SUPPLEMENTARY DATA FOR A WEB APPENDIX

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Supplementary Data 1

Explanation of I^2

I^2 is derived from Cochran's Q with this formula (k=number of studies included into meta-analysis):

$$I^2 = \frac{\left(\frac{Q}{(k-1)}\right) - 1}{\frac{Q}{(k-1)}}$$

Several methods were proposed (Higgins *et al*., 2002) to calculate the 95% uncertainty interval, a parameter comparable to confidence intervals of epidemiological risk parameters. We applied method III proposed (Higgins *et al*., 2002), based on the statistical significance of Q and using formula 26.4.36 (Abramowitz and Stegun, 1965) to calculate the variance of the uncertainty interval I^2. There are two different formulas to derive at the standard error (SE) of Q/(k-1), dependent on the magnitude of Q. If Q>k then

$$\ln(SE) = 0.5 \quad \frac{\ln(Q) - \ln(k-1)}{\sqrt{2Q} - \sqrt{(2k-3)}}$$

whereas if Q<= k, then

$$\ln(SE) = \sqrt{\left(\frac{1}{2(k-2)} * \left(1 - \frac{1}{3(k-2)^2}\right)\right)}$$

The latter formula obviously does not allow the estimation of the standard error, if there are two studies only. There is still no generally accepted cut point for I^2, above which heterogeneity should be assumed. Higgins and co-authors (2003) discussed tentative values of 25%, 50% and 75% for low, moderate and high amount of heterogeneity, respectively. An I^2 value of 0 indicates lack of heterogeneity. In case heterogeneity is detected by a fixed-effects model, it is not recommended (Petitti, 2000) to control for heterogeneity by a random-effects model. Therefore we restricted our analyses to fixed-effects models.

Use of fixed models [general variance-based method (Petitti, 2000)].

This method uses published confidence intervals to calculate the variance for each risk parameter. To derive variances and study weights from published confidence intervals we applied the following formula: Variance = ((log(RR/CIL)/1.96)**2, where RR = risk parameter (relative risk or odds ratio), CIL = lower bound of confidence interval of risk parameter, and Weight = 1/variance

Higgins JPT and Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Statist Med 21,1539-1558.
Abramowitz M and Stegun IA (1965) Handbook of mathematical functions with formulas, graphs, and mathematical tables. Dover Publications, New York.
Higgins JPT, Thompson SG, Deeks JJ and Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327,557-560.
Petitti DB (2000) Statistical methods in meta-analysis. In Pettiti DB, (ed). Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis, 2nd edn. Oxford University Press, New York, pp. 63-67, 111-113.

Supplementary Table I. Excluded studies

Author (s)	Year of publication	Type of Study	Reasons for exclusion
Adami et al.	1989	Cohort	Same cohort as study by Persson *et al*., 1996; shorter follow-up
Annegers et al.	1977	CC	More recent study (Annegers *et al*., 1979) included
Arslan et al.	2003	CC	No analysis of MHT (confounder variable)
Bertone et al	2001	Cohort	No analysis of MHT (confounder variable)
Bibbo et al.	1978	Cohort	Use of DES only
Biesma et al.	2006	Cohort	No analysis of MHT (confounder variable)
Braaten et al.	2005	Cohort	No analysis of MHT for ovarian cancer
Cunat et al.	2004	Experimental	No suitable study type
Dinger et al.	2006	Cohort	No incident cancer data
Eltabbakh et al.	1999	Case study	No suitable study type, comparison of two groups
Eltabbakh et al.	1998	Case study	Same reason as above
Fairfield et al.	2002	Cohort	No analysis of MHT (confounder variable)
Fairfield et al.	2004	Cohort	No analysis of MHT (confounder variable)
Franceschi et al.	1982	CC	No risk estimate provided
Gnagy et al.	2000	Ecologic study	Statistics provided unsuitable for pooling
Goodman et al.	2003	Cancer registry	Descriptive data only
Goodman et al.	2001	CC	Analysis of genetic polymorphisms
Grodstein et al.	1997	Cohort	RR without confidence interval provided
Hadjimichael et al.	1984	Cohort	Results refer to DES

Hannan et al.	2004	Cohort	No analysis of MHT (confounder variable)
Harlow et al.	1988	CC	OR without CI
Herrinton et al.	2001	CC	Same study as Lee *et al*., 1986
Hoover et al.	1977	Cohort	Use of DES only
Hunt et al.	1990	Cohort	Analysis for ovarian and tuboovarian carcinomas combined
Kelemen et al.	2004	Cohort	No analysis of MHT (confounder variable)
Komulainen et al.	1999	RCT	No RR for MHT provided
Larsson et al.	2004	Cohort	No analysis of MHT (confounder variable)
McGowan et al.	1988	CC	Identical study (Hartge *et al*., 1988) included providing more detailed analyses
Mink et al.	1996	Cohort	Same cohort as Folsom *et al*., 2004; shorter follow-up
Moorhead et al.	1997	Nested CC	Time sequence of HT and incident disease undetermined
Mosekilde et al.	2000	RCT	Allocation of ovarian cancer cases impossible as assignment of cancer cases to exact treatment groups in randomized and non-randomized substrata unclear
Ness et al.	2000	CC	No analysis of MHT (confounder variable)
Niwa et al.	2005	Cohort	No ovarian cancer case in MHT group
Purdie et al.	1995	CC	Later publication included (Purdie *et al*., 1999) with more detailed analyses
Purdie et al.	1996	CC	Same reason as above
Riman	2003	CC	Full publications of the same study (Riman *et al*., 2002a; Riman *et al*., 2002b) included
Rodriguez	1995	Cohort	Same cohort as Rodriguez *et al*., 2001; shorter follow-up
Rodriguez	2002	Cohort	Impact of ET on OvC risk analyses dependent on BMI and body height
Rossing et al.	1994	Cohort	only use of fertility drugs reported
Schairer et al.	1997	Cohort	Same cohort as Persson *et al*., 1996;, shorter follow-up
Schouten et al.	2003	Cohort	No analysis of MHT (confounder variable)
Schouten et al.	2004	Cohort	No analysis of MHT (confounder variable)
Tavani et al.	2000	CC	Overlap with included study (Parazzini *et al*., 1994)
Tung et al.	2005	CC	Included study (Tung *et al*., 2003) provided more extractable details of same study population

Tzonou et al.	1984	CC	RR provided, but no CI, study as published excluded; data set published later in a re-analysis included, see Table 1 (footnote to Negri *et al*., 1999)
Vessey et al.	1983	RCT	Use of DES only
West	1966	CC	no analysis of MHT
Wynder et al.	1969	CC	Unspecified female hormone therapy reported
Zhang et al.	2005	CC	No analysis of MHT (confounder variable)

Abbreviations: CC= case-control study; MHT= menopausal hormone therapy; DES=diethylstilbestrol; RR= relative risk; OR = odds ration; CI = confidence interval; RCT = randomized controlled trial; OvC = ovarian cancer; BMI = body mass index.

*Narrative reviews primarily excluded

Supplementary Table II. Summary estimates of risks in 3 hormone therapy groups (ever-use), stratified for histological subtypes

Hormone therapy	Histology	Data sets (no.)	OR / RR (95% CI)	Cochrane Q value	p	I^2 (95% uncertainty interval)
EPT	ALL	3	1.119 (0.962 to 1.301)	1.5	0.465	0.0 (0.0 to 78.0)
EPT	END	2	1.332 (0.911 to 1.948)	0.2	0.627	0.0 (-)
EPT	EPI	14	1.107 (0.975 to 1.256)	12.9	0.454	0.0 (0.0 to 49.0)
EPT	MUC	5	0.834 (0.530 to 1.315)	2.2	0.705	0.0 (0.0 to 68.6)
EPT	OTH	2	0.558 (0.321 to 0.970)	2.4	0.118	59.1 (0.0 to 80.9)
EPT	SER	5	1.231 (0.988 to 1.535)	6.9	0.139	42.4 (0.0 to69.7)
ET	ALL	3	1.194 (0.780 to 1.829)	0.5	0.776	0.0 (0.0 to 78.0)
ET	END	2	1.808 (1.080 to 3.027)	1.1	0.294	9.2 (-)
ET	EPI	18	1.163 (1.034 to 1.307)	45.3	0.000	62.5 (47.3 to 71.9)
ET	MUC	6	1.203 (0.810 to 1.785)	6.0	0.303	17.2 (0.0 to 54.8)
ET	OTH	13	1.440 (1.164 to 1.781)	24.3	0.019	50.6 (18.0 to 67.0)
ET	SER	6	1.525 (1.245 to 1.868)	4.5	0.481	0.0 (0.0 to 64.8)
MHT	ALL	11	0.964 (0.899 to 1.034)	40.8	0.000	75.5 (66.4 to 81.3)
MHT	CLE	5	1.290 (0.834 to 1.994)	3.4	0.490	0.0 (0.0 to 68.6)
MHT	END	7	0.982 (0.799 to 1.208)	25.5	0.000	76.5 (65.0 to 83.1)
MHT	EPI	28	1.089 (1.008 to 1.175)	72.3	0.000	62.7 (51.3 to 70.5)
MHT	MUC	7	0.816 (0.608 to 1.096)	7.0	0.319	14.6 (0.0 to 51.7)
MHT	OTH	6	0.943 (0.792 to 1.123)	6.0	0.306	16.6 (0.0 to 68.5)
MHT	SER	8	1.181 (1.017 to 1.371)	21.1	0.004	66.8 (46.1 to 77.5)
PRO	EPI	5	1.341 (0.842 to 2.136)	6.3	0.175	36.9 (0.0 to 67.4)

Abbreviations: EPT = Estrogen progestin therapy; ET = unopposed estrogen therapy; MHT = combination of all
regimens of menopausal hormone therapy, including unspecified / unknown preparations; PRO = progestin therapy;
OR = odds ratio; CI = confidence interval; ALL = all histological classifications combined or histology not specified; CLE = clear cell carcinoma
END = endometrioid carcinoma; EPI = epithelial carcinoma; MUC = mucinous carcinoma; OTH = other malignancies or unspecified other malignancies; SER = serous carcinoma;.

Supplementary Table III. Summary estimates of risk increases per year in 3 hormone therapy groups,
stratified by histological subtypes

Hormone therapy	Histology	Data sets (no.)	OR / RR (95% CI)	Cochrane Q value	p	I^2 (95% uncertainty interval)
EPT	ALL	2	0.965 (0.891 to 1.045)	0.73	0.393	0.0 (-)
EPT	END	3	1.079 (1.004 to 1.160)	1.12	0.572	0.0 (0.0 to 78.0)
EPT	EPI	7	1.032 (1.001 to 1.065)	5.05	0.538	0.0 (0.0 to 61.7)
EPT	MUC	4	1.027 (0.894 to 1.180)	3.19	0.363	5.9 (0.0 to 74.2)
EPT	OTH	1	1.020 (0.910 to 1.143)	-	-	-
EPT	SER	5	1.074 (1.023 to 1.127)	2.73	0.604	0.0 (0.0 to 68.6)
ET	ALL	3	1.064 (0.994 to 1.138)	0.47	0.791	0.0 (0.0 to- 78.0)
ET	END	2	1.096 (1.073 to 1.119)	0.01	0.906	0.0 (-).
ET	EPI	6	1.052 (1.035 to 1.069)	4.58	0.470	0.0 (0.0 to 64.8)
ET	MUC	3	1.112 (0.943 to 1.312)	4.24	0.120	52.8 (0.0 to 76.9)
ET	OTH	1	1.060 (1.010 to 1.112)	-	-	-
ET	SER	3	1.065 (1.024 to 1.108)	2.81	0.246	28.7 (0.0 to 81.4)
HT	ALL	2	1.071 (1.039 to 1.103)	5.02	0.025	80.1 (56.2 to 88.7)
HT	CLE	1	1.005 (0.683 to 1.478)	-	-	-
MHT	END	8	1.053 (1.028 to 1.078)	15.76	0.027	55.6 (18.0 to 72.2)
MHT	EPI	16	1.025 (1.013 to 1.037)	40.37	0.000	62.8 (46.8 to 72.6)
MHT	MUC	13	0.987 (0.948 to 1.027)	9.09	0.695	0.0 (0.0 to 50.2)
MHT	OTH	8	1.043 (1.021 to 1.065)	5.33	0.620	0.0 (0.0 to 59.1)
MHT	SER	12	1.040 (1.025 to 1.056)	12.27	0.344	10.3 (0.0 to 44.7)

Abbreviations: EPT = Estrogen progestin therapy; ET = unopposed estrogen therapy; MHT = combination of all
regimens of menopausal hormone therapy, including unspecified / unknown preparations; OR = odds ratio; CI =
confidence interval; ALL = all histological classifications combined or histology not specified; CLE = clear cell carcinoma; END = endometrioid
carcinoma; EPI = epithelial carcinoma; MUC = mucinous carcinoma; OTH = other malignancies or unspecified
other malignancies; SER = serous carcinoma.

Supplementary data 2

References of excluded studies

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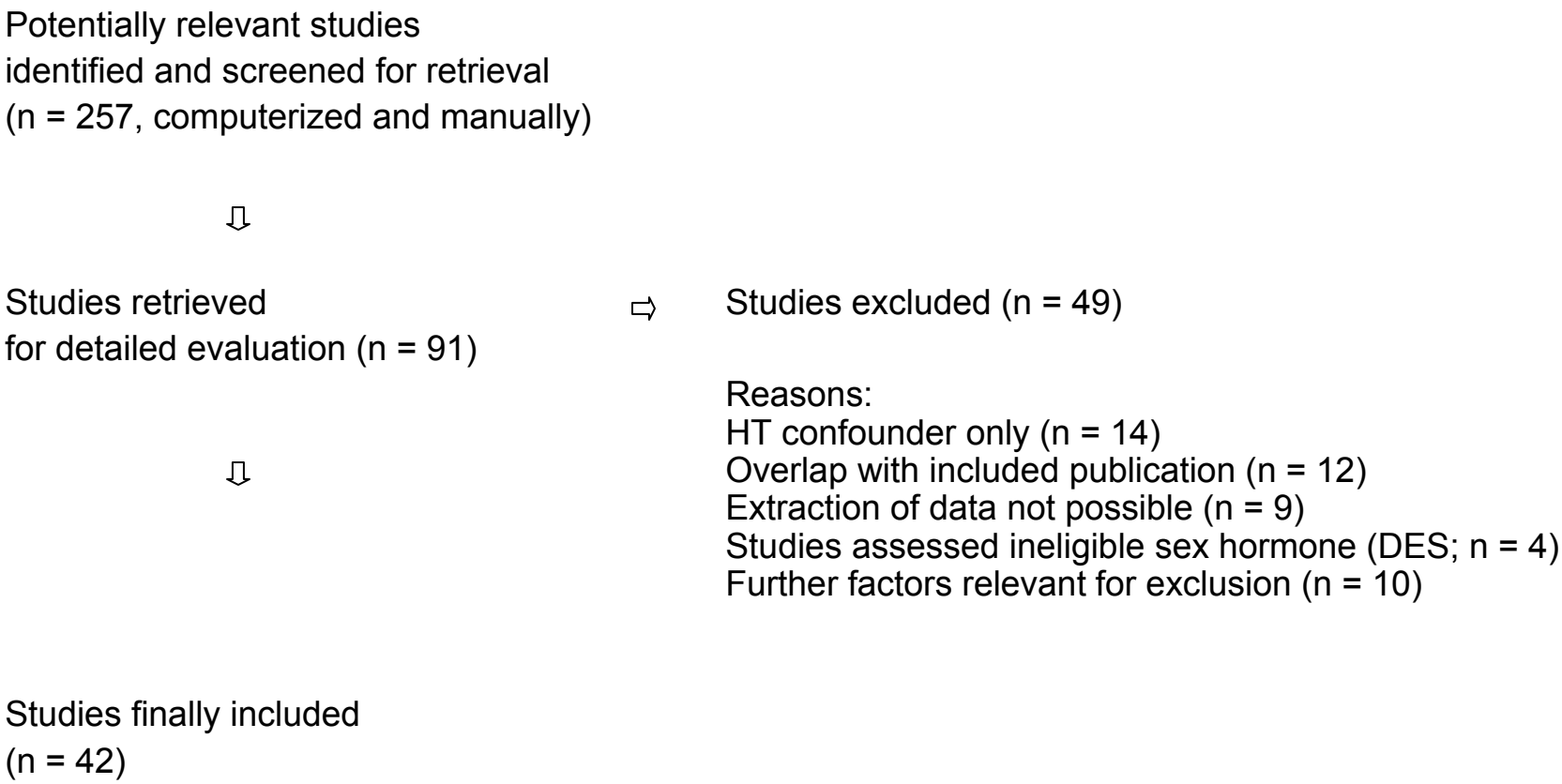
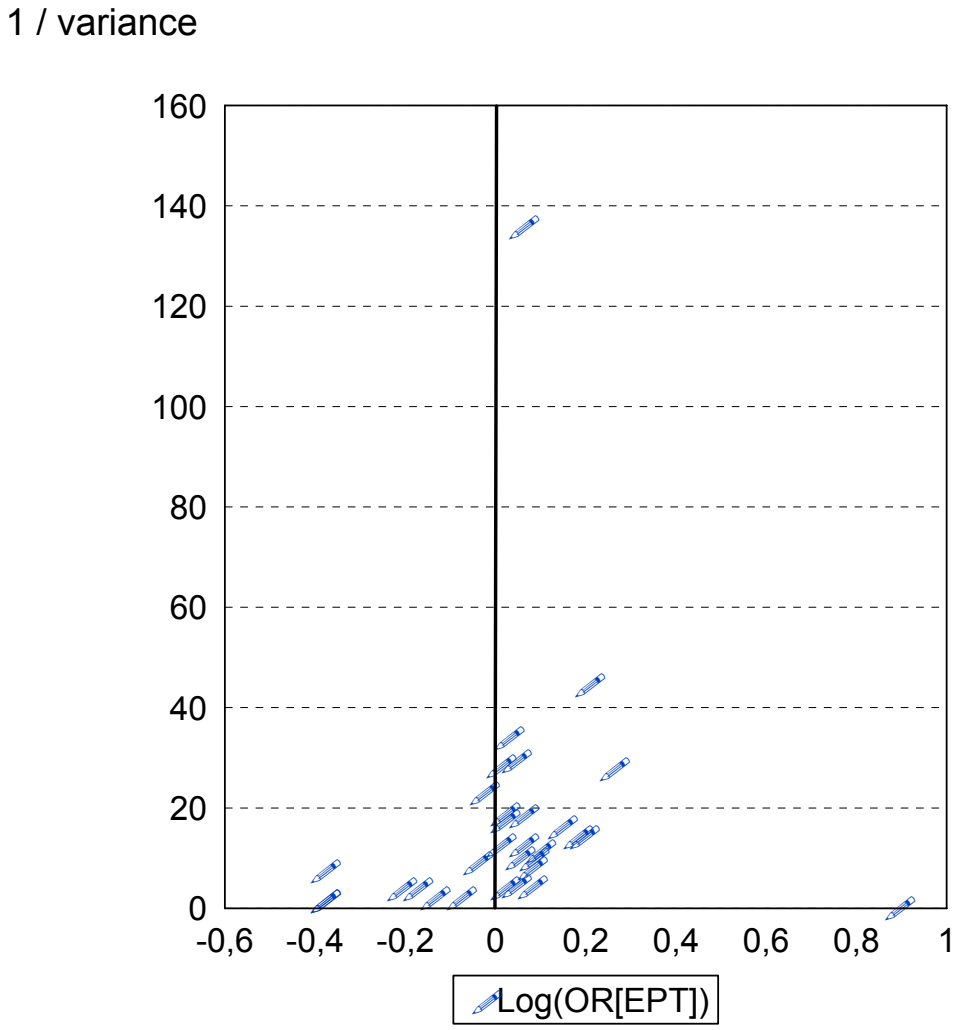


Supplementary Figure 1. Process of identification of eligible studies for meta-analyses



Supplementary Figure 2. Funnel plot: asymmetry of estrogen plus progestin therapy studies (EPT) reporting decreased and increased odds ratios (OR) for ovarian cancer risks