ovarian cancer incidence - By constituent - Noresthisterone Relative risk/95% CI	1.22 (1.04 to 1.44)
Ovarian cancer incidence - By constituent - Medroxyprogesterone acetate Relative risk/95% CI	0.99 (0.77 to 1.26)
Ovarian cancer incidence - By regimen - continuous Relative risk/95% CI	1.13 (0.95 to 1.33)
Ovarian cancer incidence - By regimen - sequential Relative risk/95% CI	1.14 (0.98 to 1.32)
Ovarian cancer incidence - By duration - <5 years Relative risk/95% CI	1.09 (0.91 to 1.3)
Ovarian cancer incidence - By duration 5 years or more Relative risk/95% CI	1.17 (1.02 to 1.34)
Mortality from ovarian cancer – current user (approximately 6.9 years follow-up) Relative risk/95% CI	1.15 (1 to 1.33)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(Analysis adjusted for important confounders)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on participant characteristics observed after the intervention. Start of follow-up and start of intervention coincide as information on duration of HRT use was obtained.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data is available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(It is possible for outcome assessors to have been aware of the intervention received but this would not affect the outcome measurement)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Bethea, 2017

Bibliographic Reference Bethea, Traci N; Palmer, Julie R; Adams-Campbell, Lucile L; Rosenberg, Lynn; A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women.; Cancer causes & control: CCC; 2017; vol. 28 (no. 5); 385-391

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1995-2013
Inclusion criteria	• Black ethnicity
Exclusion criteria	• Prevalent ovarian cancer diagnosis • prevalent diagnosis of any cancer other than non-melanoma skin cancer • diagnosis of ovarian granulosa cell cancer • bilateral oophorectomy • missing data on menopausal status.
Patient characteristics	**Age, years - mean (SD)*:** 37.8 (10.3) **Age at diagnosis of cancer cases – n (%):** <40: 12 (10.45) 40-49: 29 (25.2) 50-59: 41 (35.7) ≥60: 33 (28.7) *Mean age of total population does not meet the protocol criteria, however analysis of those taking hormone replacement therapy only in women aged 45 and over.
Intervention(s)/control	Intervention: • Ever estrogen-only hormonal menopausal users • Ever estrogen + progestogen (progestin) hormonal menopausal users Control: • No hormone replacement therapy: never-users
Duration of follow-up	18 years
Sample size	N=86 cancer cases in participants ages 45 or older Never uses or users <1 year duration: n= 61 cases

	Ever used estrogen + progestin: n=14 cases Ever used estrogen alone: n=17 cases Numbers do not add up to 86 as estrogen + progestin users and estrogen only users are not mutually exclusive. Participants could have used either.
Other information	Study indirect due to comparison of never users including some women who have used hormone replacement therapy for less than 1 year. Also, interventions overlap, as they are not mutually exclusive. Analysis adjusted for age, questionnaire cycle, parity, lactation, age at first birth, age at last birth, hysterectomy, tubal ligation, oral contraceptive use, educational attainment, and body mass index.

Outcomes

Ovarian cancer incidence

Outcome	**HRT user vs Never user**
Estrogen only Hazard ratio/95% CI	1.66 (0.9 to 3.07)
Estrogen+progestin Hazard ratio/95% CI	1.37 (0.73 to 2.55)

Critical appraisal

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for any lifestyle factors)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Taking estrogen only and estrogen + progestin were not mutually exclusive in this study. Participants may have taken either. There is not enough information on why participants would have changed intervention, but it could be due to factors that might influence the outcome such as risk factors.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Partially applicable

Bryk, 2021

Bibliographic Reference	Bryk, Saara; Katuwal, Sushmita; Haltia, Ulla-Maija; Tapper, Johanna; Tapanainen, Juha S; Pukkala, Eero; Parity, menopausal hormone therapy, and risk of ovarian granulosa cell tumor - A population-based case-control study.; Gynecologic oncology; 2021; vol. 163 (no. 3); 593-597

Study details

Country/ies where study was carried out	Finland
Study type	Case-control
Study dates	1st January 1994 to 31st December 2015

Inclusion criteria	Cases: • Women newly diagnosis with adult-type ovarian granulosa cell tumours (AGCTs) • diagnosed between 1st January 1994 to 31st December 2015 • from the Finnish Cancer Registry. Matched controls: • For each case of AGCT - 5 controls were selected from the National Population Registry (NPR) • at risk of AGCT (not specified here but assumed the study means did not have a bilateral oophorectomy) • follow up data available - such as had not emigrated; alive at the time of cancer onset of the cases; matched for age.
Exclusion criteria	• Non-systemic hormone therapy (vaginal estradiol)
Patient characteristics	Study includes women from <20 years to 80+ years of age, however for this review only the analysis performed on women aged 55+ has been extracted. **Age distribution at diagnosis, years - n:** Cases: 50-59: 135 60-69: 111 70-79: 50 80+: 42 Controls: 50-59: 677 60-69: 552 70-79: 259 80+: 205 **Hormone therapy use, 50+ years - number:** Cases: Estradiol-only: 17 Continuous estradiol-progestin: 22 Sequential estradiol-progestin: 30 Control: Estradiol-only: 124

	Continuous estradiol-progestin: 146 Sequential estradiol-progestin: 181
Intervention(s)/control	Intervention: • Oestrogen-only (estradiol) • Oestrogen + progestogen (estradiol + progestin) Control: • No hormone replacement therapy (never user) Information on postmenopausal hormone therapy (HT) was obtained from the nationwide Prescription Register of the Social Insurance Institution of Finland. Register includes data on systemic HT purchases in Finland since 1994, and access was available up until 31st December 2013. Purchase of HT after age 50 was considered postmenopausal HT.
Duration of follow-up	Not reported
Sample size	N=1634 Cases: n=272 Controls: n=1362
Other information	Conditional logistic regression model for matched cases and controls was used. Reproductive variables included parity, number of children, age at first birth, age at last birth.

Outcomes

Estradiol only

Outcome – ovarian cancer incidence	**HRT users vs non-HRT users**
Current use - within 12 months Odds ratio/95% CI	0.4 (0.15 to 1.02)
>12 months to 5 years or less use Odds ratio/95% CI	0.31 (0.11 to 0.88)

Estradiol + continuous progestin

Outcome – ovarian cancer incidence	HRT users vs non-HRT users
Current use - within 12 months Odds ratio/95% CI	0.73 (0.36 to 1.51)
>12 months to 5 years or less use Odds ratio/95% CI	0.3 (0.06 to 1.43)

Estradiol + sequential progestin

Outcome – ovarian cancer incidence	HRT users vs non-HRT users
Current use - within 12 months Odds ratio/95% CI	0.54 (0.26 to 1.12)
>12 months to 5 years or less use Odds ratio/95% CI	0.8 (0.3 to 2.13)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age

Section	Question	Answer
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No – lifestyle factors or reproductive factors not adjusted for
(B) What are the results?	7. What are the results of this study?	No excess risk of hormone therapy for ovarian cancer
(B) What are the results?	8. How precise are the results?	Not precise
(B) What are the results?	9. Do you believe the results?	Not enough confounders controlled for to confidently believe results
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell

Collaborative Group On Epidemiological Studies Of Ovarian, 2015

Bibliographic Reference Collaborative Group On Epidemiological Studies Of Ovarian, Cancer; Beral, V; Gaitskell, K; Hermon, C; Moser, K; Reeves, G; Peto, R; Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies.; Lancet (London, England); 2015; vol. 385 (no. 9980); 1835-42

Study details

Country/ies where study was carried out	Countries across Europe and North America
Study type	Nest case-control (meta-analysis of prospective cohort studies using individual participant data)
Inclusion criteria	Included studies provided information on: • HRT use • parity • oophorectomy

	• hysterectomy • if completed after 2006, at least 200 cases of ovarian cancer • cases were postmenopausal women with malignant or borderline-malignant, epithelial or non-epithelial ovarian cancer • controls were postmenopausal women without ovarian cancer or previous oophorectomy. • Postmenopausal defined as having reached natural menopause, or age 55 years.
Exclusion criteria	• Women younger than 55 years with a hysterectomy.
Patient characteristics	**Average across prospective studies (17 prospective studies):** Age at diagnosis of cases, years - mean: 65.1, measure of dispersion not reported Median year of diagnosis of cases: 2000
Intervention(s)/control	Intervention: • Oestrogen-only hormone replacement therapy • Oestrogen plus progestogen hormone replacement therapy Control: • No hormone replacement therapy
Duration of follow-up	Median duration of HRT use: 6 years
Sample size	N=52827 Cases: n=12110 Controls: n=40717
Other information	Retrospective studies were included in this meta-analysis but excluded from this review, and therefore information was not extracted. They have not been included in this review to avoid bias associated with recall of HRT use, as information on HRT use was collected after diagnosis of cancer.

Outcomes

Ovarian cancer incidence - Oestrogen-only

Outcome	HRT user vs No hormone replacement
Overall current of recent users Relative risk/95% CI	1.37 (1.26 to 1.5)
Serous tumours Relative risk/95% CI	1.58 (1.39 to 1.8)
Endometrioid tumours Relative risk/95% CI	1.34 (1.05 to 1.72)
Mucinous tumours Relative risk/95% CI	1 (0.75 to 1.33)
Clear-cell tumours Relative risk/95% CI	0.81 (0.53 to 1.25)

Ovarian cancer incidence - Oestrogen-progestogen

Outcome	HRT user vs No hormone replacement
Overall Relative risk/95% CI	1.37 (1.26 to 1.48)
Serous tumours Relative risk/95% CI	1.55 (1.38 to 1.74)
Endometrioid tumours Relative risk/95% CI	1.58 (1.26 to 1.98)
Mucinous tumours Relative risk/95% CI	0.95 (0.73 to 1.24)
Clear-cell tumours Relative risk/95% CI	0.7 (0.47 to 1.04)

Critical appraisal - CASP Critical appraisal checklist for IPD Meta-analysis

Section	Question	Answer
Is the IPD meta-analysis part of a systematic review?	Does it have a clear research question qualified by explicit eligibility criteria?	Yes (*eligibility criteria clearly reported*)
	Does it have a systematic and comprehensive search strategy for identifying trials?	Yes (*strategy reported in supplementary information*)
	Does it have a consistent approach to data collection?	Yes (*systematic methods for data collection used*)
	Does it assess the “quality” or risk of bias of included trials?	Yes (*no details reported*)
	Are all the methods prespecified in a protocol?	Yes (*draft protocol circulated to collaborators, no further details reported*)
	Has the protocol been registered or otherwise made available?	Not reported
Were all eligible trials identified?	Were fully published trials identified?	Yes
	Were trials published in the grey literature identified?	No
	Were unpublished trials identified?	Yes
Were IPD obtained for most trials?	Were IPD obtained for a large proportion of the eligible trials?	Yes (*90% of eligible trials included*)
	Was an assessment of the potential impact of missing trials undertaken?	Not reported

Section	Question	Answer
	Were the reasons for not obtaining IPD provided?	Yes (*6 studies excluded because 3 studies didn't publish on the relationship between ovarian cancer risk relating to HRT use, and 3 studies couldn't contribute to data to the analysis*)
Was the integrity of the IPD checked?	Were the data checked for missing, invalid out-of-range, or inconsistent items?	Yes (*checked via correspondence with investigators*)
	Were there any discrepancies with the trial report (if available)?	Not reported
	Were any issues queried and, if possible, resolved?	Not reported
Were the analyses prespecified in detail?	Were the detailed analysis methods included in a protocol or analysis plan?	Not reported
	Were the outcomes and methods for analysing the effects of interventions, quantifying and accounting for heterogeneity, and assessing risk of bias included?	Yes (*details of methods provided in supplementary information*)
Was the risk of bias of included trials assessed?	Were the randomisation, allocation concealment, and blinding assessed?	Not applicable
	Were the IPD checked to ensure all (or most) randomised participants were included?	Not applicable
	Were all relevant outcomes included?	Yes
	Was the quality of time-to-event-outcome data checked?	Not applicable
Were the methods of analysis appropriate?	Were the methods of assessing the overall effects of interventions appropriate?	Yes

Section	Question	Answer
	Did researchers stratify or account for clustering of participants within trials using either a one- or two-stage approach to meta-analysis?	Not applicable
	Was the choice of one- or two-stage analysis specified in advance and/or results for both approaches provided?	Not applicable
	Were the methods of assessing whether effects of interventions varied by trial characteristics appropriate?	Yes (*relevant sensitivity analyses were conducted*)
	Did researchers compare treatment effects between subgroups of trials or use meta-regression to assess whether the overall treatment effect varied in relation to trial characteristics?	Not reported
	Were the methods of assessing whether effects of interventions vary by participant characteristics appropriate?	Yes (*relevant sensitivity analyses were conducted*)
	Did researchers estimate an interaction separately for each trial and combine these across trials in a two-stage fixed effect or random effects meta-analysis? Or	Not applicable
	Did researchers incorporate one or more a treatment by participant covariate interaction terms in a regression model, whilst also accounting for clustering of participant, separating out this individual participant-level interaction from any trial-level interactions?	Not applicable

Section	Question	Answer
	If there was no evidence of a differential effect by trial or participant characteristic, was emphasis placed on the overall result?	Not applicable
	Were exploratory analyses highlighted as such?	Not applicable
Does any report of the results adhere to the Preferred Reporting Items for a Systematic review and Meta-analysis of IPD (The PRISMA-IPD Statement)?		Yes (*all results are reported in full, with effect sizes and confidence intervals reported for each meta-analysis*)

Danforth, 2007

Bibliographic Reference	Danforth, K N; Tworoger, S S; Hecht, J L; Rosner, B A; Colditz, G A; Hankinson, S E; A prospective study of postmenopausal hormone use and ovarian cancer risk.; British journal of cancer; 2007; vol. 96 (no. 1); 151-6

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1976 to 2002
Inclusion criteria	• postmenopausal women
Exclusion criteria	• Radiation as the cause of menopause • bilateral oophorectomy • diagnosis of cancer other than non-melanoma skin cancer • missing exposure or covariate information.

Patient characteristics	**Age at diagnosis, years – mean** (SD not reported) Never user: 61 Past users (E/EP): 64 Current user E only: 62 Current user EP: 58 **Duration of hormone therapy use, years – mean** Never user: 0 Past users (E/EP): 3 Current user E only: 9 Current user EP: 6 **Duration of OC use - never (%)** Never user: 66 Past users (E/EP): 58 Current user E only: 54 Current user EP: 52 **Duration of OC use - <3 years (%)** Never user: 18 Past users (E/EP): 23 Current user E only: 23 Current user EP: 22 **Duration of OC use - 3+ years (%)** Never user: 17 Past users (E/EP): 20 Current user E: 23 Current user EP: 26 **Had a simple hysterectomy (%)** Never user: 5 Past users (E/EP): 19 Current user E: 47 Current EP: 2
Intervention(s)/control	Intervention: • Estrogen only (E)

	• Estrogen + progestogen (progestin) (EP) Control: • No hormone replacement therapy
Sample size	N= 42615 Never user: n=20853 Past users (E/EP): n=10053 E only current user: n=4315 E+P current user: n=7394

Outcomes

Estrogen-only

Outcome	**<5 years vs No hormone replacement therapy**
Ovarian cancer incidence (all epithelial tumours) Relative risk/95% CI	0.98 (0.68 to 1.4)

Estrogen + progestin

Outcome	**<5 years vs No hormone replacement therapy**
Ovarian cancer incidence (all epithelial tumours) Relative risk/95% CI	1.03 (0.64 to 1.66)

Critical appraisal

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for lifestyle factors)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Felix, 2015

Bibliographic Reference	Felix, Ashley S; Bunch, Kristen; Yang, Hannah P; Arem, Hannah; Trabert, Britton; Gierach, Gretchen L; Park, Yikyung; Lowery, William J; Brinton, Louise A; Menopausal hormone therapy and mortality among women diagnosed with ovarian cancer in the NIH-AARP Diet and Health Study.; Gynecologic oncology reports; 2015; vol. 13; 13-7

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study

Study dates	1996-
Inclusion criteria	• Age 50-71
Exclusion criteria	• Bilateral oophorectomy before baseline • missing information on oophorectomy status • premenopausal • unknown menopausal status • borderline or non-epithelial ovarian cancer • women without information on MHT type.
Patient characteristics	**Mean age, (SD) – not reported** **Age at baseline entry, years - n (%)** Never users: <55: 18 (10.5) 55-59: 23 (13.5) 60-64: 42 (24.6) 65-69: 78 (45.6) ≥70: 10 (5.8) Estrogen only: <55: 6 (6.4) 55-59: 21 (22.3) 60-64: 29 (30.9) 65-69: 34 (36.2) ≥70: 4 (4.3) Estrogen plus progestin: <55: 12 (13.6) 55-59: 27 (30.7) 60-64: 25 (28.4) 65-69: 22 (25.0) ≥70: 2 (2.3) **BMI (kg/m2) - number (%):**

	Never users: Normal (<25): 52 (30.4) Overweight (25 to 29.99): 55 (32.2) Obese (>=30): 54 (31.6) Estrogen only: Normal (<25): 52 (55.3) Overweight (25 to 29.99): 21 (22.3) Obese (>=30): 16 (17.0) Estrogen+progestin: Normal (<25): 48 (54.5) Overweight (25 to 29.99): 22 (25.0) Obese (>=30): 16 (18.2) **Smoking status - number (%):** Never users: Never: 92 (53.8) Former: 53 (31) Current: 25 (14.6) Estrogen only: Never: 44 (46.8) Former: 30 (31.9) Current: 14 (14.9) Estrogen+progestin: Never: 47 (53.4) Former: 35 (39.8) Current: 5 (5.7) **Oral contraceptive use - number (%):** Never users: Never: 131 (76.6) Ever: 38 (22.2) Estrogen only: Never: 66 (70.2) Ever: 27 (28.7)

	Estrogen+progestin: Never: 50 (56.8) Ever: 36 (40.9)
Intervention(s)/control	Intervention: Hormone replacement therapy 1. Estradiol only 2. Estrogen-progestin • if dates of estrogen use and progestin use overlapped or were within 90 days of each other • Sequential EP - progestin delivered <15 days per cycle • Continuous EP - progestin delivered for 15 or more days per cycle Control: Never users
Duration of follow-up	Median follow-up time from cancer diagnosis to death or end of follow up was 3.4 years
Sample size	N=395 women diagnosed with ovarian cancer n=171 never users of HRT n=94 estrogen only HRT (ET) n=88 estrogen + progestin HRT (EP) n=42 combinations of ET and EP
Other information	Adjusted for: • stage (localized, regional/distant, missing) • grade (well-differentiated, moderately differentiated, poorly differentiated) • histology (serous, non-serous) • surgery (yes, no) • chemotherapy (yes, no) • radiotherapy (yes, no) • race (white, non-white) • parity (nulliparous, 1–2 livebirths, ≥3 live births) • diabetes (no, yes)

	• age at menopause (<45, 45–49, 50–54, ≥55, surgical) • education (≤high school degree, post-high school/some college, college/postgraduate) • years from questionnaire to diagnosis (continuous). Cohort included in CGESOC but only outcomes not reported in CGESOC have been extracted.

Outcomes

Estrogen only - Ovarian cancer-specific mortality (14 years follow-up)

Outcome	HRT use vs Never users
Overall - former use Hazard ratio/95% CI	0.8 (0.4 to 1.59)
Overall - current Hazard ratio/95% CI	1.24 (0.77 to 2.01)

Estrogen-progestin use - Ovarian cancer-specific mortality (14 years follow-up)

Outcome	HRT use vs Never users
Overall - former Hazard ratio/95% CI	1.08 (0.57 to 2.04)
Overall - current Hazard ratio/95% CI	0.94 (0.64 to 1.38)
Overall - sequential Hazard ratio/95% CI	0.91 (0.5 to 1.63)
Overall - continuous Hazard ratio/95% CI	1 (0.68 to 1.48)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for lifestyle factors)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Folsom, 2004

Bibliographic Reference	Folsom, A.R.; Anderson, J.P.; Ross, J.A.; Estrogen replacement therapy and ovarian cancer; Epidemiology; 2004; vol. 15 (no. 1); 100-104

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1986 to 2000
Inclusion criteria	• Aged 55 to 69. • Valid Iowa driver's license.
Exclusion criteria	• History of cancer other than skin cancer at baseline • bilateral oophorectomy • women who developed non-epithelial ovarian neoplasms.
Patient characteristics	BMI, highest quartile % Never: 27 Former: 23 Current: 15 Current smoker % Never: 14 Former: 17 Current: 15 Family history of ovarian cancer, first or second degree relative % Never: 2.7 Former: 2.6 Current: 2.0 Hysterectomy (%) Never: 14 Former: 29 Current: 47

Intervention(s)/control	Intervention: • Estrogen only Control: • Never users There is no data on whether women were using progestins, but study suggests the findings are mostly aimed at those who took unopposed estrogen, since data from the mid-1980s suggest no more than 20% current estrogen users took combination hormonal replacement therapy.
Duration of follow-up	Not reported
Sources of funding	Not reported
Sample size	N=31234 Never: n=21401 Former: n=7410 Current: n=2423
Other information	Participants selected from the CPS-II Nutrition Cohort which has been included in CGESOC. This publication provides further subgroups.

Outcomes

Estrogen only - ovarian cancer incidence

Outcome	**HRT users vs Never users**
Current user, 5 years or less Relative risk/95% CI	1.08 (0.5 to 2.33)
Current user, more than 5 years Relative risk/95% CI	2.53 (1.44 to 4.45)
Former users, 5 years or less Relative risk/95% CI	1.14 (0.81 to 1.61)
Former users, more than 5 years	0.69 (0.22 to 2.18)

Outcome	HRT users vs Never users
Relative risk/95% CI	

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for age at menopause)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation

Section	Question	Answer
Overall bias	Directness	Directly applicable

Hildebrand, 2010

Bibliographic Reference	Hildebrand, Janet S; Gapstur, Susan M; Feigelson, Heather Spencer; Teras, Lauren R; Thun, Michael J; Patel, Alpa V; Postmenopausal hormone use and incident ovarian cancer: Associations differ by regimen.; International journal of cancer; 2010; vol. 127 (no. 12); 2928-35

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1992 to June 30th 2007
Inclusion criteria	• Postmenopausal women.
Exclusion criteria	• Premenopausal or unknown menopausal status in 1999 • lost to follow-up after 1992 • prevalent cancer other than nonmelanoma skin cancer • unknown type or duration of hormone use • history of both estrogen only and estrogen + progestin use • use of only oral progestin or vaginal cream • current use of estrogen only with an intact uterus or current use of estrogen and progestin after hysterectomy • bilateral oophorectomy • ovarian cancer that could not be verified • verified nonepithelial ovarian cancer.
Patient characteristics	**Average age at study entry, years:** Never: 62.6

	Current estrogen only: 61.4 Former estrogen only: 66.1 Current estrogen + progestin: 57.5 Former estrogen + progestin: 59.2 **Race - white, %:** Never: 97.1 Current estrogen only: 97.2 Former estrogen only: 96.6 Current estrogen + progestin: 98.6 Former estrogen + progestin: 98.4 **Race - non-white, %:** Never: 2.9 Current estrogen only: 2.8 Former estrogen only: 3.4 Current estrogen + progestin: 1.4 Former estrogen + progestin: 1.6 **Oral contraceptive use - Never:** Never: 66.9 Current estrogen only: 53.1 Former estrogen only: 58.6 Current estrogen + progestin: 53.2 Former estrogen + progestin: 53.3 **Oral contraceptive use - <5 years:** Never: 16.4 Current estrogen only: 25.5 Former estrogen only: 23.9 Current estrogen + progestin: 22.2 Former estrogen + progestin: 24.1 **Oral contraceptive use - ≥5 years:** Never: 14.4 Current estrogen only: 17.9 Former estrogen only: 14.2 Current estrogen + progestin: 22.6 Former estrogen + progestin: 20.7

	Simple hysterectomy %: Never: 13.1 Current estrogen only: 96.5 Former estrogen only: 33.1 Current estrogen + progestin: 0 Former estrogen + progestin: 3.7
Intervention(s)/control	Intervention: • Estrogen only • Estrogen + progestin Control: • Never users
Sample size	N=54436 Estrogen only, n=13446 Estrogen + progestin, n=9275 Never users, n=31715
Other information	Participants selected from the CPS-II Nutrition Cohort which has been included in CGESOC. This publication provides further subgroups.

Outcomes

Estrogen only

Outcome – ovarian cancer incidence	**HRT user vs non-HRT user**
Current user, 1 to <10 years Relative risk/95% CI	1.7 (1.02 to 2.83)
Current user, 10 to <20 years Relative risk/95% CI	1.95 (1.2 to 3.17)
Current users, 20 years + Relative risk/95% CI	2.89 (1.71 to 4.87)

Outcome – ovarian cancer incidence	HRT user vs non-HRT user
Former users - 1 to <5 years Relative risk/95% CI	0.94 (0.61 to 1.44)
Former users - 5 years + Relative risk/95% CI	1.33 (0.79 to 2.24)

Estrogen + Progestin

Outcome – ovarian cancer incidence	HRT user vs non-HRT user
Current users - 1 to < 5 years Relative risk/95% CI	0.96 (0.51 to 1.81)
Current users - 5+ years Relative risk/95% CI	1.3 (0.81 to 2.08)
Former users - per 5 year increment Relative risk/95% CI	1.08 (0.68 to 1.71)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for lifestyle factors or age at menopause)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Koskela-Niska, 2013

Bibliographic Reference	Koskela-Niska, Virpi; Pukkala, Eero; Lyytinen, Heli; Ylikorkala, Olavi; Dyba, Tadeusz; Effect of various forms of postmenopausal hormone therapy on the risk of ovarian cancer--a population-based case control study from Finland.; International journal of cancer; 2013; vol. 133 (no. 7); 1680-8

Study details

Country/ies where study was carried out	Finland
Study type	Case-control

Study dates	1995 to 2007
Inclusion criteria	Cases: Women aged 50 or older with ovarian cancer during 1995 to 2007, registered in the national Cancer Registry. Matched controls: 3 controls without ovarian cancer matched to each case, alive on the date of cancer diagnosis and matched for age, place or registered and in the Finnish National Population Register.
Exclusion criteria	• Oophorectomy before the index date (diagnosis of cancer date)
Patient characteristics	**Age – number (%):** 50-54: Cases: 435 (11) Controls: 1267 (11) 55-59: Cases: 653 (16) Controls: 1842 (16) 60-64: Cases: 686 (17) Controls: 1919 (17) 65-69: Cases: 684 (17) Controls: 1948 (17) 70-74: Cases: 738 (19) Controls: 2138 (19) 75-79: Cases: 638 (16) Controls: 1845 (16) 80+: Cases: 124 (3) Controls: 366 (3) **Hysterectomy – number (%):** Cases: 245 (6) Controls: 943 (8)

Intervention(s)/control	Intervention: Estrogen only Estrogen + progestin Control: No postmenopausal hormone therapy
Duration of follow-up	Not reported
Sample size	N=15283 Cases: n=3958 Controls: 11325

Outcomes

Ovarian cancer incidence

Outcome	E only vs non-HRT users	EP continuous vs non-HRT users	EP sequential vs non-HRT users
Serous			
5+ years duration of use – unknown recency Relative risk/95% CI	1.45 (1.2 to 1.75)	1.18 (0.67 to 2.1)	1.32 (1.01 to 1.71)
Endometrioid			
5+ years duration of use – unknown recency Relative risk/95% CI	1.25 (0.88 to 1.76)	1.93 (0.59 to 6.28)	1.88 (1.24 to 2.86)
Mucinous			
5+ years duration of use – unknown recency Relative risk/95% CI	0.35 (0.19 to 0.67)	0.82 (0.14 to 4.71)	0.57 (0.26 to 1.25)
Clear cell			
5+ years duration of use – unknown recency Relative risk/95% CI	0.72 (0.23 to 2.29)	0.21 (0.02 to 2.48)	1.71 (0.67 to 4.4)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, place of residence, parity, ages at birth of first and last child and hysterectomy.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No – no adjustments for age at menopause or lifestyle factors.
(B) What are the results?	7. What are the results of this study?	Hormone replacement therapy does not have an effect on ovarian cancer.
(B) What are the results?	8. How precise are the results?	Some imprecision
(B) What are the results?	9. Do you believe the results?	Not all confounders have been appropriately adjusted for.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell

Lacey, 2002

Bibliographic Reference	Lacey, James V Jr; Mink, Pamela J; Lubin, Jay H; Sherman, Mark E; Troisi, Rebecca; Hartge, Patricia; Schatzkin, Arthur; Schairer, Catherine; Menopausal hormone replacement therapy and risk of ovarian cancer.; JAMA; 2002; vol. 288 (no. 3); 334-41

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1979 to cancer diagnosis date
Inclusion criteria	• Women who were menopausal before the start of follow-up • women who became menopausal during follow-up. • Menopause defined as no menstrual period for at least 3 months, or as a result of hysterectomy with at least 1 ovary retained.
Exclusion criteria	• Bilateral oophorectomy • women diagnosed as having ovarian cancer or breast cancer before follow-up • unknown menopausal status • non epithelial ovarian cancer
Participant characteristics	**Age, n:** Estrogen only: <55: 24 55-59: 25 60-64: 27 65-69: 31 70-74: 34 75-79: 35 80+: 32 Estrogen + progestogen: <55: 2

	55-59: 7 60-64: 11 65-69: 9 70-74: 7 75-79: 5 80+: 2 None: <55: 65 55-59: 56 60-64: 48 65-69: 43 70-74: 41 75-79: 40 80+: 46 Mean age at start of follow-up: 56.6
Intervention(s)/control	Intervention • Estrogen only hormone replacement therapy • Estrogen + progestin hormone replacement therapy Control • Never user of hormone replacement therapy
Duration of follow-up	Mean follow-up of 13.4 years (range 1 month to 19.8 years)
Sources of funding	Not industry funded
Sample size	N=44241
Other information	Cohort included in CGESOC. Only additional subgroups extracted from this publication. Adjusted for attained age, menopause type (natural, surgical, or unknown) duration of oral contraceptive use (none, 2 years or less, more than 2 years)

Outcomes

Ovarian cancer incidence - Estrogen only

Outcome	E only HRT use vs Never HRT user
<4 years duration of use Relative risk/95% CI	1.3 (0.96 to 1.9)
4 to 9 years duration of use Relative risk/95% CI	1.6 (1 to 2.6)
10 to 19 years duration of use Relative risk/95% CI	1.8 (1.1 to 3)
20 or more years duration of use Relative risk/95% CI	3.2 (1.7 to 5.7)

Ovarian cancer incidence - Estrogen + Progestin therapy

Outcome	EP HRT use vs Never HRT user
Less than 2 years use Relative risk/95% CI	1.6 (0.78 to 3.3)
2 or more years use Relative risk/95% CI	0.8 (0.35 to 1.8)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for age at menopause or reproductive history)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Morch, 2009

Bibliographic Reference	Morch, Lina Steinrud; Lokkegaard, Ellen; Andreasen, Anne Helms; Kruger-Kjaer, Susanne; Lidegaard, Ojvind; Hormone therapy and ovarian cancer.; JAMA; 2009; vol. 302 (no. 3); 298-305

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study

Study dates	1 January 1995 to 31 December 2005
Inclusion criteria	• Women at least 50 years
Exclusion criteria	• Women with a previous ovarian cancer diagnosis • if after 1st January 1995, or prior to 50th birthday women had a bilateral oophorectomy, or bilateral salpingo-oophorectomy • aged 80 years or older.
Patient characteristics	**Age, mean (SD)** Never users: 62.5 (8.8) Previous users (E/EP): 62.4 (7.5) Current users (E/EP): 61.5 (7.5) E only: 63.5 (7.9) EP: 60.6 (6.8)
Intervention(s)/control	Intervention: • Estrogen only hormone replacement therapy • Estrogen + progestin hormone replacement therapy Control: • Never users of hormone replacement therapy
Sample size	N= 857877 Never HRT users: n=575883 Previous users (E/EP): n=198184 Current users (E/EP): n=83810 E only: n=28590 EP: n=60310
Other information	Cohort included in CGESOC. Only additional subgroups extracted from this publication.

Outcomes

Estrogen only

Outcome	Estrogen only vs Never user
Ovarian cancer incidence - by route of administration - oral Relative risk/95% CI	1.34 (1.12 to 1.6)
Ovarian cancer incidence - by route of administration - transdermal Relative risk/95% CI	1.13 (0.74 to 1.71)

Estrogen + Progestin

Outcome	Estrogen + Progestin vs Never user
Oral estrogen + progestin Relative risk/95% CI	1.48 (1.32 to 1.65)
Transdermal estrogen + progestin Relative risk/95% CI	1.13 (0.74 to 1.71)
Noresthiserone acetate Relative risk/95% CI	1.55 (1.36 to 1.76)
Medroxyprogesterone Relative risk/95% CI	1.37 (0.99 to 1.89)
Levonorgestrel Relative risk/95% CI	1.3 (0.92 to 1.85)
Cyproterone acetate Relative risk/95% CI	0.87 (0.39 to 1.93)
Long-cycle estrogen + progestin Relative risk/95% CI	2.05 (1.44 to 2.93)
Cyclical estrogen + progestin – current user Relative risk/95% CI	1.5 (1.31 to 1.72)

Outcome	Estrogen + Progestin vs Never user
Continuous estrogen + progestin – current user Relative risk/95% CI	1.4 (1.16 to 1.69)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for age at menopause or lifestyle factors)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious

Section	Question	Answer
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Rodriguez, 2001

Bibliographic Reference	Rodriguez, C; Patel, A V; Calle, E E; Jacob, E J; Thun, M J; Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women.; JAMA; 2001; vol. 285 (no. 11); 1460-5

Study details

Country/ies where study was carried out	United States and Puerto Rico
Study type	Prospective cohort study
Study dates	1982 to 1996
Inclusion criteria	Female participants from the Cancer Prevention Study II mortality cohort.
Exclusion criteria	• History of cancer, other than non-melanoma skin cancer, at baseline • premenopausal • unknown menopausal status or unknown age at menopause • incomplete data on estrogen use • exclusive use of estrogen cream or injections • estrogen replacement therapy use at age younger than 35 • hysterectomy • artificial menopause • any report of previous ovarian surgery (as could not distinguish bilateral oophorectomy from partial oophorectomy)

Patient characteristics	**Age - years %** <60 Never user: 56.2 Former user: 42.0 Baseline user: 72.4 60-69 Never user: 28.6 Former user: 47.8 Baseline user: 24.2 ≥70 Never user: 15.2 Former user: 10.3 Baseline user: 3.4 **Race/ethnicity** White Never user: 93.5 Former user: 96.1 Baseline user: 96.5 Black Never user: 4.3 Former user: 2.4 Baseline user: 1.9 Other Never user: 1.7 Former user: 1.2 Baseline user: 1.1 **Oral contraceptive use** Never Never user: 80.4 Former user: 75.4 Baseline user: 71.3 <5 Never user: 9.0

	Former user: 12.9 Baseline user: 12.1 5-9 Never user: 4.2 Former user: 4.9 Baseline user: 6.1 ≥10 Never user: 4.2 Former user: 3.2 Baseline user: 6.8 Former users were defined as women whose total years of use added to their age at first use was less than their age at enrolment. Baseline users were defined as women who said they were still using estrogen at baseline, or whose total years of use added to their age at first use was within a year of enrolment.
Intervention(s)/control	Intervention: • Estrogen replacement therapy The majority of baseline users were likely to be taking unopposed estrogens as combined therapies were not available until the 1970s. The study does not specify whether some of the women took combined therapies, therefore there is some potential for indirectness. Control: • Never users of hormone replacement therapy
Duration of follow-up	14 years
Sources of funding	Not reported
Sample size	N=211581 Never users: n=165321 Former users: n=35236 Baseline users: n=11024
Other information	CPS-mortality cohort included in CGESOC. Only additional subgroups have been extracted. Adjustments made for

	• age at enrolment • race • duration of oral contraceptive use • number of live births • age at menopause • body mass index • age at menarche • tubal ligation. Other potential confounders were identified, but made no difference to the analysis and were not included in the final analysis: • Exercise • education • smoking • daily acetaminophen use • family history of breast/ovarian cancer. Baseline users not included in the analysis, as it is not clear whether they continued to use hormone therapy during follow-up periods, and time since last use not given.

Outcomes

Ovarian cancer mortality – former users (14 years follow-up)

Outcome	Former user vs Never users
Years of use <10, <15 years since last use Rate ratio/95% CI	1.17 (0.85 to 1.6)
Year of use <10, 15 or more years since last use Rate ratio/95% CI	1.07 (0.87 to 1.32)
Years of use 10 or more, <15 years since last use Rate ratio/95% CI	2.05 (1.29 to 3.25)

Outcome	Former user vs Never users
Years of use 10 or more, 15 or more years since last use Rate ratio/95% CI	1.31 (0.79 to 2.17)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for reproductive history)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious

Section	Question	Answer
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Schneider, 2009

Bibliographic Reference	Schneider, C; Jick, S S; Meier, C R; Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations.; Climacteric: the journal of the International Menopause Society; 2009; vol. 12 (no. 6); 514-24

Study details

Country/ies where study was carried out	United Kingdom
Study type	Nested case-control
Study dates	1987 to 2007
Inclusion criteria	None specified
Exclusion criteria	• History of any cancer • stroke • myocardial infarction • venous thromboembolism.
Patient characteristics	**Age at start of follow-up, mean (SD):** 51.3 (6.1)
Intervention(s)/control	Intervention: • Group 1: Women who received at least one prescription for any dosage form of estradiol/dydrogesterone below the age of 70, and never received a prescription for any other estrogen-containing HRT.

	• Group 2: Frequency matched women (matched on year of first HRT prescription and age), who received at least 1 prescription for oral conjugated equine estrogen (CEE) plus norgestrel, oral estradiol plus norethisterone acetate or oral CEE plus medroxyprogesterone acetate (MPA), and never received a prescription for any other HRT. Control: • Group 3: Frequency matched comparison group of women (matched on age) who have never received HRT prescriptions
Duration of follow-up	HRT users mean 6 years. Nonusers mean 5.7 years.
Sample size	N=602 ovarian cancer cases n=86 cases n=516 controls
Other information	Study does not specify if participants had bilateral oophorectomy or not. Adjusted for smoking status, BMI, use of oral contraceptives, progesterone preparations and vaginal estrogens.

Outcomes

Ovarian cancer incidence

Outcome	**HRT user vs non-HRT use**
Estradiol/dydrogesterone Odds ratio/95% CI	0.76 (0.16 to 3.63)
CEE/norgestrel Odds ratio/95% CI	1.28 (0.67 to 2.44)
Estradiol/norethisterone Odds ratio/95% CI	0.7 (0.36 to 1.38)
CEE/MPA Odds ratio/95% CI	1.03 (0.46 to 2.3)

Critical appraisal – CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Smoking status, BMI, use of oral contraceptives, progesterone preparations and vaginal estrogens.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No *(No adjustments for age at menopause)*
(B) What are the results?	7. What are the results of this study?	There is no difference in risk of ovarian cancer if taking hormonal replacement therapy
(B) What are the results?	8. How precise are the results?	Imprecise
(B) What are the results?	9. Do you believe the results?	Cannot confidently believe results due to not all confounders adjusted for and imprecise.
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell

Simin, 2020

Bibliographic Reference	Simin, Johanna; Tamimi, Rulla M; Callens, Steven; Engstrand, Lars; Brusselaers, Nele; Menopausal hormone therapy treatment options and ovarian cancer risk: A Swedish prospective population-based matched-cohort study.; International journal of cancer; 2020; vol. 147 (no. 1); 33-44

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective cohort study
Study dates	1 July 2005 to 31st December 2012
Inclusion criteria	• Women aged 40 or older at first prescription • received 1 or more prescriptions of systemic HRT between July 2005 and December 2012.
Exclusion criteria	• Aged younger than 40 on first prescription • women with a history of malignancy apart from nonskin cancer melanoma • received prior cancer treatment therapy • women who had undergone hysterectomy with concomitant oophorectomy or salpingo-oophorectomy • tubal ligation.
Patient characteristics	**Age, years %** <60 MHT users: 37.4 Non-users: 37.4 60-69 MHT users: 32.2 Non-users: 30.7 ≥70 MHT users: 30.4 Non-users: 31.8
Intervention(s)/control	Intervention: • Systemic HRT

	• Current users classified as having received at least 1 prescription in the last 6 months of follow-up. Control: • Non-users of HRT
Duration of follow-up	7 years
Sample size	N=1155496 MHT users: n=288950 Non-users: n=866546
Other information	Analysis adjusted for hysterectomy, ever parous, thrombotic events, year of birth, smoking-related disorders, alcohol-related disorders, obesity, diabetes mellitus and osteoporosis.

Outcomes

Epithelial ovarian cancer

Outcome	Estrogen only vs non-HRT user	Estrogen plus progestin vs non-HRT user
Current users by age - <60 years Odds ratio/95% CI	0.16 (0.1 to 0.25)	0.96 (0.72 to 1.27)
Current users by age - 60-69 Odds ratio/95% CI	0.16 (0.11 to 0.25)	1.68 (1.29 to 2.18)
Current users by age - 70+ Odds ratio/95% CI	0.42 (0.33 to 0.54)	1.77 (1.26 to 2.5)
Past user by age - <60 years Odds ratio/95% CI	0.1 (0.06 to 0.19)	0.49 (0.33 to 0.75)
Past user by age - 60-69 years Odds ratio/95% CI	0.15 (0.1 to 0.21)	1.4 (1.12 to 1.77)
Past user by age - 70+ Odds ratio/95% CI	0.36 (0.28 to 0.46)	0.8 (0.54 to 1.18)

Non-epithelial ovarian cancer

Outcome	Estrogen only vs non-HRT user	Estrogen plus progestin vs non-HRT user
Current user by age - <60 Odds ratio/95% CI	NA	2.47 (1.26 to 4.83)
Current user by age - 60-69 Odds ratio/95% CI	0.32 (0.08 to 1.33)	2.16 (0.78 to 6)
Current user by age - 70+ Odds ratio/95% CI	0.96 (0.42 to 2.22)	1.13 (0.16 to 8.19)
Past user by age - <60 estrogen only figure assumed 0.02 (but reported 0.22 but not possible) Odds ratio/95% CI	0.16 (0.02 to 1.14)	0.32 (0.04 to 2.32)
Past user by age - 60-69 Odds ratio/95% CI	0.11 (0.02 to 0.8)	0.7 (0.17 to 2.87)
Past user by age - 70+ Odds ratio/95% CI	0.13 (0.02 to 0.95)	NA
Current–user - by oral route of administration Odds ratio/95% CI	0.34 (0.28 to 0.41)	1.48 (1.25 to 1.75)
Current–user - by cutaneous route of administration Odds ratio/95% CI	0.11 (0.06 to 0.2)	1.28 (0.81 to 2.02)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for reproductive history or age at menopause)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Trabert, 2012

Bibliographic Reference	Trabert, B; Wentzensen, N; Yang, H P; Sherman, M E; Hollenbeck, A; Danforth, K N; Park, Y; Brinton, L A; Ovarian cancer and menopausal hormone therapy in the NIH-AARP diet and health study.; British journal of cancer; 2012; vol. 107 (no. 7); 1181-7

Study details

Country/ies where study was carried out	United States
Study type	Prospective cohort study
Study dates	1996 to 2006
Inclusion criteria	Not reported
Exclusion criteria	• Previous diagnosis of cancer other than non-melanoma skin cancer • prior diagnosis of cancer other than non-melanoma skin cancer on death certificate • premenopausal at baseline • bilateral oophorectomy or unknown oophorectomy status • menstrual periods that stopped due to radiation or chemotherapy • non-epithelial ovarian cancer, borderline histology or non-primary ovarian cancer • missing values for hormone use variables.
Patient characteristics	**Age – number (%)** <55 Never user: 3789 (9) Oestrogen-only: 2069 (11.6) Oestrogen+ progestin only: 3154 (16) 55-59 Never user: 7832 (18.6) Oestrogen-only: 4036 (22.5) Oestrogen+ progestin only: 6423 (32.6) 60-64: Never user: 12374 (29.3)

	Oestrogen-only: 5186 (28.9) Oestrogen+ progestin only: 5870 (29.8) 65-69: Never user: 16330 (38.7) Oestrogen-only: 5898 (32.9) Oestrogen+ progestin only: 3921 (19.9) 70+: Never user: 1879 (4.4) Oestrogen-only: 733 (4.1) Oestrogen+ progestin only: 358 (1.8)
Intervention(s)/control	Intervention: Oestrogen-only Oestrogen + progestin only Control: Never users
Duration of follow-up	Mean for ovarian cancer cases: 4.7 years. Mean for non-cases: 8.9 years.
Sample size	N=92601 Oestrogen-only: n=17922 Oestrogen+ progestin: n=19726 Never user: 42204
Other information	Analysis adjusted for continuous age, race, parity, duration or oral contraceptive use, and body mass index.

Outcomes

Ovarian cancer incidence

Outcome	Continuous estrogen and progestin vs non-HRT user	Sequential estrogen and progestin vs non-HRT user	Any combined E+P vs non-HRT user	Estrogen only vs non-HRT user
Duration <10 years (unknown recency)	1.37 (0.94 to 1.99)	1.81 (1.18 to 2.78)	1.33 (0.98 to 1.79)	1.25 (0.71 to 2.2)

Outcome	Continuous estrogen and progestin vs non-HRT user	Sequential estrogen and progestin vs non-HRT user	Any combined E+P vs non-HRT user	Estrogen only vs non-HRT user
Relative risk/95% CI				
Duration 10 or more years (unknown recency) Relative risk/95% CI	1.72 (0.95 to 3.11)	1.13 (0.57 to 2.23)	1.68 (1.13 to 2.49)	2.15 (1.3 to 3.57)

Serious ovarian cancer

Outcome	Continuous estrogen and progestin vs non-HRT user	Sequential estrogen and progestin vs non-HRT user
Overall Relative risk/95% CI	2.02 (1.32 to 3.08)	1.87 (1.14 to 3.08)

Other ovarian cancer types

Outcome	Continuous estrogen and progestin vs non-HRT user	Sequential estrogen and progestin vs non-HRT user
Overall Relative risk/95% CI	0.87 (0.49 to 1.53)	1.31 (0.74 to 2.31)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for lifestyle factors)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

Tsilidis, 2011

Bibliographic Reference	Tsilidis, Konstantinos K; Allen, Naomi E; Key, Timothy J; Dossus, Laure; Kaaks, Rudolf; Bakken, Kjersti; Lund, Eiliv; Fournier, Agnes; Dahm, Christina C; Overvad, Kim; Hansen, Louise; Tjonneland, Anne; Rinaldi, Sabina; Romieu, Isabelle; Boutron-Ruault, Marie-Christine; Clavel-Chapelon, Francoise; Lukanova, Annekatrin; Boeing, Heiner; Schutze, Madlen; Benetou, Vassiliki; Palli, Domenico; Berrino, Franco; Galasso, Rocco; Tumino, Rosario; Sacerdote, Carlotta; Bueno-de-Mesquita, H Bas; van Duijnhoven, Franzel J B; Braem, Marieke G M; Onland-Moret, N Charlotte; Gram, Inger T; Rodriguez, Laudina; Duell, Eric J; Sanchez, Maria-Jose; Huerta, Jose Maria; Ardanaz, Eva; Amiano, Pilar; Khaw, Kay-Tee; Wareham, Nick; Riboli,

Elio; Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition.; Cancer causes & control : CCC; 2011; vol. 22 (no. 8); 1075-84

Study details

Country/ies where study was carried out	10 European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom
Study type	Prospective cohort study
Study dates	1992 to 2002
Inclusion criteria	Not reported
Exclusion criteria	• Prevalent cancer at recruitment • bilateral ovariectomy • incomplete follow up data • those who did not return baseline lifestyle questionnaire • lack of detailed data on HT use • pre or perimenopausal women at recruitment • women who had never menstruated • women with missing information on both ever and current HT use • non-epithelial ovarian tumour, or ovarian tumour with low malignant potential.
Patient characteristics	**Age, years - mean (SD):** Never users: 59 (6.2) Estrogen only: 56.9 (5.1) Estrogen + progestin: 54.5 (4.8) **BMI, kg/m2 - mean (SD):** Never users: 26 (4.6) Estrogen only: 24.9 (3.8) Estrogen + progestin: 24 (3.6) **Never cigarette smoking (%):** Never users: 60.2

	Estrogen only: 53.3 Estrogen + progestin: 54.4 **Never oral contraceptive use (%)** Never users: 62.4 Estrogen only: 43.1 Estrogen + progestin: 36.7
Intervention(s)/control	Intervention: • Estrogen only hormone replacement therapy • Estrogen or progestin hormone replacement therapy Control: • Never users of hormone replacement therapy
Duration of follow-up	Average 9 years
Sources of funding	Not reported
Sample size	N=126920 Never users: n=70386 Former users: n=17391 Current users: n=37630 Missing: n=1513
Other information	Cohort included in CGESOC. Only additional subgroups extracted from this publication. Analysis adjusted for body mass index, cigarette smoking status, unilateral ovariectomy, simple hysterectomy, age at menarche, number of full-term pregnancies, duration of oral contraceptive use.

Outcomes

Estrogen only

Outcome	**HRT user vs Never user**
Constituent - estradiol compounds Hazard ratio/95% CI	2.2 (1.36 to 3.56)

Outcome	HRT user vs Never user
Conjugated equine estrogens Hazard ratio/95% CI	2.08 (0.92 to 4.7)
Administration - cutaneous Hazard ratio/95% CI	1.11 (0.4 to 3.06)
Administration - oral Hazard ratio/95% CI	2.06 (1.15 to 3.67)

Estrogen + progestin

Outcome	HRT user vs Never user
Constituent - micronized progesterone Hazard ratio/95% CI	1.26 (0.63 to 2.53)
Constituent - progesterone derivatives Hazard ratio/95% CI	1.06 (0.67 to 1.67)
Regimen - sequential – current users Hazard ratio/95% CI	1.19 (0.77 to 1.86)
Regimen - continuous – current users Hazard ratio/95% CI	1.47 (0.81 to 2.65)

Critical appraisal

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Analysis adjusted for some but not all appropriate confounders – no adjustments for age at menopause)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the start of the intervention. Start of follow-up and intervention coincide.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Information on intervention was collected via questionnaires before the outcome was known)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Use of HRT based on participant answers. These may be subject to some bias but not enough information on the accuracy.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for most eligible participants)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Outcome assessors could have known intervention status but this would not affect the measurement of the outcome.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variation
Overall bias	Directness	Directly applicable

AGCTs: adult-type ovarian granulosa cell tumours; BMI: body mass index; CASP: Critical Appraisal Skills Programme; CEE: conjugated equine estrogen; CI: confidence interval; CGESOC: Collaborative Group on Epidemiological Studies of Ovarian Cancer; CPS-(II): Cancer Prevention Study (II); E/P: estrogen/progestogen; FIGO: International Federation of Gynaecology and Obstetrics; HRT: hormone replacement therapy; HT: hormone therapy; IPD: individual patient data; MHT: menopausal hormone therapy; MPA: medroxyprogesterone acetate; NA: not available; NPR: National Population Registry; OC: oral contraception; PRISMA: The Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT: randomised controlled trial; SD: standard deviation

Appendix E Forest plots

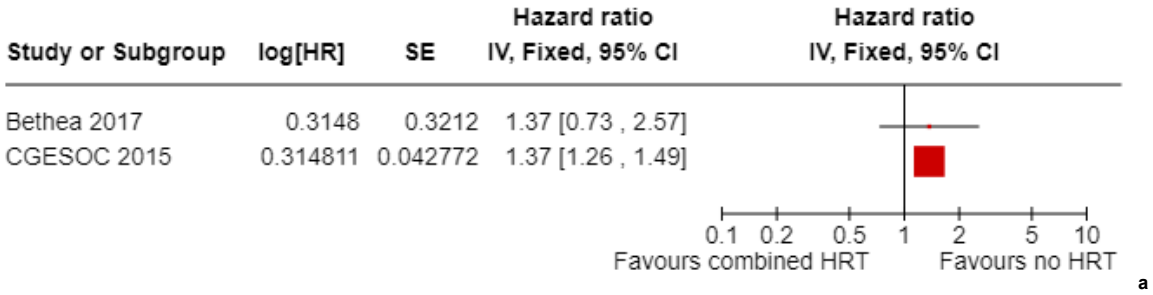
Forest plots for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here unless they provide information on subgroups; the quality assessment for such outcomes is provided in the GRADE profiles in Appendix F.

In some instances, where possible due to similarity of outcomes, observational evidence has been presented on the same forest plot as RCT evidence so that they can be compared visually. Analyses remain separate for RCT evidence and observational evidence. Please refer to the footnotes of relevant forest plots for more information where this is the case.

Comparison 1: Oestrogen + progestogen, any combined versus no-HRT

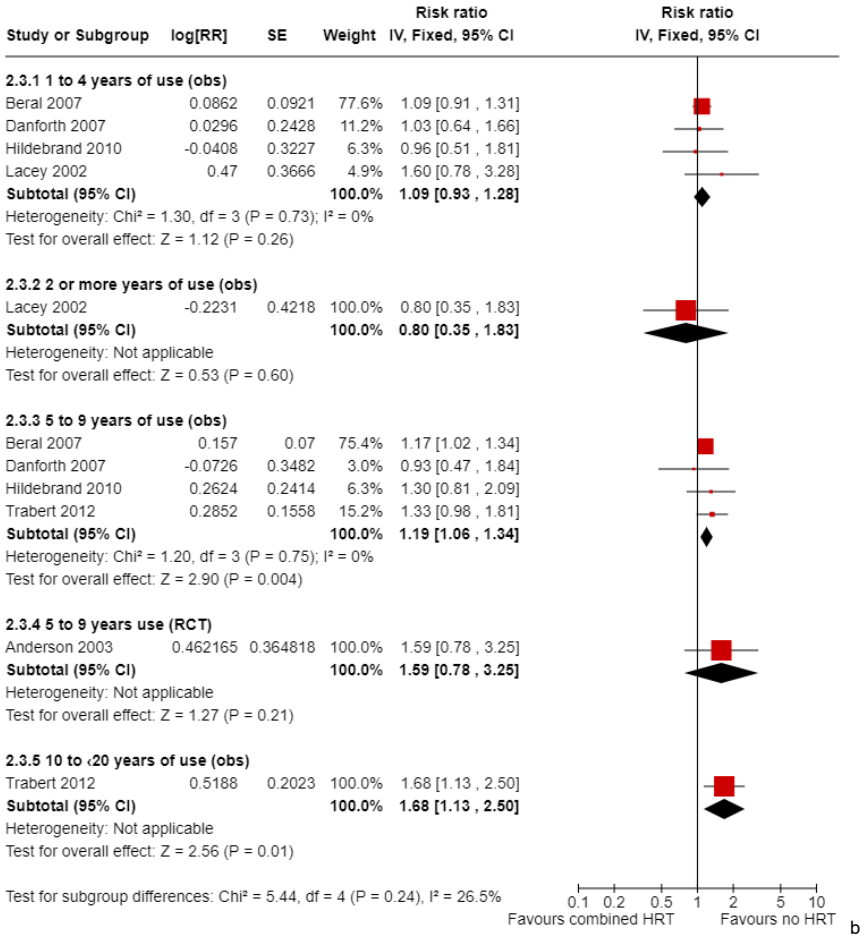
Figure 2: Incidence of ovarian cancer – current users, overall



[a]

[a] Effect estimate for CGESOC 2015 is a risk ratio but has been presented under hazard ratio in the forest plot for presentational purposes.

Figure 3: Incidence of ovarian cancer–current users, by years of use



b

[b] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. See table 3 for full GRADE profile for observational evidence and table 6 for full GRADE profile for RCT evidence. Test for subgroup differences for observational evidence: $Chi^2 = 4.77$, df=3 (P=0.19), $I^2 = 37.1\%$.

Figure 4: Incidence of ovarian cancer– age at first use for current users

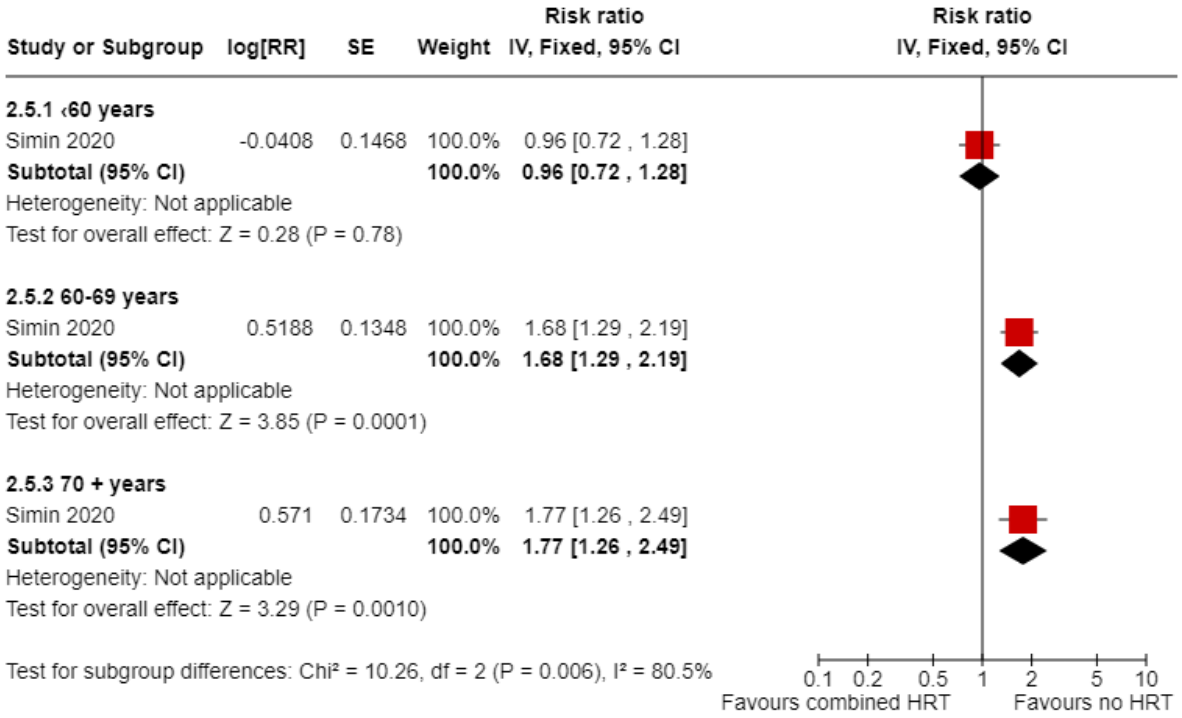


Figure 5: Incidence of ovarian cancer – by constituent

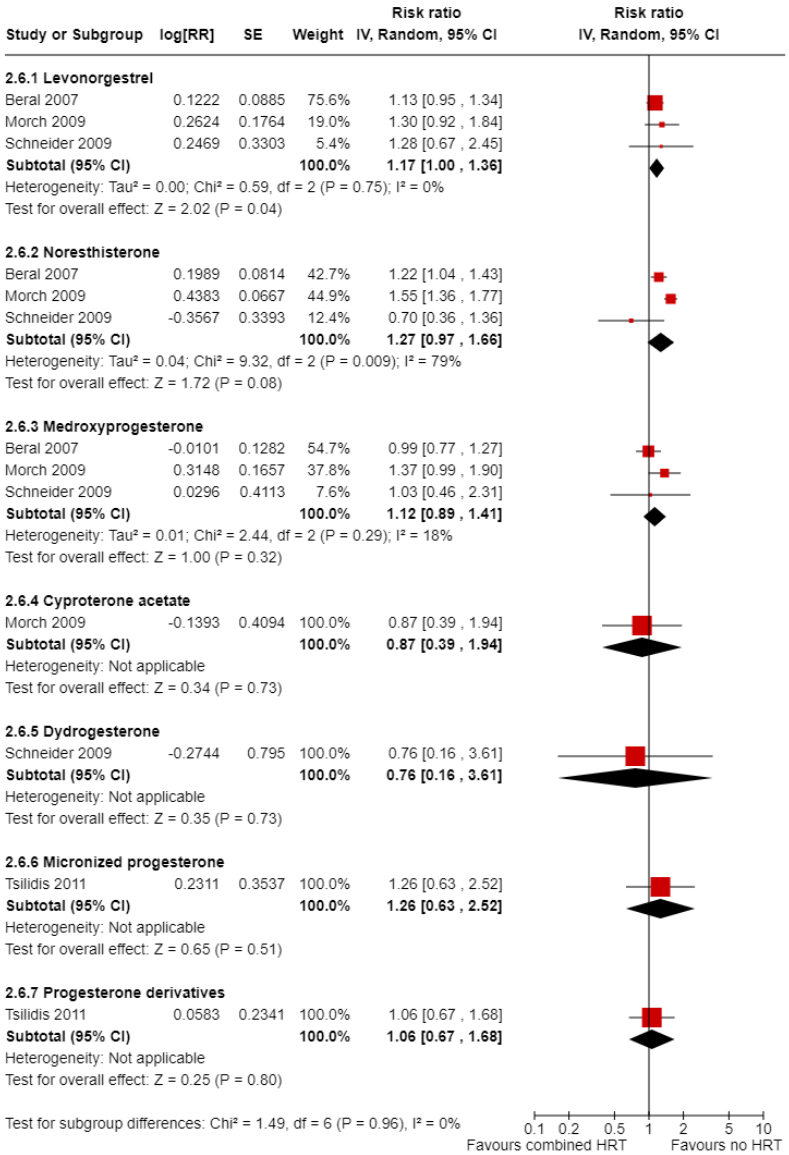


Figure 6: Incidence of ovarian cancer, by mode of administration, epithelial

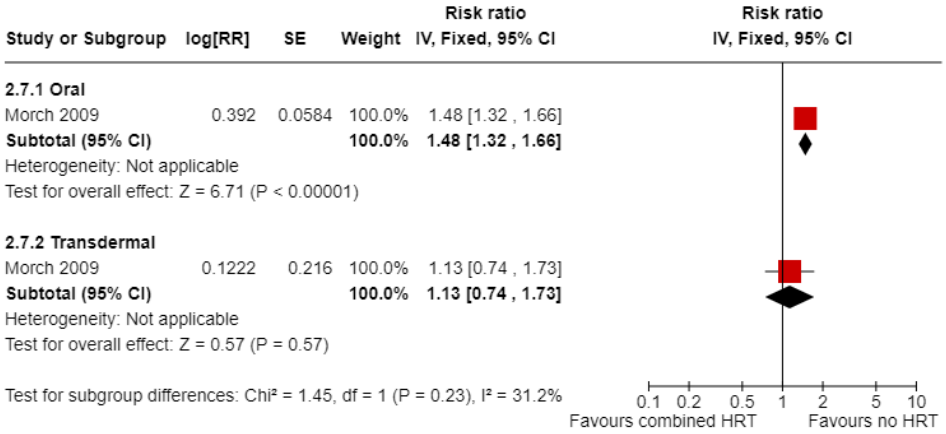


Figure 7: Incidence, by mode of administration, non-epithelial

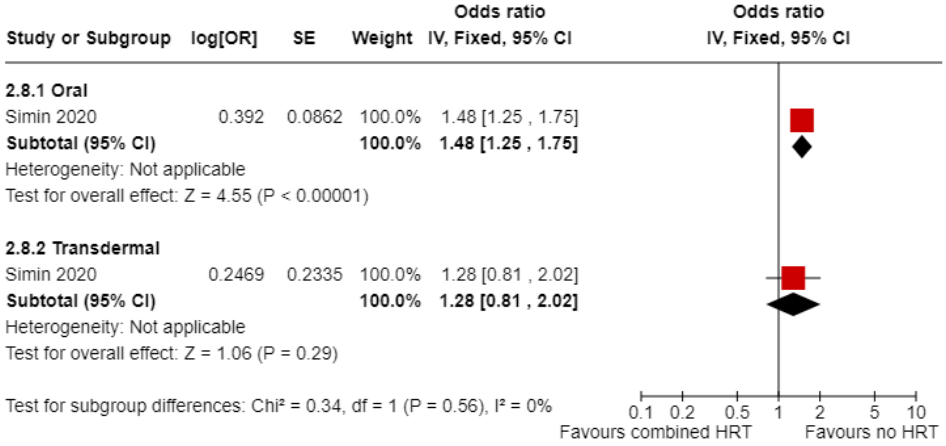


Figure 8: Incidence – by histological type, for specified duration 5-9 years use

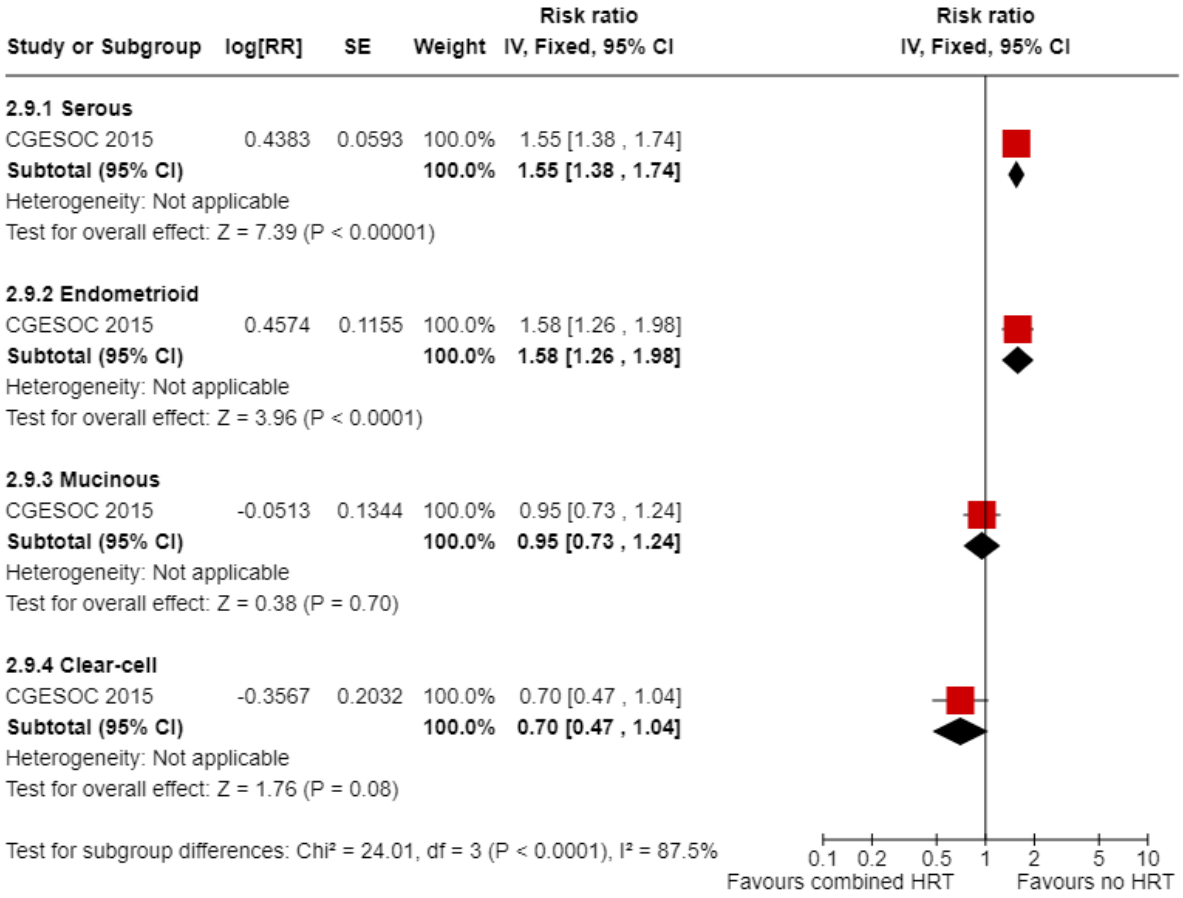


Figure 9: 5-year survival, current users, by duration of use

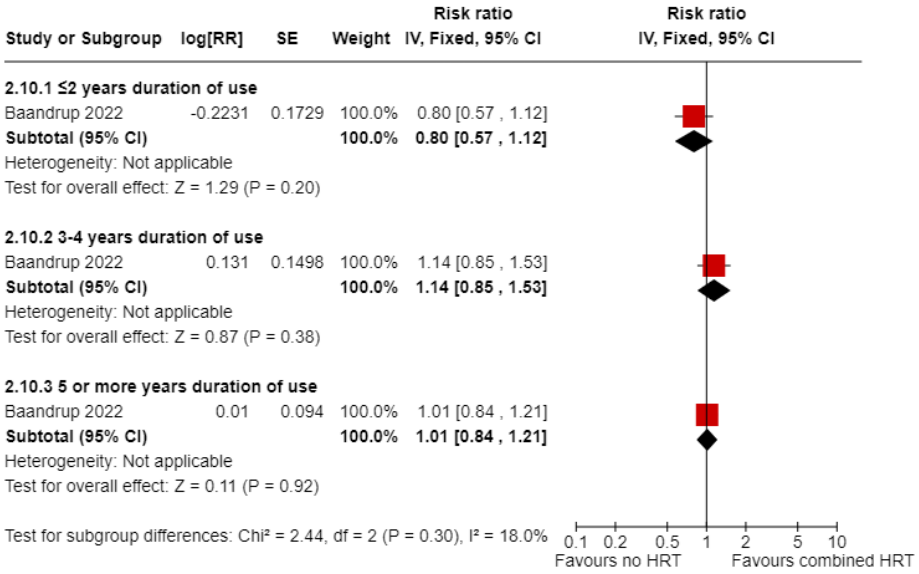


Figure 10: 5-year survival, past users, by time since last use

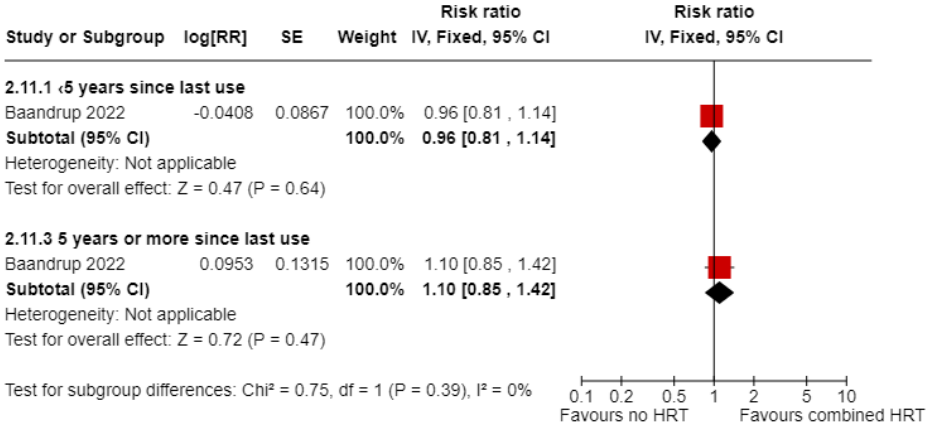


Figure 11: 10-year survival, current users, by duration of use

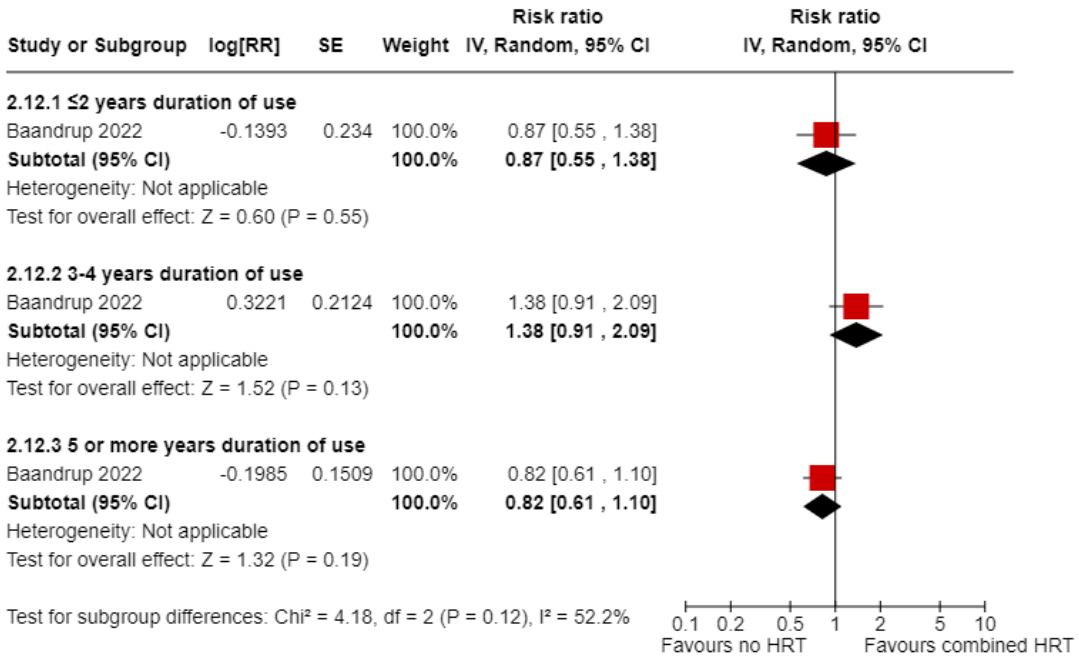
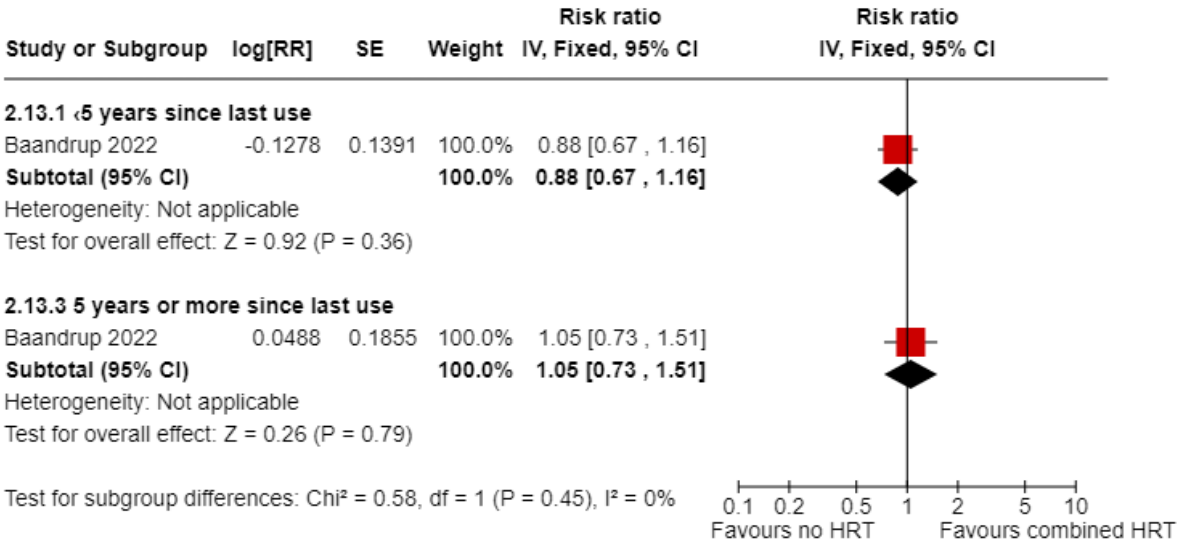


Figure 12: 10-year survival, past users, by time since last use



Comparison 2: Continuous oestrogen + progestogen versus no-HRT

Figure 13: Incidence of ovarian cancer – overall (current users)

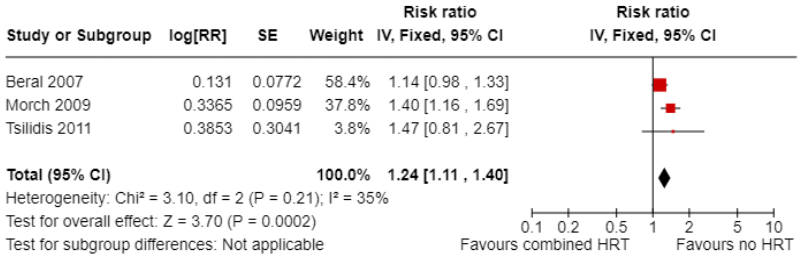
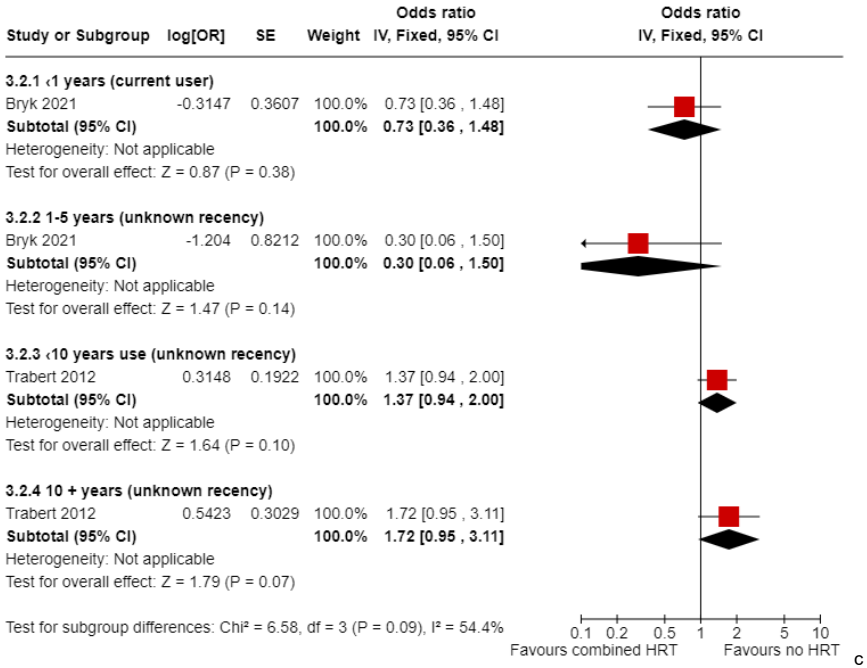


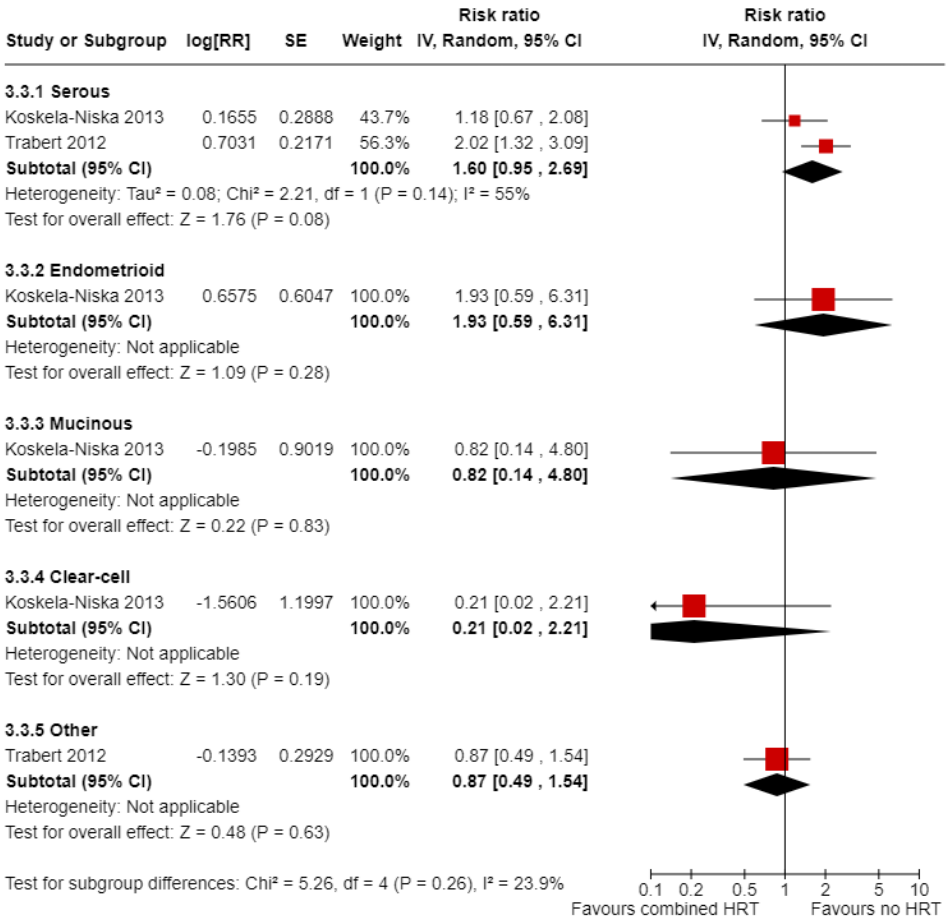
Figure 14: Incidence of ovarian cancer by duration of use



[c]

[c] Effect estimates for <10 years use and 10+ years use are risk ratios, but labelled as odds ratio in this forest plot for presentational purposes

Figure 15: Incidence of ovarian cancer by histological type, for specified duration 5-9 years use (unknown recency)



Comparison 3: Sequential oestrogen + progestogen versus no-HRT

Figure 16: Incidence of ovarian cancer- current users, overall

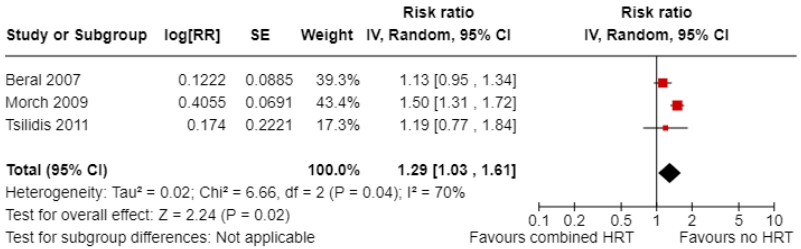
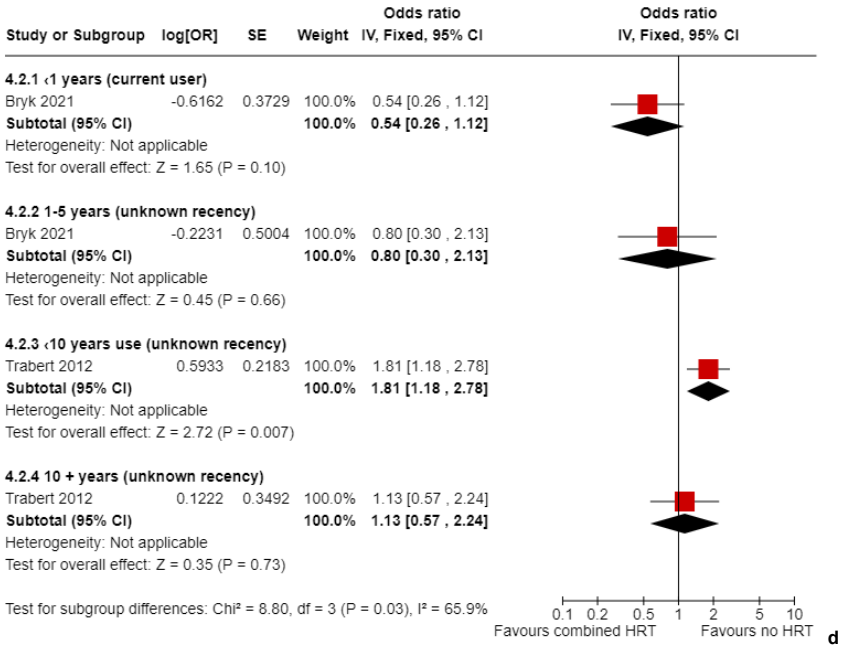
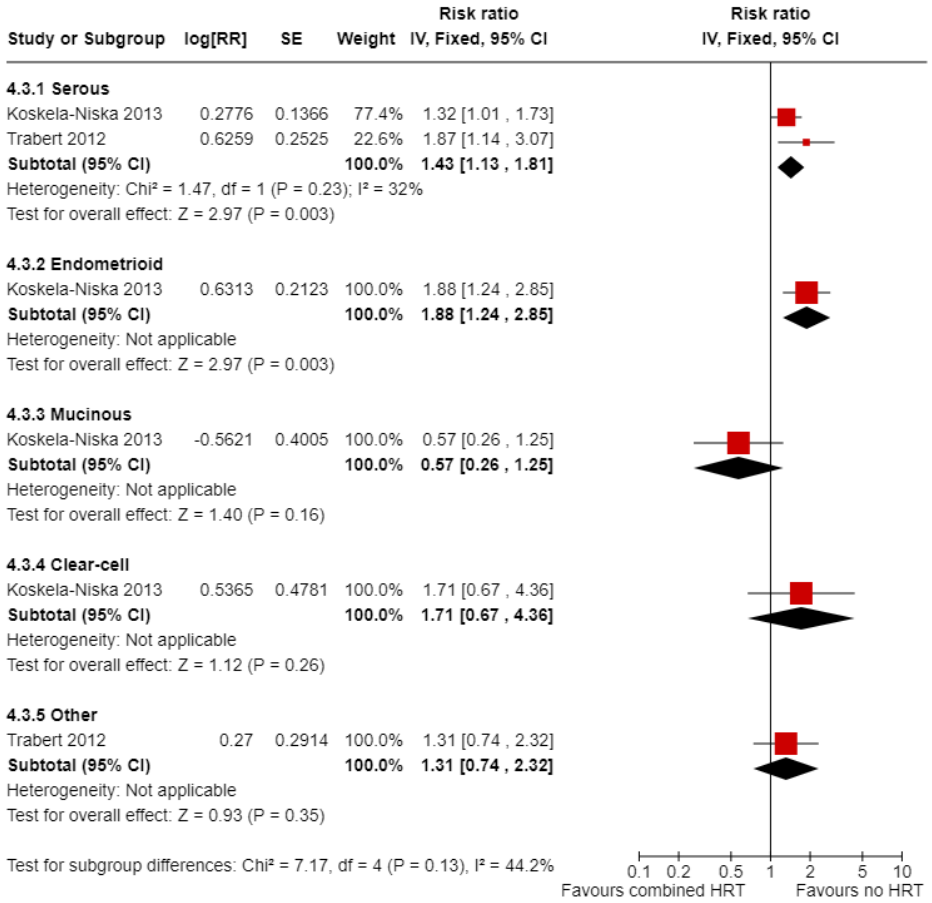


Figure 17: Incidence of ovarian cancer, by duration of use



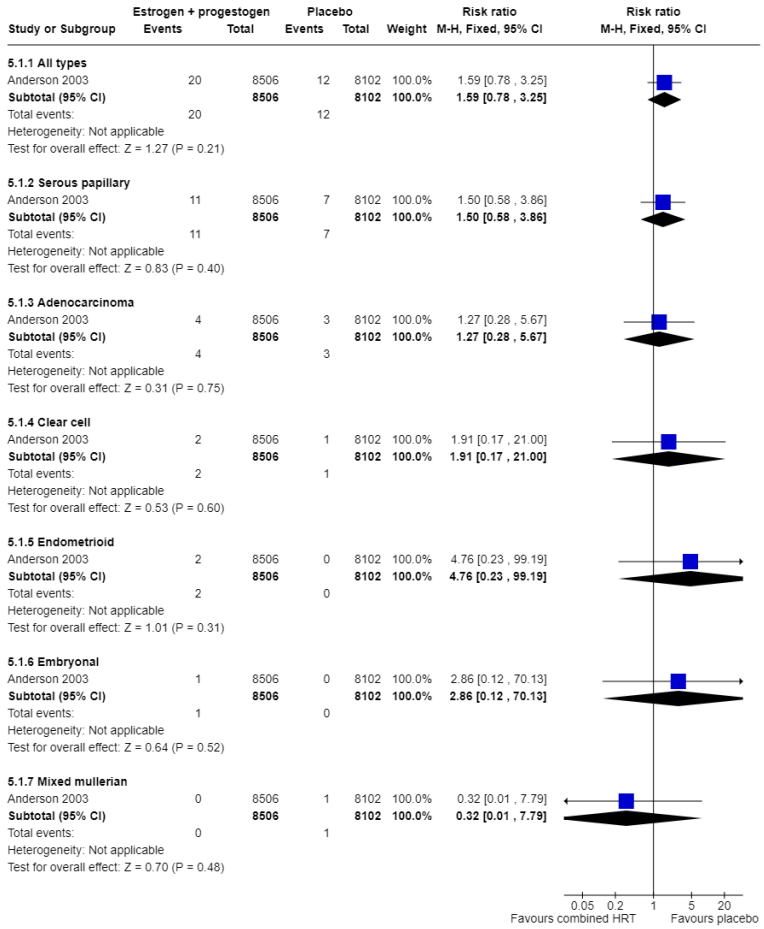
[d] Effect estimates for <10 years use and 10+ years use are risk ratios, but labelled as odds ratio in this forest plot for presentational purposes

Figure 18: Incidence of ovarian cancer by histological type, for specified duration 5-9 years of use



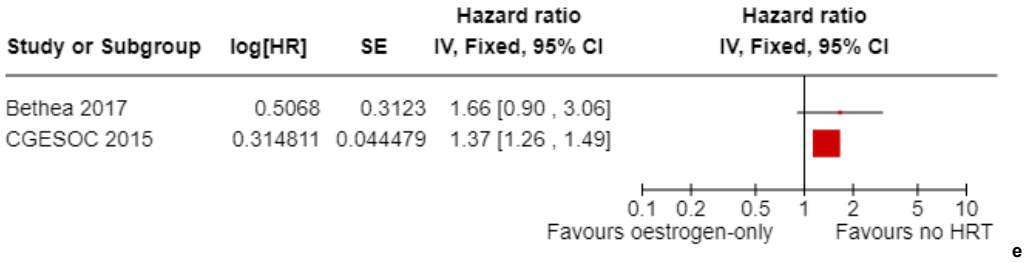
Comparison 4: Oestrogen + progestogen versus placebo

Figure 19: Incidence of ovarian cancer, by type



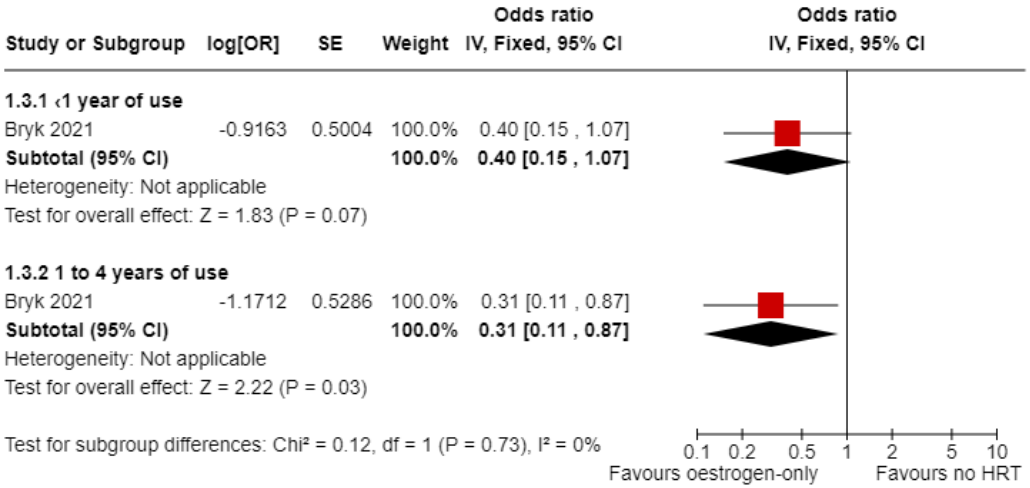
Comparison 5: Oestrogen-only versus no-HRT

Figure 20: Incidence of ovarian cancer – current users, overall



[e]

Figure 21: **Incidence of ovarian cancer – current users, by years of use**



[e] Effect estimate for CGESOC 2015 is a risk ratio but has been presented under hazard ratio in the forest plot for presentational purposes.

Figure 22: Incidence of ovarian cancer – current users, by years of use

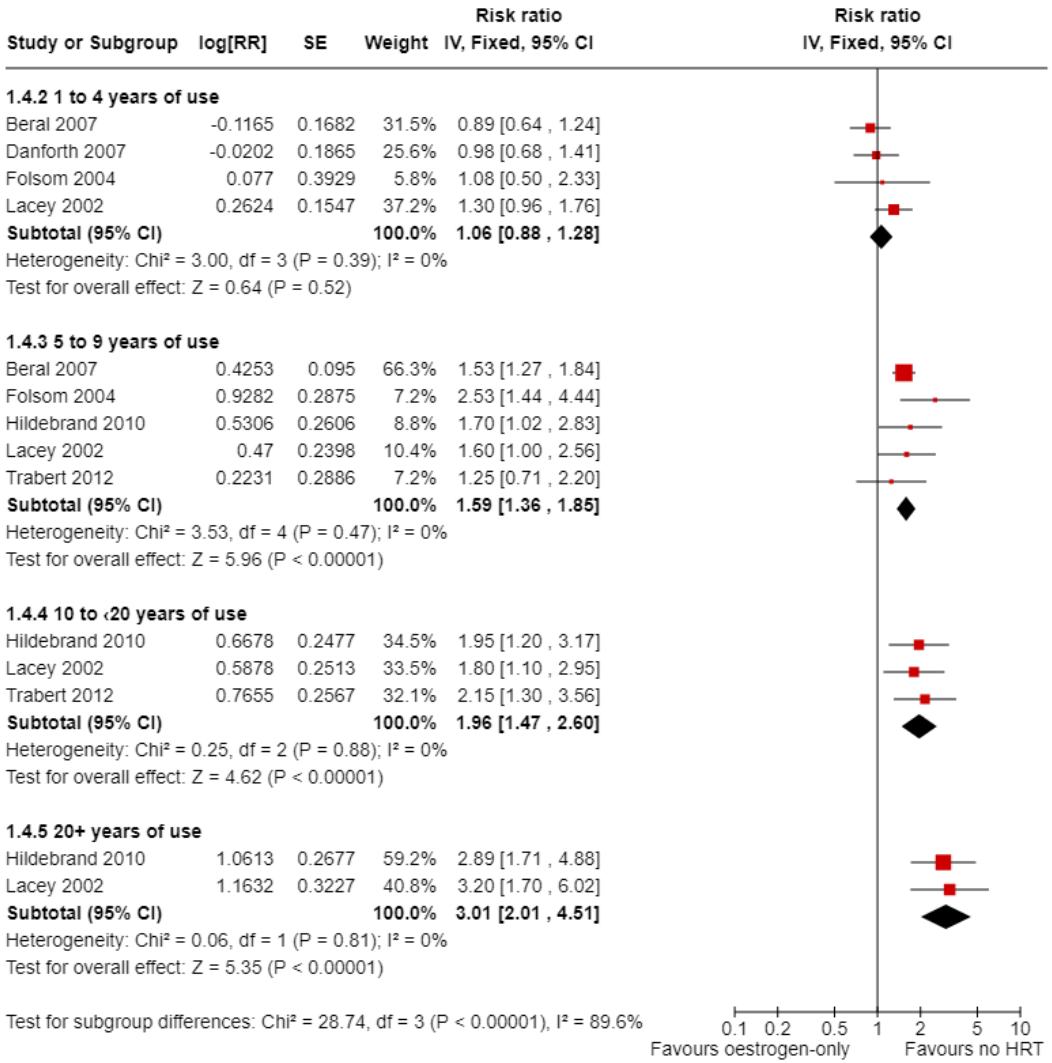


Figure 23: Incidence of ovarian cancer, past user by years of use, unknown years since last use

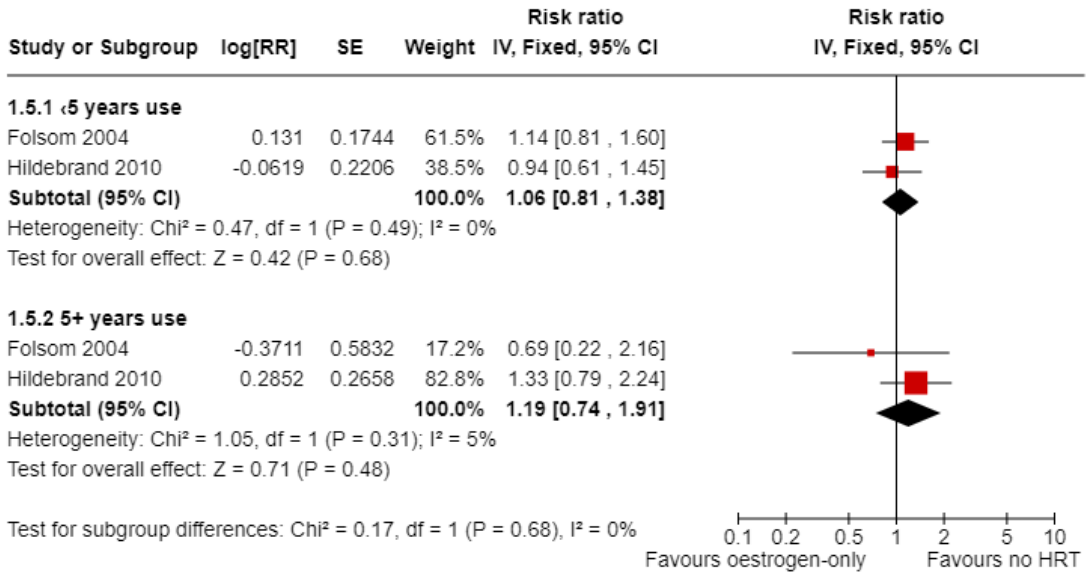


Figure 24: Incidence of ovarian cancer, current user, by age at first use

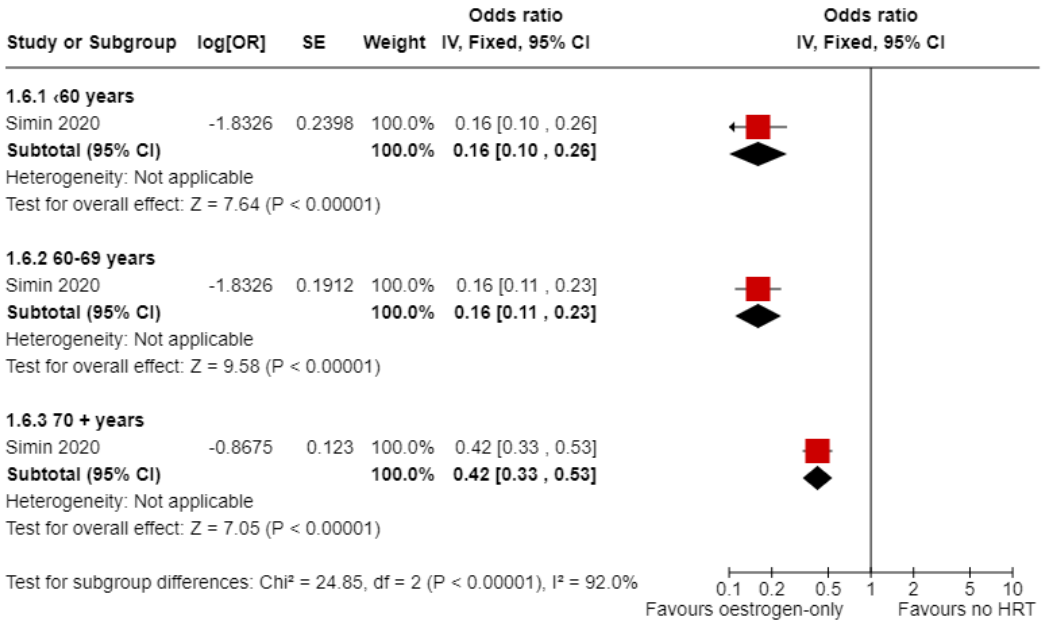


Figure 25: Incidence of ovarian cancer – by constituent

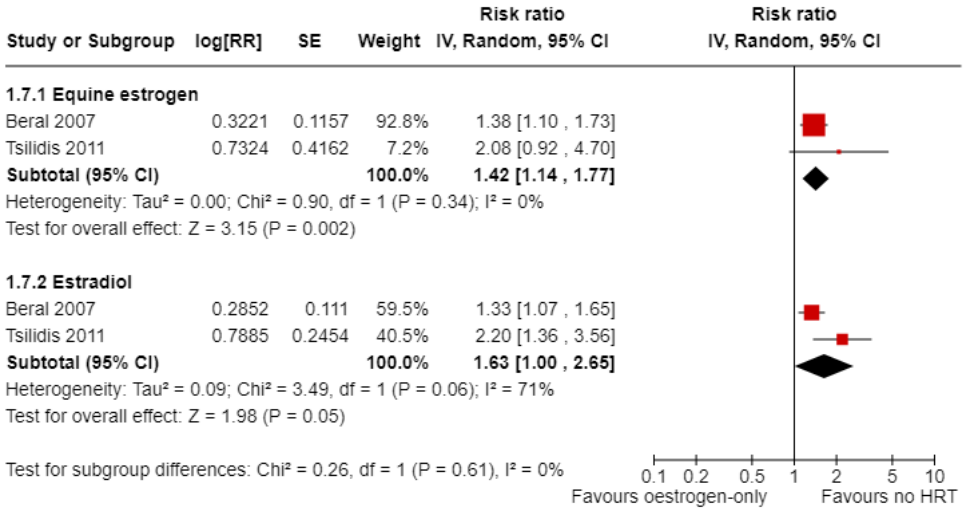


Figure 26: Incidence – by mode of administration – epithelial

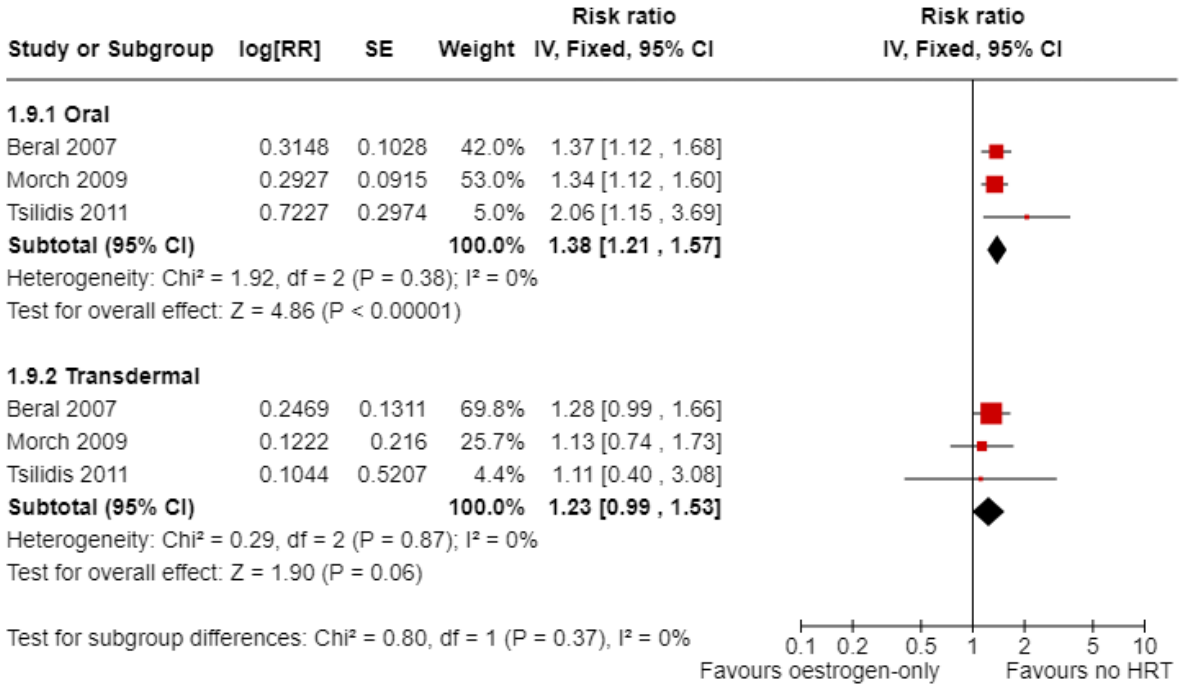


Figure 27: Incidence of ovarian cancer, by mode of administration – non-epithelial

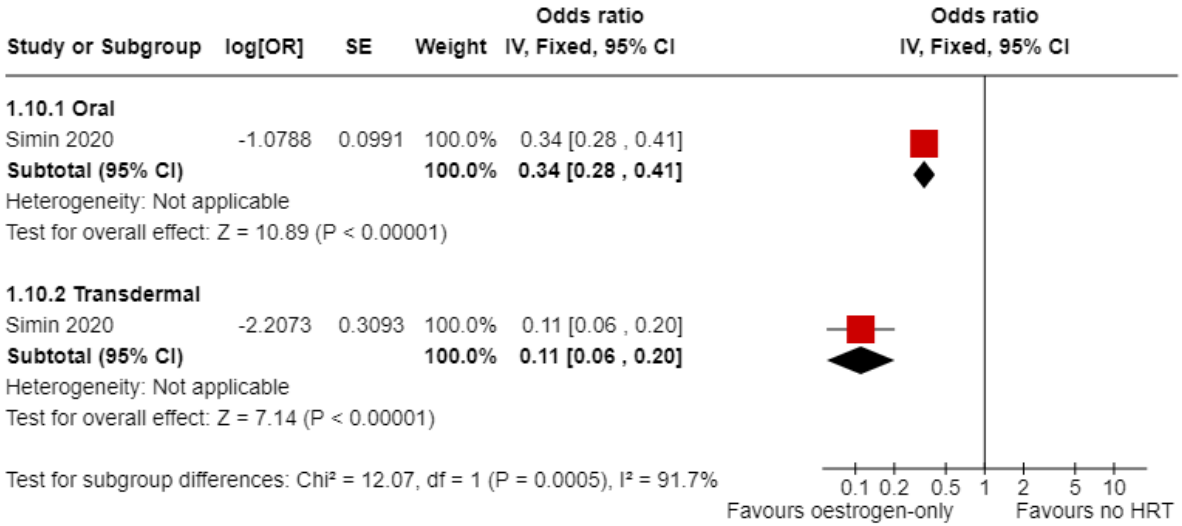


Figure 28: Incidence of ovarian cancer, by histological type, specified duration 5-9 years use

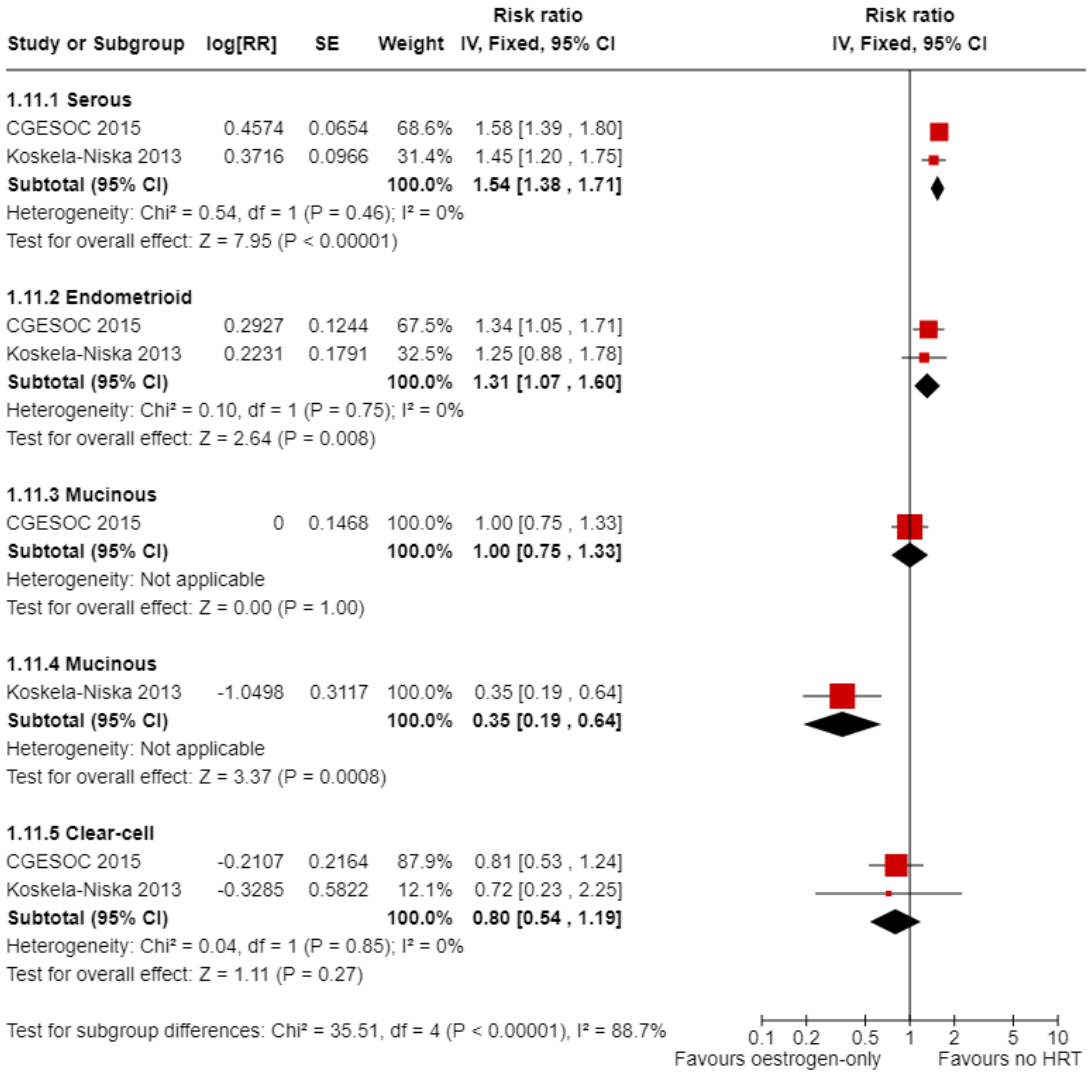


Figure 29: 5-year survival, current users, by duration of use

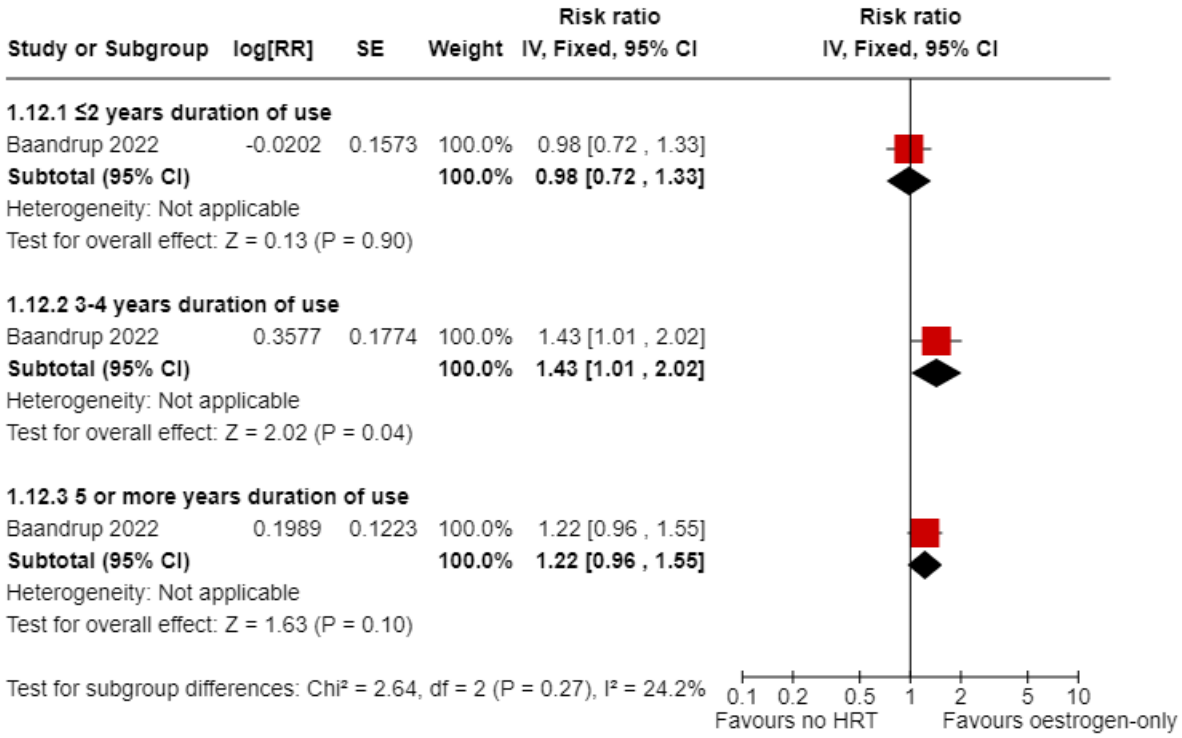


Figure 30: 5-year survival, past users, unknown duration of use, by time since last use

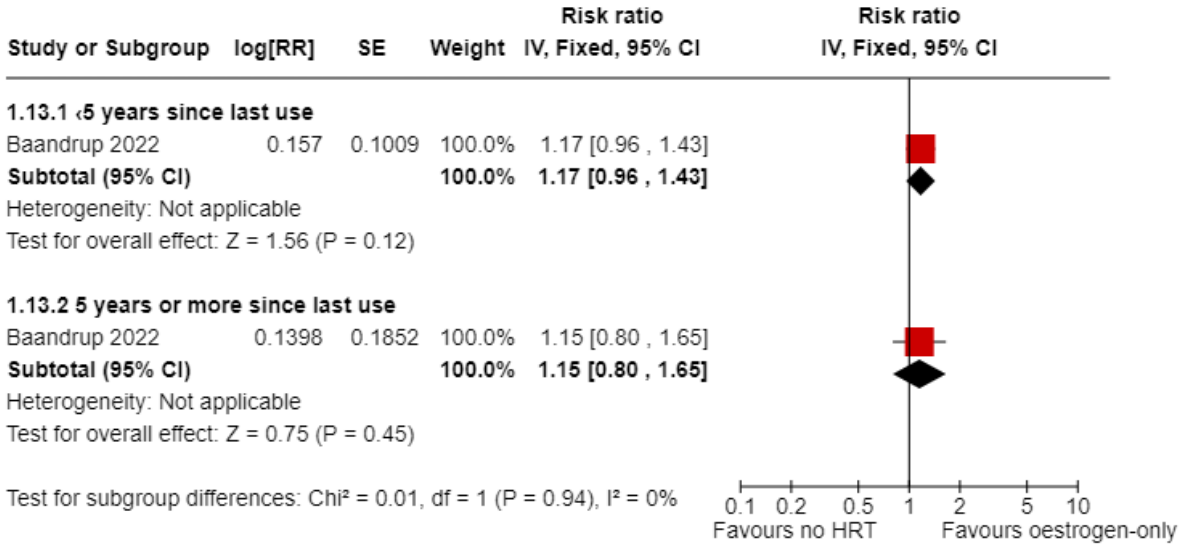


Figure 31: 10-year survival, current users, by duration of use

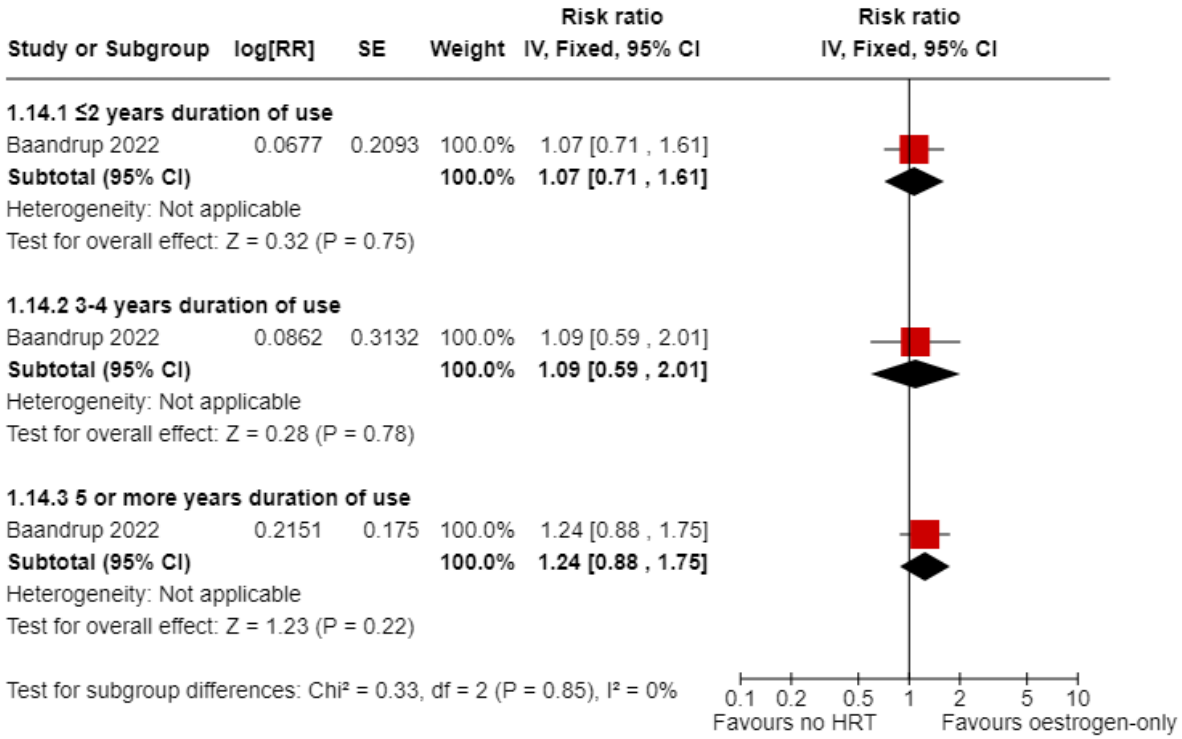


Figure 32: 10-year survival, past users, unknown duration of use, by time since last use

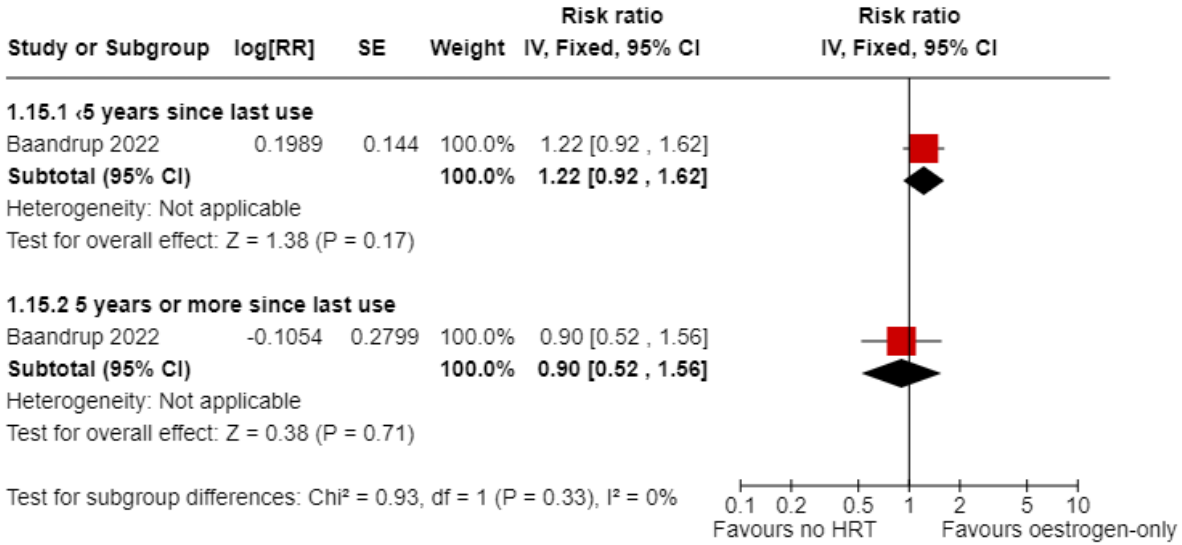


Figure 33: Mortality – current users, by duration of use

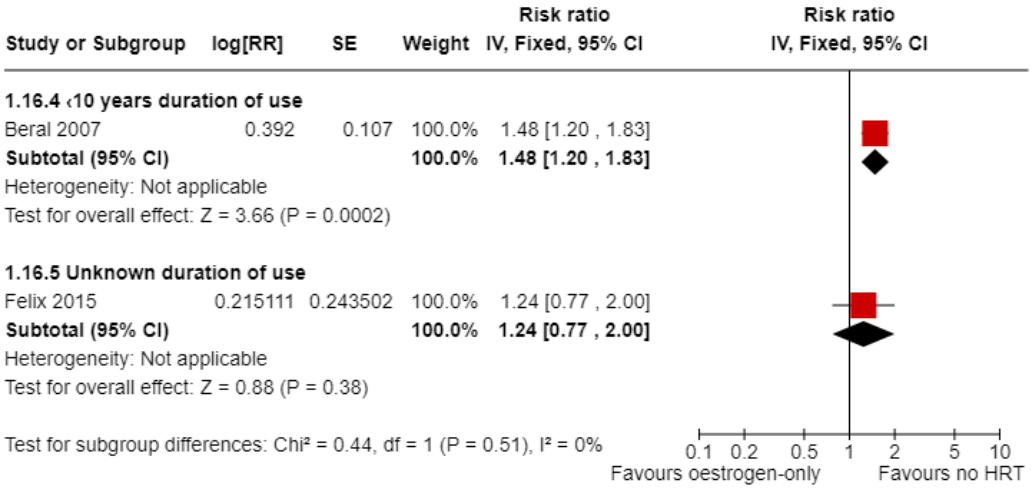


Figure 34: Mortality – past users, less than 15 years since last use

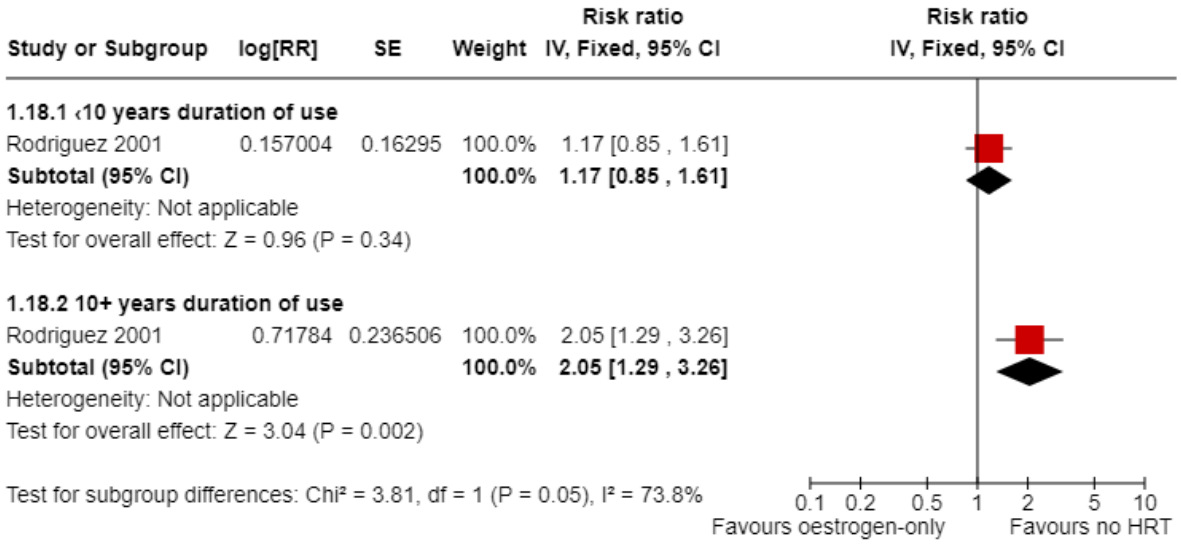
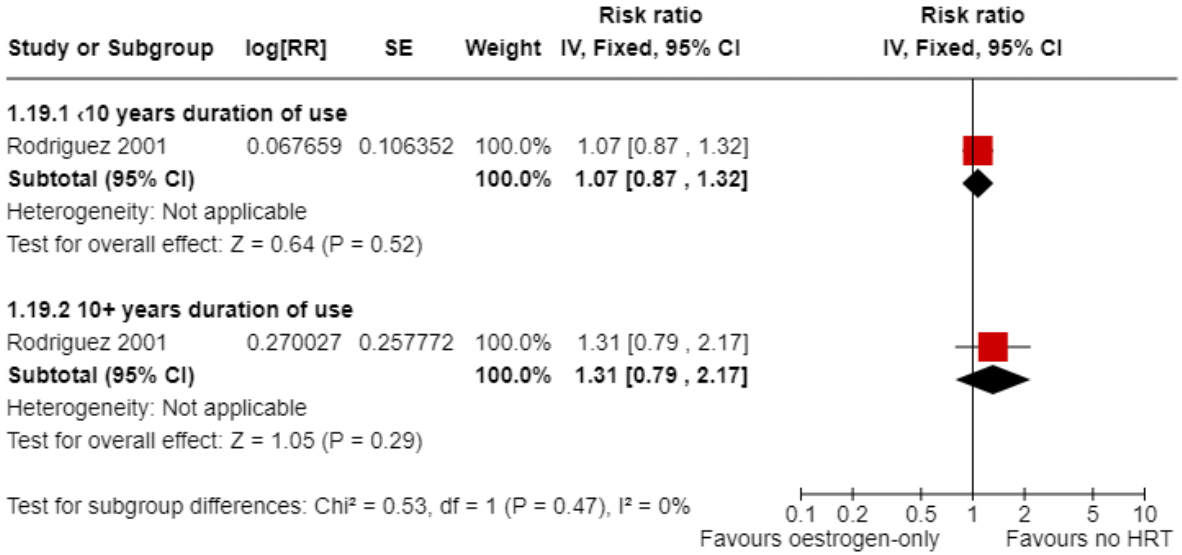


Figure 35: Mortality – past users, more than 15 years since last use



Appendix F GRADE tables

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

See Appendix L for absolute risk tables

Table 3: Comparison 1: Oestrogen + progestogen, any combined versus no-HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	No HRT	Relative (95% CI)	Absolute		
Incidence of ovarian cancer – current users												
Overall (any duration)												
1 (Bethea 2017)	observational studies	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	not reported	not reported	HR 1.37 (0.73 to 2.57)	See Appendix L	VERY LOW	CRITICAL
Overall (any duration)												
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.37 (1.26 to 1.49)	See Appendix L	HIGH	CRITICAL
By years of use – 1 to 4 years of use												
4[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.09 (0.93 to 1.28)	See Appendix L	MODERATE	CRITICAL
By years of use – 2 or more years of use												
1 (Lacey 2002)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 0.8 (0.35 to 1.83)	See Appendix L	VERY LOW	CRITICAL
By years of use – 5 to 9 years of use												
4[6]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.19 (1.06 to 1.34)	See Appendix L	MODERATE	CRITICAL
By years of use – 10 to <20 years of use												
1 (Trabert 2012)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.68 (1.13 to 2.5)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer – age at first use for current users												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	No HRT	Relative (95% CI)	Absolute		
<60 years												
1 (Simin 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 0.96 (0.72 to 1.28)	See Appendix L	VERY LOW	CRITICAL
60-69 years												
1 (Simin 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.68 (1.29 to 2.19)	See Appendix L	LOW	CRITICAL
70 + years												
1 (Simin 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.77 (1.26 to 2.49)	See Appendix L	LOW	CRITICAL
Incidence of ovarian cancer – by constituent												
Levonorgestrel												
3[7]	observational studies and case control	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.17 (1 to 1.36)	See Appendix L	MODERATE	CRITICAL
Noresthisterone												
3[7]	observational studies	serious[8]	serious[9]	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.27 (0.97 to 1.66)	See Appendix L	VERY LOW	CRITICAL
Medroxyprogesterone												
3[7]	observational studies	serious[8]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.12 (0.89 to 1.41)	See Appendix L	LOW	CRITICAL
Cyproterone acetate												
1 (Morch 2009)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 0.87 (0.39 to 1.94)	See Appendix L	VERY LOW	CRITICAL
Dydrogesterone												
1 (Schneider 2009)	case control	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	OR 0.76 (0.16 to 3.61)	See Appendix L	VERY LOW	CRITICAL
Micronized progesterone												
1 (Tsilidis 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 1.26 (0.63 to 2.52)	See Appendix L	VERY LOW	CRITICAL
Progesterone derivatives												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	No HRT	Relative (95% CI)	Absolute		
1 (Tsilidis 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 1.06 (0.67 to 1.68)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer – by mode of administration												
Oral (epithelial)												
1 (Morch 2009)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.48 (1.32 to 1.66)	See Appendix L	LOW	CRITICAL
Transdermal (epithelial)												
1 (Morch 2009)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 1.13 (0.74 to 1.73)	See Appendix L	VERY LOW	CRITICAL
Oral (non-epithelial)												
1 (Simin 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	OR 1.48 (1.25 to 1.75)	See Appendix L	VERY LOW	CRITICAL
Transdermal (non-epithelial)												
1 (Simin 2020)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	OR 1.28 (0.81 to 2.02)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer – by histological type, for specified duration 5-9 years use												
Serous												
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.55 (1.38 to 1.74)	See Appendix L	HIGH	CRITICAL
Endometrioid												
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.58 (1.26 to 1.98)	See Appendix L	HIGH	CRITICAL
Mucinous												
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 0.95 (0.73 to 1.24)	See Appendix L	MODERATE	
Clear cell												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	No HRT	Relative (95% CI)	Absolute		
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 0.7 (0.47 to 1.04)	See Appendix L	MODERATE	CRITICAL
5-year survival												
Current users - ≤2 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 0.8 (0.57 to 1.12)	Not calculable	VERY LOW	CRITICAL
Current users – 3-4 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.14 (0.85 to 1.53)	Not calculable	VERY LOW	CRITICAL
Current users – 5 or more years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.01 (0.84 to 1.21)	Not calculable	LOW	CRITICAL
Past users, unknown duration of use - <5 years since last use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 0.96 (0.81 to 1.14)	Not calculable	LOW	CRITICAL
Past users, unknown duration of use – 5 years or more since last use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.1 (0.85 to 1.42)	Not calculable	VERY LOW	CRITICAL
10-year survival												
Current users ≤2 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 0.87 (0.55 to 1.38)	Not calculable	VERY LOW	CRITICAL
Current users – 3-4 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.38 (0.91 to 2.09)	Not calculable	VERY LOW	CRITICAL
Current users – 5 or more years duration of use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 0.82 (0.61 to 1.1)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use - <5 years since last use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, any combined	No HRT	Relative (95% CI)	Absolute		
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 0.88 (0.67 to 1.16)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use – 5 years or more since last use												
1 (Baandrup 2022)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 1.05 (0.73 to 1.51)	Not calculable	VERY LOW	CRITICAL
Mortality												
Current users, by years of use - <10 years of use (up to 14 years follow up)												
1 (Beral 2007)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	not reported	not reported	RR 1.15 (1 to 1.32)	Not calculable	MODERATE	CRITICAL
Current users, by years of use – Unknown duration of use (14 years follow up)												
1 (Felix 2015)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	RR 0.94 (0.64 to 1.38)	Not calculable	VERY LOW	CRITICAL
Past user, unknown duration of use or time since last use (14 years follow up)												
1 (Felix 2015)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	not reported	not reported	HR 1.08 (0.57 to 2.05)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio;
1 Very serious risk of bias in the evidence contributing to the outcomes as per CASP or ROBINS-I
2 Study indirect as some women in the no hormone replacement group used hormone replacement therapy for less than a year
3 95 % CI crosses 2 MIDs
4 Beral 2007; Danforth 2007; Hildebrande 2010; Lacey 2002
5 95% CI crosses 1 MID
6 Beral 2007; Danforth 2007; Hildebrand 2010; Trabert 2012
7 Beral 2007; Morch 2009; Schneider 2009
8 Serious risk of bias in the evidence contributing to outcomes as per CASP or ROBINS-I
9 Serious heterogeneity unexplained by subgroup analysis

Table 4: Comparison 2: Continuous oestrogen + progestogen versus no-HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, continuous	No-HRT	Relative (95% CI)	Absolute		
Incidence of ovarian cancer												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, continuous	No-HRT	Relative (95% CI)	Absolute		
Overall (current users)												
3[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.24 (1.11 to 1.40)	See Appendix L	LOW	CRITICAL
By duration of use - <1 years (current user)												
1 (Bryk 2021)	case control	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	OR 0.73 (0.36 to 1.48)	See Appendix L	VERY LOW	CRITICAL
By duration of use – 1-5 years (unknown recency)												
1 (Bryk 2021)	case control	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	OR 0.3 (0.06 to 1.5)	See Appendix L	VERY LOW	CRITICAL
By duration of use - <10 years use (unknown recency)												
1 (Trabert 2012)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.37 (0.94 to 2)	See Appendix L	VERY LOW	CRITICAL
By duration of use – 10 + years (unknown recency)												
1 (Trabert 2012)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.72 (0.95 to 3.11)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer by histological type, for specified duration 5-9 years use (unknown recency)												
Serous												
2[6]	observational studies	very serious[4]	serious[7]	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.60 (0.95 to 2.69)	See Appendix L	VERY LOW	CRITICAL
Endometrioid												
1 (Koskela-Niska 2013)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	RR 1.93 (0.59 to 6.31)	See Appendix L	VERY LOW	CRITICAL
Mucinous												
1 (Koskela-Niska 2013)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	RR 0.82 (0.14 to 4.8)	See Appendix L	VERY LOW	CRITICAL
Clear-cell												
1 (Koskela-Niska 2013)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	RR 0.21 (0.02 to 2.21)	See Appendix L	VERY LOW	CRITICAL
Other												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, continuous	No-HRT	Relative (95% CI)	Absolute		
1 (Trabert 2012)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	RR 0.87 (0.49 to 1.54)	See Appendix L	VERY LOW	CRITICAL
Mortality, unknown duration of use or time since last use (14 years follow up)												
1 (Felix 2015)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	not reported	not reported	HR 1 (0.68 to 1.48)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio
1 Beral 2007; Morch 2009; Tsilidis 2011
2 Serious risk of bias in the evidence contributing to outcomes as per CASP and ROBINS-I
3 95% CI crosses 1 MID
4 Very serious risk of bias in the evidence contributing to outcomes as per CASP or ROBINS-I
5 95% CI crosses 2 MIDs
6 Koskela-Niska 2013; Trabert 2012
7 Serious heterogeneity unexplained by subgroup analysis

Table 5: Comparison 3: Sequential oestrogen + progestogen versus no-HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, sequential	No-HRT	Relative (95% CI)	Absolute		
Incidence of ovarian cancer												
Overall (current users)												
3[1]	observational studies	serious[2]	serious[3]	no serious indirectness	serious[4]	none	not reported	not reported	RR 1.29 (1.03 to 1.61)	See Appendix L	LOW	CRITICAL
By duration of use - <1 years –(current user)												
1 (Bryk 2021)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	not reported	not reported	OR 0.54 (0.26 to 1.12)	See Appendix L	VERY LOW	CRITICAL
By duration of use – 1-5 years (unknown recency)												
1 (Bryk 2021)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	OR 0.8 (0.3 to 2.13)	See Appendix L	VERY LOW	CRITICAL
By duration of use - <10 years use (unknown recency)												
1 (Trabert 2012)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	not reported	not reported	RR 1.81 (1.18 to 2.78)	See Appendix L	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen, sequential	No-HRT	Relative (95% CI)	Absolute		
By duration of use – 10 + years (unknown recency)												
1 (Trabert 2012)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.13 (0.57 to 2.24)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer by histological type, for specified duration 5-9 years use (unknown recency)												
Serous												
2[7]	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	not reported	not reported	RR 1.43 (1.13 to 1.81)	See Appendix L	LOW	CRITICAL
Endometrioid												
1 (Koskela-Niska 2013)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	not reported	not reported	RR 1.88 (1.24 to 2.85)	See Appendix L	VERY LOW	CRITICAL
Mucinous												
1 (Koskela-Niska 2013)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	not reported	not reported	RR 0.57 (0.26 to 1.25)	See Appendix L	VERY LOW	CRITICAL
Clear-cell												
1 (Koskela-Niska 2013)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.71 (0.67 to 4.36)	See Appendix L	VERY LOW	CRITICAL
Other												
1 (Trabert 2012)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	RR 1.31 (0.74 to 2.32)	See Appendix L	VERY LOW	CRITICAL
Mortality, unknown duration of use or time since last use (14 years follow up)												
1 (Felix 2015)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	not reported	not reported	HR 0.91 (0.5 to 1.66)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio
1 Beral 2007; Morch 2009; Tsilidis 2011
2 Serious risk of bias in the evidence contributing to outcomes as per CASP or ROBINS-I
3 Serious heterogeneity unexplained by subgroup analysis
4 95% CI crosses 1 MID
5 Very serious risk of bias in the evidence contributing to outcomes as per CASP or ROBINS-I
6 95% CI crosses 2 MIDs
7 Koskela-Niska 2013; Trabert 2012

Table 6: Comparison 4: Oestrogen + progestogen versus placebo (data from RCTs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + progestogen	Placebo	Relative (95% CI)	Absolute		
Incidence of ovarian cancer by type												
Incidence – All types												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	20/8506 (0.24%)	12/8102 (0.15%)	RR 1.59 (0.78 to 3.25)	7 more per 1000 (from 3 fewer to 27 more)	LOW	CRITICAL
Incidence – Serous papillary												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/8506 (0.13%)	7/8102 (0.09%)	RR 1.5 (0.58 to 3.86)	0 more per 1000 (from 0 fewer to 2 more)	LOW	CRITICAL
Incidence – Adenocarcinoma												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/8506 (0.05%)	3/8102 (0.04%)	RR 1.27 (0.28 to 5.67)	0 more per 1000 (from 0 fewer to 2 more)	LOW	CRITICAL
Incidence – Clear cell												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/8506 (0.02%)	1/8102 (0.01%)	RR 1.91 (0.17 to 21)	0 more per 1000 (from 0 fewer to 2 more)	LOW	CRITICAL
Incidence – Endometrioid												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/8506 (0.02%)	0/8102 (0%)	RR 4.76 (0.23 to 99.19)	0 more per 1000 (from 0 fewer to 0 more)	LOW	CRITICAL
Incidence – Embryonal												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/8506 (0.01%)	0/8102 (0%)	RR 2.86 (0.12 to 70.13)	0 more per 1000 (from 0 fewer to 0 more)	LOW	CRITICAL
Incidence – Mixed mullerian												
1 (Anderson 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/8506 (0%)	1/8102 (0.01%)	RR 0.32 (0.01 to 7.79)	0 fewer per 1000 (from 0 fewer to 1 more)	LOW	CRITICAL

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio
1 95% CI crosses 2 MIDs

Table 7: Comparison 5: Oestrogen-only versus no-HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
Incidence of ovarian cancer – current users												
Overall												
1 (Bethea 2017)	observational studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	not reported	not reported	HR 1.66 (0.9 to 3.07)	not calculable	VERY LOW	CRITICAL
Overall												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.37 (1.26 to 1.5)	See Appendix L	HIGH	CRITICAL
By years of use - <1 year of use												
1 (Bryk 2021)	case control	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	OR 0.4 (0.15 to 1.07)	See Appendix L	VERY LOW	CRITICAL
By years of use – 1 to 4 years of use												
1 (Bryk 2021)	case control	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	OR 0.31 (0.11 to 0.88)	See Appendix L	VERY LOW	CRITICAL
By years of use – 1 to 4 years of use												
4[5]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.06 (0.88 to 1.28)	See Appendix L	VERY LOW	CRITICAL
By years of use – 5 to 9 years of use												
5[6]	observational studies	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.59 (1.36 to 1.85)	See Appendix L	MODERATE	CRITICAL
By years of use – 10 to <20 years of use												
3[8]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.96 (1.47 to 2.6)	See Appendix L	LOW	CRITICAL
By years of use – 20+ years of use												
2[9]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 3.01 (2.01 to 4.51)	See Appendix L	LOW	CRITICAL
Incidence of ovarian cancer – past users												
Unknown years since last use, by years of use - <5 years use												
2[10]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.06 (0.81 to 1.38)	See Appendix L	VERY LOW	CRITICAL
Unknown years since last use, by years of use – 5+ years use												
2[10]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 1.19 (0.74 to 1.91)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer – current user, by age at first use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
<60 years												
1 (Simin 2020)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 0.16 (0.1 to 0.26)	See Appendix L	LOW	CRITICAL
60-69 years												
1 (Simin 2020)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 0.16 (0.11 to 0.23)	See Appendix L	LOW	CRITICAL
70 + years												
1 (Simin 2020)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported -	not reported	OR 0.42 (0.33 to 0.53)	See Appendix L	LOW	CRITICAL
Incidence of ovarian cancer – by constituent												
Equine oestrogen												
2[12]	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.42 (1.14 to 1.77)	See Appendix L	LOW	CRITICAL
Estradiol												
2[12]	observational studies	very serious[4]	serious[13]	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.63 (1 to 2.65)	See Appendix L	VERY LOW	CRITICAL
Incidence of ovarian cancer – by mode of administration												
Oral (epithelial)												
3[14]	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.38 (1.21 to 1.57)	See Appendix L	VERY LOW	CRITICAL
Transdermal (epithelial)												
3[14]	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.23 (0.99 to 1.53)	See Appendix L	LOW	CRITICAL
Oral (non-epithelial)												
1 (Simin 2020)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 0.34 (0.28 to 0.41)	See Appendix L	LOW	CRITICAL
Transdermal (non-epithelial)												
1 (Simin 2020)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	OR 0.11 (0.06 to 0.2)	See Appendix L	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
Incidence of ovarian cancer – by histological type for specified duration of use 5-9 years use												
Serous												
2[15]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 1.54 (1.38 to 1.71)	6 more per 1000 (from See Appendix L	HIGH	CRITICAL
Endometrioid												
2[15]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	nserious[3]	none	not reported	not reported	RR 1.31 (1.07 to 1.6)	See Appendix L	MODERATE	CRITICAL
Mucinous												
1 (CGESOC 2015; includes 17 prospective studies)	observational studies	no serious risk of bias	very serious[16]	no serious indirectness	very serious[11]	none	not reported	not reported	RR 1 (0.75 to 1.33)	See Appendix L	VERY LOW	CRITICAL
Mucinous												
1 (Koskela-Niska 2013)	case control	serious[7]	very serious[16]	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 0.35 (0.19 to 0.64)	See Appendix L	VERY LOW	CRITICAL
Clear-cell												
2[15]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 0.8 (0.54 to 1.19)	See Appendix L	MODERATE	CRITICAL
5-year survival												
Current users ≤2 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 0.98 (0.72 to 1.33)	Not calculable	VERY LOW	CRITICAL
Current users - 3-4 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.43 (1.01 to 2.02)	Not calculable	VERY LOW	CRITICAL
Current users - 5 or more years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.22 (0.96 to 1.55)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use - <5 years since last use												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.17 (0.96 to 1.43)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use - 5 years or more since last use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.15 (0.8 to 1.65)	Not calculable	VERY LOW	CRITICAL
10 year survival												
Current users ≤2 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 1.07 (0.71 to 1.61)	Not calculable	VERY LOW	CRITICAL
Current users - 3-4 years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 1.09 (0.59 to 2.01)	Not calculable	VERY LOW	CRITICAL
Current users - 5 or more years duration of use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.24 (0.88 to 1.75)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use - <5 years since last use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.22 (0.92 to 1.62)	Not calculable	VERY LOW	CRITICAL
Past users, unknown duration of use - 5 years or more since last use												
1 (Baandrup 2022)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 0.9 (0.52 to 1.56)	Not calculable	VERY LOW	CRITICAL
Mortality												
Current users, by years of use - <10 years of use (follow-up 6.9 years)												
1 (Beral 2007)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.48 (1.20 to 1.83)	Not calculable	MODERATE	CRITICAL
Current users, by years of use - Unknown duration of use (follow-up 14 years)												
1 (Felix 2015)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	HR 1.24 (0.77 to 2)	Not calculable	VERY LOW	CRITICAL
Past users, <15 years since last use - <10 years duration of use (follow-up 14 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	No HRT	Relative (95% CI)	Absolute		
1 (Rodriguez 2001)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.17 (0.85 to 1.61)	Not calculable	VERY LOW	CRITICAL
Past users, <15 years since last use – 10+ years duration of use (follow-up 14 years)												
1 (Rodriguez 2001)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	RR 2.05 (1.29 to 3.26)	Not calculable	LOW	CRITICAL
Past users, 15 or more years since last use - <10 years duration of use (follow-up 14 years)												
1 (Rodriguez 2001)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	not reported	not reported	RR 1.07 (0.87 to 1.32)	Not calculable	VERY LOW	CRITICAL
Past users, 15 or more years since last use – 10+ years duration of use (follow-up 14 years)												
1 (Rodriguez 2001)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	not reported	not reported	RR 1.31 (0.79 to 2.17)	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; OR: odds ratio; RR: risk ratio
1 Very serious risk of bias in the evidence contributing to outcomes as per ROBINS-I
2 Study indirect as some women in the no hormone replacement group used hormone replacement therapy for less than a year
3 95% CI crosses 1 MID
4 Very serious risk of bias in the evidence contributing to the outcomes as per CASP or ROBINS-I
5 Beral 2007; Danforth 2007; Folsom 2004; Lacey 2002
6 Beral 2007; Folsom 2004; Hildebrand 2010; Lacey 2002; Trabert 2012
7 Serious risk of bias in the evidence contributing to outcomes as per CASP or ROBINS-I
8 Hildebrand 2010; Lacey 2002; Trabert 2012
9 Hildebrand 2010; Lacey 2002
10 Folsom 2004; Hildebrand 2010
11 95% CI crosses 2 MIDs
12 Beral 2007; Tsilidis 2011
13 Serious heterogeneity unexplained by subgroup analysis
14 Beral 2007; Morch 2009; Tsilidis 2011
15 CGESOC 2015; Koskela-Niska 2013
16 Very serious heterogeneity unexplained by subgroup analysis. Studies not meta-analysed due to heterogeneity
16 Beral 2007; Felix 2015

Appendix G Economic evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

Excluded effectiveness studies

Study	Reason
American Medical, Association (2002) Long-term use of estrogen-only hormone replacement therapy (HRT) linked with increased risk of ovarian cancer. Ginecologia y obstetricia de Mexico 70: 409-10	- Study design - not a systematic review, randomised controlled trial, or observational study
Bakken, Kjersti, Alsaker, Elin, Eggen, Anne Elise et al. (2004) Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. International journal of cancer 112(1): 130-4	- Cohort already included Included under CGESOC. This publication does not provide any additional outcomes or subgroup analysis.
Beral, Valerie; Banks, Emily; Reeves, Gillian (2002) Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet (London, England) 360(9337): 942-4	- Outcomes - reported outcomes do not match the review protocols
Besevic, Jelena, Gunter, Marc J, Fortner, Renee T et al. (2015) Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study. British journal of cancer 113(11): 1622-31	- Cohort already included EPIC cohort already included in the review. This publication does not provide additional information in terms of outcomes
Bhupathiraju, Shilpa N, Grodstein, Francine, Stampfer, Meir J et al. (2016) Exogenous Hormone Use: Oral Contraceptives, Postmenopausal Hormone Therapy, and Health Outcomes in the Nurses' Health Study. American journal of public health 106(9): 1631-7	- Cohort already included Narrative review of cohort that is already included in the review
Braem, M G M, Onland-Moret, N C, van den Brandt, P A et al. (2010) Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. American journal of epidemiology 172(10): 1181-9	- Intervention- oestrogen-only & combined HRT not reported separately
Brieger, Katharine K, Phung, Minh Tung, Mukherjee, Bhramar et al. (2022) High Prediagnosis Inflammation-Related Risk Score Associated with Decreased Ovarian Cancer Survival. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 31(2): 443-452	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Canchola, Alison J, Chang, Ellen T, Bernstein, Leslie et al. (2010) Body size and the risk of ovarian cancer by hormone therapy use in the California Teachers Study cohort. Cancer causes & control : CCC 21(12): 2241-8	- Intervention- oestrogen-only & combined HRT not reported separately
Chiaffarino, F, Pelucchi, C, Parazzini, F et al. (2001) Reproductive and hormonal factors and ovarian cancer. Annals of oncology : official	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias

Study	Reason
journal of the European Society for Medical Oncology 12(3): 337-41	
Garg, P P, Kerlikowske, K, Subak, L et al. (1998) Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. Obstetrics and gynecology 92(3): 472-9	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias Meta-analysis of studies that did not collect data on HRT before the outcome was know
Glud, Eva, Kjaer, Susanne K, Thomsen, Birthe L et al. (2004) Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. Archives of internal medicine 164(20): 2253-9	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Graff-Iversen, S, Hammar, N, Thelle, D S et al. (2004) Hormone therapy and mortality during a 14-year follow-up of 14 324 Norwegian women. Journal of internal medicine 256(5): 437-45	- Outcomes - reported outcomes do not match the review protocols
Greiser, Claudia M; Greiser, Eberhard M; Doren, Martina (2007) Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. Human reproduction update 13(5): 453-63	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias Systematic review - most included studies did not meet the study design criteria, or they have already been included in this review
Guidozzi, F (2013) Estrogen therapy in gynecological cancer survivors. Climacteric : the journal of the International Menopause Society 16(6): 611-7	- Study design - not a systematic review, randomised controlled trial, or observational study
Harris, Benjamin S, Bishop, Katherine C, Kuller, Jeffrey A et al. (2020) Hormonal management of menopausal symptoms in women with a history of gynecologic malignancy. Menopause (New York, N.Y.) 27(2): 243-248	- Study design - not a systematic review, randomised controlled trial, or observational study
Harris, Holly R, Guertin, Kristin A, Camacho, Tareq F et al. (2022) Racial disparities in epithelial ovarian cancer survival: An examination of contributing factors in the Ovarian Cancer in Women of African Ancestry consortium. International journal of cancer 151(8): 1228-1239	- Intervention- oestrogen-only & combined HRT not reported separately Comparator also not placebo or no HRT (different races compared to each other)
Holm, Marianne, Olsen, Anja, Kyro, Cecilie et al. (2018) The Influence of Menopausal Hormone Therapy and Potential Lifestyle Interactions in Female Cancer Development-a Population-Based Prospective Study. Hormones & cancer 9(4): 254-264	- Cohort already included Cancer cases from the Danish Cancer Registry. Years of case diagnosis covered in Baandrup 2022 therefore this publication is excluded to avoid overlap. No additional outcomes provided in this publication
Hopkins, M L, Fung, M Fung Kee, Le, T et al. (2004) Ovarian cancer patients and hormone replacement therapy: a systematic review. Gynecologic oncology 92(3): 827-32	- Population Systematic review where population of included studies are women with ovarian cancer
Jacobson, Michelle, Coakley, Nadia, Bernardini, Marcus et al. (2021) Risk reduction strategies for BRCA1/2 hereditary ovarian cancer syndromes: a clinical practice guideline. Hereditary cancer in clinical practice 19(1): 39	- Study design - not a systematic review, randomised controlled trial, or observational study
Khoja, Lilah, Weber, Rachel Palmieri, Australian Ovarian Cancer Study, Group et al. (2022) Endometriosis and menopausal hormone therapy impact the hysterectomy-ovarian cancer	- Outcomes - reported outcomes do not match the review protocols

Study	Reason
association. Gynecologic oncology 164(1): 195-201	
Koskela-Niska, V, Lyytinen, H, Riska, A et al. (2013) Ovarian cancer risk in postmenopausal women using estradiol-progestin therapy - a nationwide study. Climacteric : the journal of the International Menopause Society 16(1): 48-53	- Comparison - not placebo or no HRT HRT users were compared to expected number of cases in the population, and no appropriate adjustments made for confounding
Koskela-Niska, Virpi, Pukkala, Eero, Lyytinen, Heli et al. (2015) Postmenopausal hormone therapy-also use of estradiol plus levonorgestrel-intrauterine system is associated with an increased risk of primary fallopian tube carcinoma. International journal of cancer 137(8): 1947-52	- Outcomes - reported outcomes do not match the review protocols
Koskela-Niska, Virpi, Riska, Annika, Lyytinen, Heli et al. (2012) Primary fallopian tube carcinoma risk in users of postmenopausal hormone therapy in Finland. Gynecologic oncology 126(2): 241-4	- Outcomes - reported outcomes do not match the review protocols
Kotsopoulos, Joanne, Lubinski, Jan, Neuhausen, Susan L et al. (2006) Hormone replacement therapy and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Gynecologic oncology 100(1): 83-8	- Intervention- oestrogen-only & combined HRT not reported separately
Lacey Jr., J.V., Mink, P.J., Lubin, J.H. et al. (2003) Postmenopausal estrogen-only, but not estrogen + progestin, was associated with an increased risk of ovarian cancer. Evidence-based Obstetrics and Gynecology 5(1): 53-54	- Study design - not a systematic review, randomised controlled trial, or observational study Commentary on prospective cohort study already included
Lacey, James V Jr, Brinton, Louise A, Leitzmann, Michael F et al. (2006) Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. Journal of the National Cancer Institute 98(19): 1397-405	- Cohort already included More recent data on the same cohort has already been included in this review
Lee, Alice W, Ness, Roberta B, Roman, Lynda D et al. (2016) Association Between Menopausal Estrogen-Only Therapy and Ovarian Carcinoma Risk. Obstetrics and gynecology 127(5): 828-836	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Lee, Alice W, Wu, Anna H, Wiensch, Ashley et al. (2020) Estrogen Plus Progestin Hormone Therapy and Ovarian Cancer: A Complicated Relationship Explored. Epidemiology (Cambridge, Mass.) 31(3): 402-408	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Lete, I., Fiol, G., Nieto, L. et al. (2021) The use of menopausal hormone therapy in women survivors of gynecological cancer: Safety report based on systematic reviews and meta-analysis. European Journal of Gynaecological Oncology 42(5): 1058-1067	- Population Systematic review where included studies are women with a gynaecological cancer receiving hormone replacement therapy
Li, K, Husing, A, Fortner, R T et al. (2015) An epidemiologic risk prediction model for ovarian cancer in Europe: the EPIC study. British journal of cancer 112(7): 1257-65	- Intervention- oestrogen-only & combined HRT not reported separately

Study	Reason
Liu, Yang, Ma, Lan, Yang, Xiaoling et al. (2019) Menopausal Hormone Replacement Therapy and the Risk of Ovarian Cancer: A Meta-Analysis. Frontiers in endocrinology 10: 801	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias Systematic review - most studies do not meet the study design criteria. Relevant studies already included in the review
Manson, JoAnn E, Aragaki, Aaron K, Bassuk, Shari S et al. (2019) Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Annals of internal medicine 171(6): 406-414	- Outcomes - reported outcomes do not match the review protocols
Michaelson-Cohen, Rachel and Beller, Uziel (2009) Managing menopausal symptoms after gynecological cancer. Current opinion in oncology 21(5): 407-11	- Outcomes - reported outcomes do not match the review protocols
Mills, P.K., Riordan, D.G., Cress, R.D. et al. (2005) Hormone replacement therapy and invasive and borderline epithelial ovarian cancer risk. Cancer Detection and Prevention 29(2): 124-132	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Moorman, Patricia G, Schildkraut, Joellen M, Calingaert, Brian et al. (2005) Menopausal hormones and risk of ovarian cancer. American journal of obstetrics and gynecology 193(1): 76-82	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Morch, L.S. and Lidegaard, O. (2009) Hormone therapy use and risk of ovarian cancer: Reply. JAMA 302(20): 2204	- Study design - not a systematic review, randomised controlled trial, or observational study
Morch, Lina Steinrud, Lokkegaard, Ellen, Andreasen, Anne Helms et al. (2012) Hormone therapy and different ovarian cancers: a national cohort study. American journal of epidemiology 175(12): 1234-42	- Cohort already included Cohort is included in CGESOC, this publication does not provide any additional outcomes or subgroup analysis
Negri, E, Tzonou, A, Beral, V et al. (1999) Hormonal therapy for menopause and ovarian cancer in a collaborative re-analysis of European studies. International journal of cancer 80(6): 848-51	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Pearce, Celeste Leigh, Chung, Karine, Pike, Malcolm C et al. (2009) Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer 115(3): 531-9	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias Systematic review - most of the included studies do not meet the criteria due to study design. Relevant studies already included in the review
Pike, Malcolm C, Pearce, Celeste L, Peters, Ruth et al. (2004) Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. Fertility and sterility 82(1): 186-95	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Riman, Tomas, Dickman, Paul W, Nilsson, Staffan et al. (2002) Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. American journal of epidemiology 156(4): 363-73	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias

Study	Reason
Riman, Tomas, Dickman, Paul W, Nilsson, Staffan et al. (2002) Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. Journal of the National Cancer Institute 94(7): 497-504	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Risch, H A (1996) Estrogen replacement therapy and risk of epithelial ovarian cancer. Gynecologic oncology 63(2): 254-7	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Rodriguez, C, Calle, E E, Coates, R J et al. (1995) Estrogen replacement therapy and fatal ovarian cancer. American journal of epidemiology 141(9): 828-35	- Cohort already included More recent data from this cohort has already been included in this review
Saeaib, Nungrutai, Peeyananjarassri, Krantarat, Liabsuetrakul, Tippawan et al. (2020) Hormone replacement therapy after surgery for epithelial ovarian cancer. The Cochrane database of systematic reviews 1: cd012559	- Population Systematic review including women who have undergone surgery for ovarian cancer
Shapiro, Samuel, Stevenson, John C, Mueck, Alfred O et al. (2015) Misrepresentation of the risk of ovarian cancer among women using menopausal hormones. Spurious findings in a meta-analysis. Maturitas 81(2): 323-6	- Study design - not a systematic review, randomised controlled trial, or observational study
Shi, Li-feng; Wu, Yan; Li, Cai-yun (2016) Hormone therapy and risk of ovarian cancer in postmenopausal women: a systematic review and meta-analysis. Menopause (New York, N.Y.) 23(4): 417-24	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias Systematic review - most of the included studies are not relevant as HRT use was collected after cancer diagnosis, or cohort has already been included in the review
Simin, Johanna, Khodir, Habiba, Fornes, Romina et al. (2022) Association between menopausal hormone therapy use and mortality risk: a Swedish population-based matched cohort study. Acta oncologica (Stockholm, Sweden) 61(5): 632-640	- Outcomes - reported outcomes do not match the review protocols
Simin, Johanna, Tamimi, Rulla, Lagergren, Jesper et al. (2017) Menopausal hormone therapy and cancer risk: An overestimated risk?. European journal of cancer (Oxford, England : 1990) 84: 60-68	- Cohort already included Cohort already included in a more recent publication (Simin 2020)
Steinberg, Julia, Yap, Sarsha, Goldsbury, David et al. (2021) Large-scale systematic analysis of exposure to multiple cancer risk factors and the associations between exposure patterns and cancer incidence. Scientific reports 11(1): 2343	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Tavani, A, Ricci, E, La Vecchia, C et al. (2000) Influence of menstrual and reproductive factors on ovarian cancer risk in women with and without family history of breast or ovarian cancer. International journal of epidemiology 29(5): 799-802	- Study design - observational study: information on HRT use collected after the outcome was known and therefore subject to recall bias
Trabert, Britton, Brinton, Louise A, Anderson, Garnet L et al. (2016) Circulating Estrogens and Postmenopausal Ovarian Cancer Risk in the Women's Health Initiative Observational Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen Intervention compares circulating levels of hormone

Study	Reason
Cancer Research, cosponsored by the American Society of Preventive Oncology 25(4): 648-56	
Vickers, Madge R, Martin, Jeannett, Meade, Tom W et al. (2007) The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC women's health 7: 2	- Outcomes - reported outcomes do not match the review protocols

Excluded economic studies

No economic evidence was identified for this review. See Supplement 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

There are overarching research recommendations related to all health outcomes addressed in this guideline update (including ovarian cancer), for:

- trans-men and non-binary people registered female at birth who are not taking gender-affirming hormone therapy at the time of taking HRT or in the follow-up period
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

Appendix L Absolute risk tables and calculations

Absolute risk tables and calculations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing ovarian cancer?

Absolute risks were calculated according to age group. For certain subgroups (age at first use; constituent; mode of administration; histological type) it was not possible to calculate the absolute risks due to lack of information on their background risks.

Table 8: Summary of ovarian cancer cases with current use of combined HRT in people who, if they used it, started HRT at 50 (observational studies)

	50-54 years old
Number of ovarian cancer cases over a 5-year period per 1000 people who are not HRT users	1
Number of ovarian cancer cases over a 5-year period per 1000 people who are HRT users	2 (from 2 to 2)

Table 9: Summary of ovarian cancer cases with current use of oestrogen-only HRT in people who, if they used it, started HRT at 50 years old (observational studies)

	50-54 years old
Number of ovarian cancer cases over a 5-year period per 1000 people who are not HRT users	1
Number of ovarian cancer cases over a 5-year period per 1000 people who are HRT users	2 (from 2 to 2)

Calculations

Absolute risks for HRT users were calculated by applying the relevant risk ratios to the risk of ovarian cancer in never users.

The rate of ovarian cancer incidence in never users of HRT was calculated by solving the following formula:

Incidence among all women in a given age range = [proportion of women who are current users × (RRcurrent × β)] + [proportion of never users × β]

Where:

β = risk of ovarian cancer in never users

RRcurrent = The average ovarian cancer relative risk for HRT users versus never users [RR (current vs never users)] in the general population is taken from the risks in supplementary webfigure 3 in CGESOC 2015, which includes HRT users of oestrogen-only and combined HRT. This is given as RR 1.37.

The proportion of women using HRT in each age band is estimated using NHS HRT data on Hormone Replacement Therapy in 2017 and dividing by the ONS census population figures for women in that age band for 2017.

The ovarian cancer 5 year incidence for all women in each age band is taken from ONS ovarian cancer registration statistics for 2017.

See Supplement 19 for calculations.

Absolute risks using randomised controlled trial data

Table 10: Number of ovarian cancer cases with no use and current use of combined HRT in people who, if they used it, started HRT at 63 and used it for 6 years

	63-69 years old
Number of ovarian cancer cases over an approximate 6-year period per 1000 people who never used HRT	1
Number of ovarian cancer cases over an approximate 6-year period per 1000 people who started HRT at 63 and used for approximately 6 years	2 NS (from 1 to 3)

In Table 10, NS means that the difference between a figure for HRT users and the corresponding figure for non-HRT users is non-significant.