

3.1.4 OTHER HEALTH RISKS

Breast cancer

Summary

Women without previous breast cancer:

Evidence from high quality systematic reviews, updated with recent randomised controlled trials and observational studies confirms an increased risk of breast cancer with HRT use. However, it is important to recognise that the observed effect in both RCT and observational studies relies heavily upon data from women who are older and/or who have been taking HRT for a longer duration. In contrast, there was no apparent increase in risk amongst HRT-naïve women exposed to a shorter duration of HRT use. It is not possible to precisely determine the duration of therapy after which risk is elevated, but greater than 2–5 years appears to be associated with significantly increased risk.

The currently available evidence suggests that the risk of breast cancer may diminish as time passes after the cessation of HRT use.

There is some suggestion that the magnitude of the risk increase may be more pronounced with combined oestrogen/progestogen therapy than oestrogen alone, however it is important to bear in mind the differing populations receiving the different types of HRT. This may independently influence this finding.

The magnitude of any increased risk should be considered in the context of the absolute risk of breast cancer in this population.

Women with previous breast cancer:

Evidence summarised in a recent systematic review indicated no increase in breast cancer recurrence with HRT use, but a reduction in breast cancer mortality. As this evidence is primarily from observational studies, healthy user bias and in particular more regular medical follow-up of the women receiving HRT, may have confounded the results. Furthermore, the evidence is primarily from women with less severe previous breast cancer and therefore it is not clear if the results are generalisable to all women with previous breast cancer.

The following section presents the current evidence relating to the association between use of HRT and breast cancer incidence and breast cancer-related mortality. The results are presented separately for two populations of women: women who have not had prior breast cancer and women who have had prior breast cancer.

Women without prior breast cancer

Existing systematic reviews

Overall, six existing systematic reviews were identified: one systematic review of RCTs (level I evidence) and five systematic reviews of observational studies (level III-2 evidence). The characteristics and quality of the included systematic reviews are summarised in Table 64. For further details see Appendix B (Section 9.1.4).

TABLE 64 HRT: BREAST CANCER (NO PRIOR BREAST CANCER) — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Hemminki & McPherson (1997)	Systematic review of RCTs (9) Poor	Postmenopausal women	HRT Any administration Any dose	Placebo, no therapy or vitamins and mineral	Incidence
Level III-2 evidence					
Humphrey (2002)	Systematic review of observational studies (31) Good	Postmenopausal women	HRT Administration and dose not specified	Not specified but assumed to be no therapy	Incidence Mortality
Nanda <i>et al.</i> (2002)	Systematic review of observational studies (10) Good	Postmenopausal women	HRT Administration and dose not specified	No HRT	Mortality
Bush <i>et al.</i> (2001)	Systematic review of observational studies (54 publications) Poor	Postmenopausal women	HRT Administration and dose not specified	No HRT	Incidence Mortality
Beral <i>et al.</i> (1997)	Reanalysis of observational studies (51) Fair	Postmenopausal women 51 studies	HRT Administration and dose not specified	Not specified but assumed to be no therapy	Incidence
Sillero-Arenas <i>et al.</i> (1992)	Systematic review of observational studies (37) Good	Postmenopausal women	HRT Administration and dose not specified	No HRT	Incidence

See Section 9.1.4.

Abbreviations: RCT, randomised controlled trial.

The systematic review of RCTs (Hemminki & McPherson, 1997) was deemed to be a poor quality review due to the fact that a very limited literature search was performed, there was no formal attempt to assess the quality of each of the included studies and very little information regarding the characteristics of each included study was given. In addition, data regarding breast cancer outcomes was reported only incidentally in each of the included studies and was not a primary focus. Therefore, there is the potential for significant bias in this review and it will not be considered further.

Of the five systematic reviews which included results predominantly from observational studies, the most recent of these by Humphrey (2002) and Nanda *et al.* (2002) are of high methodologic quality (see Appendix B). Other reviews include a good quality meta-analysis from Sillero-Arenas *et al.* (1992) and a study from Bush *et al.* (2001) considered to be of poor quality due to a lack of quality assessment of included studies and insufficient detail regarding each included study. The Bush review (2002) is not considered further. Finally a collaborative reanalysis of data from observational studies was published by Beral *et al.* (1997). Although somewhat different to a classic systematic review it was the first study to draw significant attention to the increased risk of breast cancer associated with long-term HRT use and is considered to be of fair methodological quality.

The main results of each of the systematic reviews of observational studies are summarised in Table 65. While the results of the many studies included in each of the systematic reviews were somewhat variable, all systematic reviews concluded that the use of HRT, particularly for a long duration, is associated with an increased incidence of breast cancer. Paradoxically, the reviews that examined the association between breast cancer mortality and HRT suggest that the risk of death due to breast cancer is reduced in women who use HRT. However, it should be noted that the healthy user and surveillance biases associated with observational studies may have influenced to this result.

TABLE 65 HRT: BREAST CANCER (NO PRIOR BREAST CANCER) — RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Number of included studies	Results and conclusion
Level III-2 evidence		
Humphrey (2002)	31 (8 meta-analyses, 10 cohorts, 1 nested case-control and 12 case-controls)	<p>Incidence</p> <p>The authors note the inconsistency between the results of different studies. However, among the studies showing an increased risk, it is mostly seen in relation to current and long-term use. They also suggest that combined therapy may result in greater risk compared with oestrogen therapy.</p> <p>Mortality</p> <p>Of the six studies evaluating the association between HRT and breast cancer mortality, one showed an increased risk, four showed a decreased risk and one showed no association. The authors conclude that a reduction in breast cancer mortality in HRT users is a fairly consistent finding; however this may be a result of selection bias.</p>
Nanda et al. (2002)	10 studies (9 cohorts and 1 nested case-control)	<p>Mortality</p> <p>Relative risks of mortality due to breast cancer ranged from 0.40 to 1.89 with most studies showing a 20-30% risk reduction. Two studies showed a statistically significant decrease in risk, while two studies showed an increased risk which was not statistically significant. The authors state that the evidence suggests a decreased risk, however this may be due to bias associated with observational studies or may reflect a real difference in the biology of tumours between HRT users and non-users.</p>
Beral et al. (1997)	51 studies (case-control and cohort analysed as nested case-control)	<p>Incidence</p> <p>The relative risk of breast cancer in ever-users versus never-users was 1.14 (SE 0.031). When analyses were carried out by study type, the risk was increased but non-significant for cohort studies (RR 1.04; SE 0.047) and significant for case-control studies (RR 1.27; SE 0.091). Analyses were also performed based on duration of use and time since last use and the authors concluded that while risk of breast cancer was higher among HRT users, the risk increased with increasing duration of use. After HRT use ceased, the risk decreased and was negligible after 5 years.</p>
Sillero-Arenas et al. (1992)	37 studies (1 RCT, 13 cohorts and 23 case-controls)	<p>Incidence</p> <p>The authors performed a formal meta-analysis and found that the overall RR of developing breast cancer associated with HRT was 1.06 (1.00, 1.12). The result remained significant for women undergoing natural menopause (RR 1.13; 1.04, 1.22) but was not for women undergoing surgical menopause or hysterectomy/single oophorectomy. Other factors significantly associated with breast cancer were longer-term therapy (> 12 years), shorter time since menopause and the use of conjugated oestrogens alone. The authors conclude that "hormone replacement therapy could promote breast cancer".</p>

Abbreviations: RCT, randomised controlled trial; RR, relative risk; SE, standard error.

Original studies

There is extensive evidence regarding the association between HRT and breast cancer incidence and mortality in the two most recent, good quality reviews. These reviews included studies published up to 2000 (Humphrey, 2002; Nanda *et al.* 2002). Therefore, a search for original studies was conducted for the years 2000-2003 to update the evidence provided by the systematic reviews.

The search identified two RCTs: the Women's Health Initiative (WHI) study (Rossouw *et al.*, 2002; Chlebowski *et al.* 2003) and the Heart and Estrogen/progestin Replacement Study (HERS: Hulley *et al.*, 1998; Hulley *et al.*, 2002)). Both were considered to be good quality, albeit conducted in older women than those for whom HRT is likely to be initiated in Australia.

In addition there were four cohort studies (De Lignieres *et al.*, 2002; Olsson *et al.*, 2001; Olsson *et al.*, 2003; Porch *et al.*, 2002; Schairer *et al.*, 2000) and eight case-control studies (Chen *et al.*, 2002; Daling *et al.*, 2002; Fernandez *et al.*, 2003; Kirsh & Kreiger, 2002; Newcomb *et al.*, 2002; Newcomer *et al.*, 2003; Ratanawichitrasin *et al.*, 2002; Weiss *et al.*, 2002) which were of variable quality and considered to be level III-2 evidence. For details of the characteristics and quality of each of the included studies see Table 66. For further details see Appendix B (Section 9.1.4).

TABLE 66 HRT: BREAST CANCER (NO PRIOR BREAST CANCER) — ORIGINAL STUDIES

Study	Study details Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Rossouw <i>et al.</i> (2002); Chlebowski <i>et al.</i> (2003)	Double-blind RCT WHI Mean follow-up 5.2 years Good	Postmenopausal women aged 50-79 with intact uterus Mean age 63 15% FH of BC N=16608	EPRT Oral CEE and MPA 0.625 mg/2.5 mg daily N=8506	Placebo N=8102	Incidence Mortality
Hulley <i>et al.</i> (1998); Hulley <i>et al.</i> (2002)	Double-blind RCT HERS I with open-label follow-up HERS II Mean follow-up 6.8 years Good	Postmenopausal women aged < 80 with intact uterus and existing CVD Mean age 67 12% FH of BC N=2763	EPRT Oral CEE and MPA 0.625 mg/2.5 mg daily HERS I=1380 HERS II=1156	Placebo HERS I N=1383 HERS II=1165	Incidence Mortality
Level III-2 evidence					
De Lignieres <i>et al.</i> (2002)	Cohort Mean follow-up 8.9 years Poor	Postmenopausal or > 50 years Mean age 50 12% FH of BC N=3175	HRT Mode of administration and dose not specified N=1739	No HRT N=1436	Incidence
Porch <i>et al.</i> (2002)	Cohort Mean follow-up 5.9 years Good	Postmenopausal women Mean age ~58 6% FH of BC N=17835	HRT Not creams or preparations termed "other" Any dose N=11240	No HRT N=6595	Incidence
Olsson <i>et al.</i> (2001); Olsson <i>et al.</i> (2003)	Cohort Mean follow-up 8.5 years Good	Women aged 25-65 ^a Mean age unknown N=29508	HRT Mode of administration and dose not specified N=3270	No HRT N=26238	Incidence

Study	Study details Study quality	Population N	Intervention N	Comparator N	Outcomes
Schairer <i>et al.</i> (2000)	Cohort Mean follow-up 10.2 years Fair	Women peri or postmenopausal before or during study Mean age 58 years N=46355	HRT Mode of administration and dose not specified N=277021 py	No HRT N=196666 py	Incidence
Fernandez <i>et al.</i> (2003)	Case-control (hospital-based) Fair	Postmenopausal women 45-75 years N=11689	HRT Mode of administration and dose not specified N=896	No HRT N=10793	Incidence
Newcomer <i>et al.</i> (2003)	Case-control (population-based) Fair	Postmenopausal women 17% FH of BC < 75 years N=5812	HRT Oral, transdermal or injectable Any dose N=1643	No HRT N=4169	Incidence
Chen <i>et al.</i> (2002)	Nested case-control Good	Postmenopausal or > 55 years 44% FH of BC 50-74 years N=1597	HRT Oral Any dose N=883	No HRT N=514	Incidence
Daling <i>et al.</i> (2002); Weiss <i>et al.</i> (2002)	Case-control (population-based) Good	Postmenopausal or > 55 years 22% FH of BC 35-65 years N=3823	HRT Oral or transdermal Any dose N=2496	No HRT N=1327	Incidence
Kirsh & Kreiger (2002)	Case-control (population-based) Good	Postmenopausal women 9% FH of BC 20-74 years N=807	HRT Oral or injectable Any dose N=252	No HRT N=555	Incidence
Newcomb <i>et al.</i> (2002)	Case-control (population-based) Good	Postmenopausal women 0.6% FH of BC 50-79 years N=10869	HRT Oral or transdermal Any dose N=2910	No HRT N=7959	Incidence
Ratanawichitrasin (2002)	Case-control (hospital-based) Poor	Thai women aged > 50 years 37% FH of BC Mean age ~ 62 N=1913	HRT Mode of administration and dose not specified N=669	Never-use HRT N=1244	Incidence

See Section 9.1.4.

Abbreviations: BC, breast cancer; CEE, conjugated equine oestrogen; FH, family history; HERS, Heart and Estrogen/progestin Replacement Study; HRT, hormone replacement therapy; MPA, medroxyprogesterone acetate; py, person-years; WHI, Women's Health Initiative.

a A sub-analysis was performed on women who had undergone natural menopause and it is these results which were included in the following section.

As a considerable body of evidence is available for ERT and EPRT, the results are presented below by HRT type. It should be noted that two studies were considered to be of poor methodological quality and therefore will be excluded from analysis in this review. The cohort study by De Lignieres *et al.* (2003) was considered to be of poor methodological quality due to the substantial risk of misclassification due to inconsistent data ascertainment, and poor and inconsistent adjustment for potential confounders. The case-control study by Ratanawichitrasin *et al.* (2002) was considered to be of poor methodological quality due to a high risk of selection bias (only 33% of potential cases were included in the analysis for reasons that are not given, and the cases and controls were recruited during different time frames). There was a further risk of bias due to the case and control groups being interviewed by different hospital personnel (surgeons vs others respectively).

Effect by HRT type: oestrogen only

Eight original studies published since 2000 were identified that examined the association between ERT and breast cancer risk and mortality. All were considered level III-2 evidence; three were cohort studies and five were case-control studies. There were no RCTs available for this analysis.

Ever-use versus never-use

Six observational studies provided data regarding the association between the ever-use of ERT and breast cancer risk. While five studies showed no increased risk, the study by Newcomb *et al.* (2002) showed a statistically significant increased risk of 23%. These results are summarised in Table 67 and Figure 22.

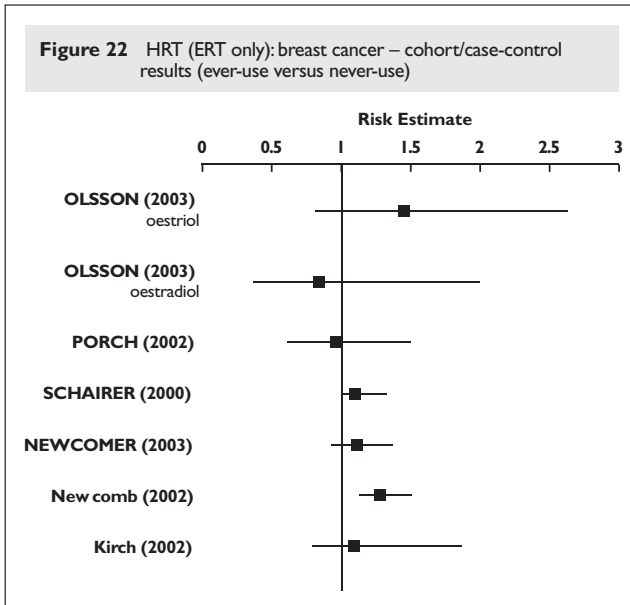
TABLE 67 HRT (ERT ONLY): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (EVER-USE VERSUS NEVER-USE)

Study	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of risk measure	Risk estimate
Olsson (2003) a oestriol	Cohort	15/475	153/6707	HR	1.45 (0.80, 2.63)
Olsson (2003) a oestradiol	Cohort	10/382	153/6707	HR	0.81 (0.34, 1.96)
Porch (2002)	Cohort	101/33370 py	146/38762 py	RR	0.96 (0.65, 1.42)
Schairer (2000)	Cohort	805/179401 py	761/196666 py	RR	1.1 (1.0, 1.3)
Newcomer (2003)	Case-control	415/534	1875/2294	OR	1.1 (0.9, 1.3)
Newcomb (2002)	Case-control	1007/1027	3827/4132	RR	<i>1.23 (1.09, 1.39)</i>
Kirsch (2002)	Case-control	75/76	272/283	OR	1.08 (0.7, 1.69)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; OR, odds ratio; py, person-years; RR, risk ratio.

^a Includes only women who had undergone natural menopause.



The effect of ERT upon breast cancer was not consistent across studies, even though two of the studies showed a significant effect. This is somewhat consistent with the Humphrey review which suggests that the magnitude of the risk increase may not be as pronounced with ERT as it appears to be with EPRT. However, it is important to remember that ERT is predominantly given to hysterectomised women whilst combined therapy is given to woman with an intact uterus, and therefore a direct comparison may not be appropriate.

Duration of ever-use of therapy

Five studies provided evidence regarding the effect of the duration of ERT therapy on breast cancer risk, with durations ranging from < 1 year to ≥ 10 years. Risk estimates were non-significant with the exception being that shown for ≥ 5 years by Newcomb *et al.* (2002) where a 36% greater risk was seen. These results are shown in Table 68 and Figure 23.

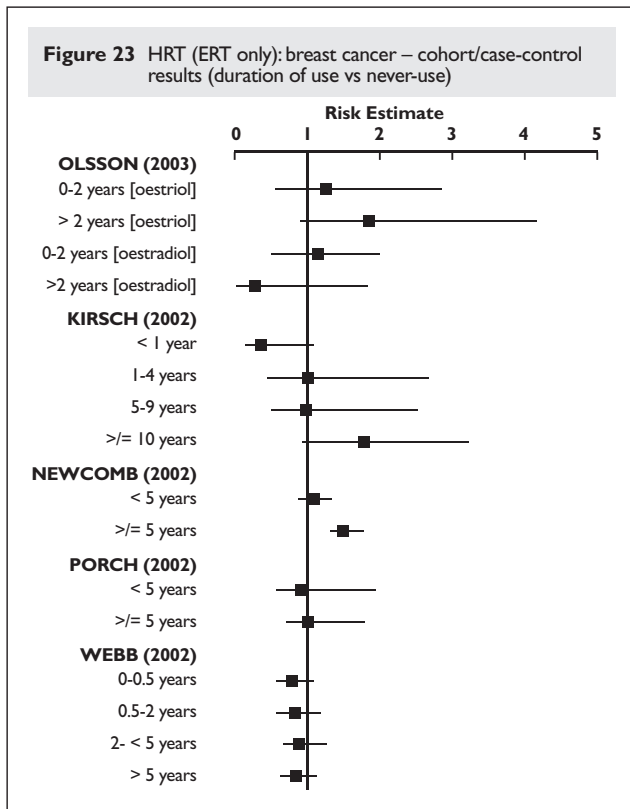
TABLE 68 HRT (ERT ONLY): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (DURATION OF USE VS NEVER-USE)

Author	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of measure	Risk estimate
<i>Olsson (2003)</i> ^a					
0-2 years (oestriol)	Cohort	8/290	153/6707	HR	1.26 (0.56, 2.86)
> 2 years (oestriol)	Cohort	7/185	153/6707	HR	1.89 (0.81, 4.39)
0-2 years (oestradiol)	Cohort	8/245	153/6707	HR	1.11 (0.41, 2.98)
> 2 years (oestradiol)	Cohort	2/137	153/6707	HR	0.35 (0.07, 1.86)
<i>Kirsch (2002)</i>					
< 1 year	Case-control	7/10	272/283	OR	0.34 (0.11, 1.10)
1-4 years	Case-control	11/13	272/283	OR	0.99 (0.4, 2.46)
5-9 years	Case-control	14/18	272/283	OR	1.0 (0.44, 2.24)
≥ 10 years	Case-control	39/28	272/283	OR	1.74 (0.93, 3.24)
<i>Newcomb (2002)</i>					
< 5 years	Case-control	402/409	3827/4132	RR	1.08 (0.92, 1.27)
≥ 5 years	Case-control	605/578	3827/4132	RR	1.36 (1.17, 1.58)
<i>Porch (2002)</i>					
< 5 years	Cohort	33/10963 py	146/38762 py	RR	0.96 (0.58, 1.58)
≥ 5 years	Cohort	68/22155 py	146/38762 py	RR	0.99 (0.65, 1.53)
<i>Weiss (2002)</i>					
0-0.5 years	Case-control	113/141	672/655	OR	0.83 (0.63, 1.10)
0.5-2 years	Case-control	110/137	672/655	OR	0.85 (0.63, 1.14)
2-5 years	Case-control	131/165	672/655	OR	0.88 (0.66, 1.17)
> 5 years	Case-control	353/439	672/655	OR	0.84 (0.66, 1.06)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; nr, not reported; OR, odds ratio; py, person-years; RR, risk ratio.

^a Includes only women who had undergone natural menopause.



Current-use and duration of current-use

Five studies provided data regarding the association between current-use of ERT and risk of developing breast cancer (see Table 69 and Figure 22). One of the four studies showed a significantly increased risk of breast cancer associated with current-use of ERT with an increased risk of 25% (Newcomb *et al.*, 2002). In addition, Newcomb *et al.* (2002) showed that current-use of HRT for five or more years increased the risk of developing breast cancer by 34%.

TABLE 69 HRT (ERT ONLY): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (CURRENT-USE AND DURATION OF CURRENT-USE VS NEVER-USE)

Author	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of measure	Risk estimate
<i>Newcomer (2003)</i>					
Current ^a	Case-control	166/230	1875/2294	OR	0.9 (0.7, 1.2)
<i>Newcomb (2002)</i>					
Current ^b	Case-control	600/641	3827/4132	RR	1.25 (1.08, 1.45)
< 5 years duration	Case-control	157/192	3827/4132	RR	1.07 (0.84, 1.37)
≥ 5 years duration	Case-control	443/449	3827/4132	RR	1.34 (1.12, 1.59)
<i>Weiss (2002)</i>					
Current ^c	Case-control	450/577	672/655	OR	0.84 (0.67, 1.06)
0 - < 0.5 years duration	Case-control	22/32	672/655	OR	0.79 (0.45, 1.40)
0.5 - < 2 years duration	Case-control	47/63	672/655	OR	0.86 (0.56, 1.31)
2 - < 5 years duration	Case-control	88/100	672/655	OR	1.01 (0.71, 1.43)
≥ 5 years duration	Case-control	292/381	672/655	OR	0.81 (0.63, 1.04)
<i>Chen (2000)</i>					
Current ^d	Case-control	132/111	243/271	OR	1.17 (0.85, 1.60)
<i>Schairer (2000)</i>					
Current ^e	Cohort	243/55008 py	761/196666 py	RR	1.1 (1.0, 1.3)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HRT, hormone replacement therapy; nr, not reported; OR, odds ratio; py, person-years; RR, risk ratio.

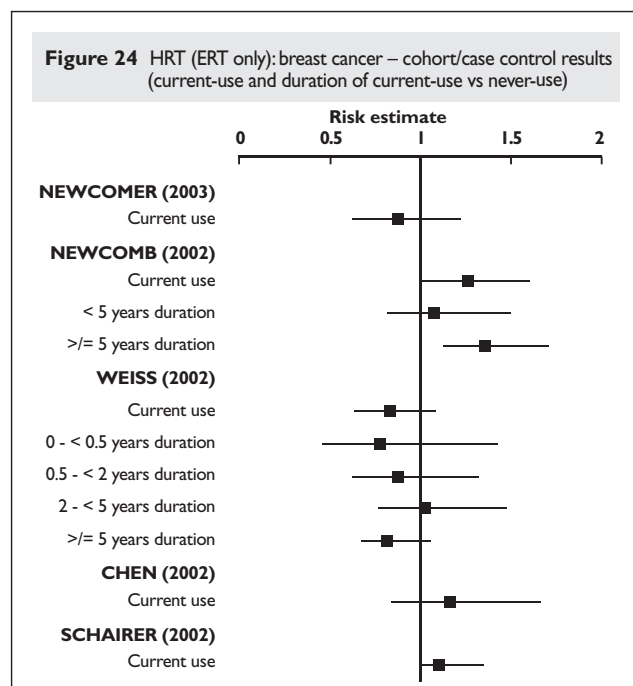
^a Defined as recent use, within two years of the reference date.

^b Defined as at least 6 months of therapy within the 12 months preceding the reference date.

^c Defined as use within 6 months prior to the reference date.

^d Defined as having had at least two prescriptions filled in the 6 months preceding the reference date.

^e Not defined.



Past-use and years since last use

Four studies examined the association between past use of ERT and breast cancer risk. Both Newcomer *et al.* (2003) and Weiss *et al.* (2002) showed no association between past use and breast cancer risk.

Two studies examined the association between past-use of ERT and breast cancer risk at different time points since last use. Schairer *et al.* (2000) showed a significantly increased risk of breast cancer associated with use in the past 1-2 years (RR 1.4) but not beyond two years. Similarly, Newcomb *et al.* (2002) showed an increased risk associated with use of ERT within the last 5 years (RR 1.76) but not beyond 5 years. These results are summarised in Table 70 and Figure 25.

TABLE 70 HRT (ERT ONLY): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (PAST-USE AND YEARS SINCE PAST-USE VS NEVER-USE)

Author	Study type	HRT (or case/control)	No HRT (or case/control)	Type of measure	Risk estimate
<i>Newcomer(2003)</i>					
Past use ^a	Case-control	249/304	1875/2294	OR	1.1 (0.9, 1.4)
<i>Newcomb(2002)</i>					
< 5 years since last use	Case-control	84/53	3827/4132	RR	<i>1.76 (1.21, 2.56)</i>
5-9 years since last use	Case-control	54/50	3827/4132	RR	1.22 (0.8, 1.87)
10-19 years since last use	Case-control	161/162	3827/4132	RR	1.12 (0.87, 1.43)
≥ 20 years since last use	Case-control	107/112	3827/4132	RR	1.04 (0.77, 1.4)
<i>Weiss (2002)</i>					
Past use ^b	Case-control	260/306	672/655	OR	0.86 (0.69, 1.07)
<i>Schairer(2000)</i>					
1-2 years since last use	Cohort	77/15533 py	761/196666 py	RR	<i>1.4 (1.1, 1.8)</i>
> 2-4 years since last use	Cohort	55/12171 py	761/196666 py	RR	1.2 (0.9, 1.6)
>4-6 years since last use	Cohort	35/10463 py	761/196666 py	RR	0.9 (0.6, 1.3)
> 6 years since last use	Cohort	309/67836 py	761/196666 py	RR	1.1 (0.9, 1.2)

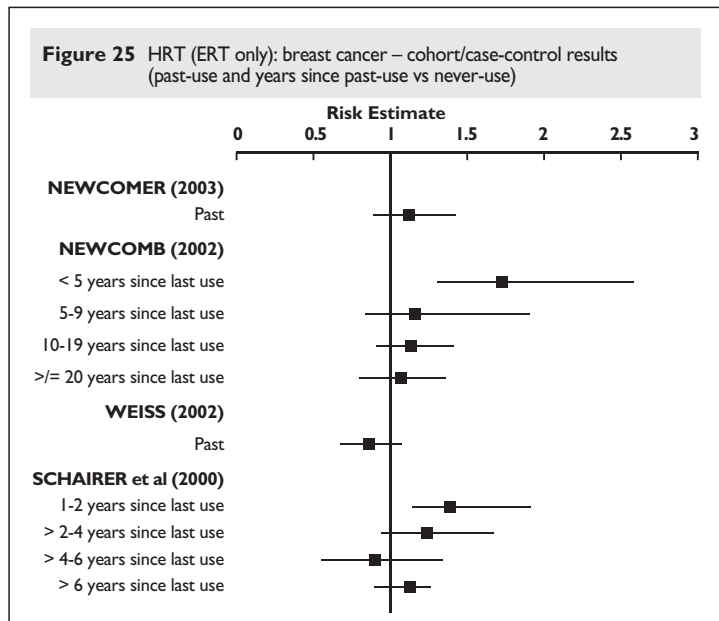
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HRT, hormone replacement therapy; OR, odds ratio; py, person-years; RR, risk ratio.

Past-use defined as greater than two years prior to reference date

^a Defined as use greater than 2 years prior to the reference date.

^b Defined as use greater than 6 months prior to the reference date.



In summary, on the basis of the currently available evidence from observational studies, there is a suggestion that an increased risk of breast cancer is present shortly after cessation of HRT use, but that this diminishes over time.

Effect by HRT type: oestrogen combined with progestogen

Ten studies provided evidence regarding the association between use of combined oestrogen and progesterone therapy (EPRT) and breast cancer risk and breast cancer-related mortality. Two studies were randomised controlled trials (level II evidence), while three were cohort studies and five were case-control studies (level III-2 evidence). The characteristics and quality of these studies are summarised in Table 66.

The Heart and Estrogen/progestogen Replacement Study (HERS) and HERS II by Hulley and associates (1998; 2002) examined the risk of breast cancer in women with existing coronary heart disease who were taking combined continuous oestrogen and progestogen therapy. The mean age of the women at the commencement of the HERS study was 67 years and there was no requirement for the women to be HRT naïve. In both the initial double-blind phase of the study (mean 4.1 years follow-up) and the subsequent open-label phase (an additional mean 2.7 years follow-up) there was no significant increase in risk of breast cancer in the EPRT groups compared with the placebo group.

The Women's Health Initiative (WHI) study examined the risk of breast cancer associated with the use of combined continuous oestrogen and progestogen therapy (Rossouw *et al.*, 2002; Chlebowski *et al.*, 2003). The mean age at the beginning of the WHI study was 63 years. The planned duration of the trial was 8.5 years, however the trial was stopped after a mean follow-up period of 5.2 years after an interim analysis showed increased breast cancer risk in the EPRT arm. The overall increased risk of breast cancer shown in the trial was 26%, resulting in 8 more invasive breast cancers in women taking EPRT per 10,000 person years. When examined over time, cumulative hazard ratios were comparable for the first four years of treatment however after this point the curve for the EPRT arm rose more quickly than the curve for placebo arm. It should be noted that the analysis presented in the more recent publication from this study by Chlebowski *et al.* (2003) showed a 24% increased risk of invasive breast cancer for all women (adjusted 95% CI 0.97, 1.59).

Just over 25% of women in the WHI trial had used HRT previously or were using it when recruited into the study. When the analysis was confined to women who were HRT-naïve at the time of entry into the study, the results showed no increased risk of breast cancer in the EPRT treatment arm. It is important to note that a similar result was seen in the analysis presented by Chlebowski *et al.* (2003). In contrast, when analyses were confined to the women who had previously used HRT, the risk of breast cancer in the EPRT arm was significantly increased.

The results of these two studies are summarised in Table 71 and Figure 26.

TABLE 71 HRT (EPRT): BREAST CANCER — RCT RESULTS

Author	Study type	HRT	No HRT	Type of measure	Risk estimate
Hulley (1998) ^{a,b}	RCT	32/1380	25/1383	HR	1.30 (0.77, 2.19)
Hulley (2002) ^{a,c}	RCT	5.9/1000 py	4.7/1000 py	HR	1.27 (0.84, 1.94)
Rossouw (2002) — all women	RCT	166/8506	124/8102	HR	1.26 (1.00, 1.59)
Rossouw (2002) — HRT naïve women	RCT	114/6280	102/6024	HR	1.06 (0.81, 1.38)
Rossouw (2002) - < 5 yr use	RCT	32/1538	15/1467	HR	2.13 (1.15, 3.94)
Rossouw (2002) — 5-10 yr use	RCT	11/426	2/357	HR	4.61 (1.01, 21.02)
Rossouw (2002) > 10 yr use	RCT	9/262	5/253	HR	1.81 (0.60, 5.43)

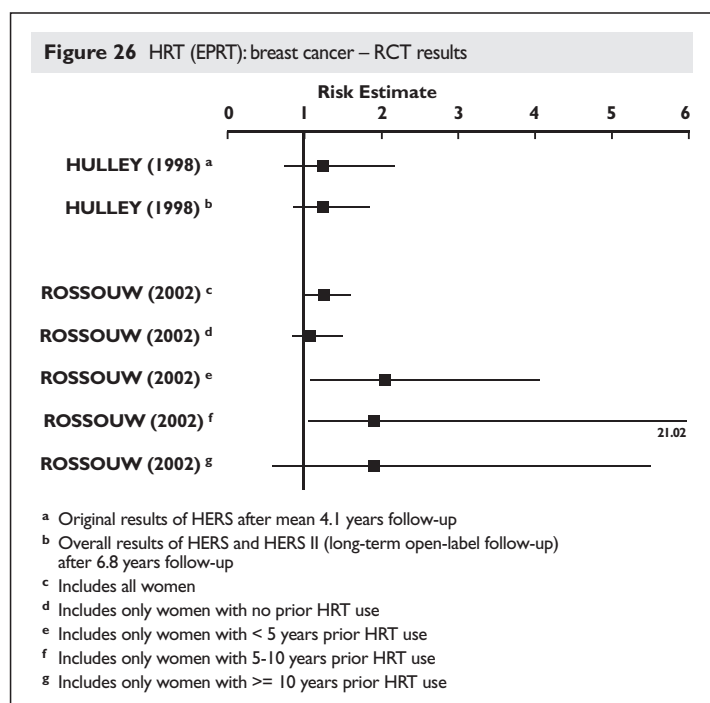
Note: Risk estimates in *italics* are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; py, person-years.

^a Includes women with coronary heart disease

^b Original results of HERS after mean 4.1 years follow-up

^c Overall results of HERS and HERS II (long-term open-label follow-up) after 6.8 years follow-up. ITT analysis adjusted for potential confounders.



Importantly, the increased risk of breast cancer appears to be apparent only in women with prior HRT use (even when compared to comparable controls). It is not present when the analysis is confined to those women who were HRT-naïve at the beginning of the trial. The latter group is likely to be more representative of women commencing HRT therapy in Australia.

In addition to the data regarding breast cancer risk, breast cancer-related mortality was noted in both trials. In the study by Hulley *et al.* (2002) outlining the overall results of the HERS and HER II studies, three breast cancer-related deaths occurred in the EPRT arm compared with none in the placebo arm. In the WHI study (Rossouw *et al.*, 2002) death due to breast cancer occurred in three women in the HRT arm and two women in the placebo arm.

Ever-use versus never-use

Three cohort studies and three case-control studies provided data regarding the association between use of EPRT and breast cancer risk. An increased risk was seen in all studies, however this was statistically significant in only three of the studies. A 37% increased risk was seen in the Porch *et al.* (2002) study while a 43% increased risk was shown in the case-control study by Newcomb *et al.* (2002). In addition, Olsson *et al.* (2003) examined the association between continuous or sequential EPRT and breast cancer and found an increased risk for both types of EPRT. These results are summarised in Table 72 and Figure 27.

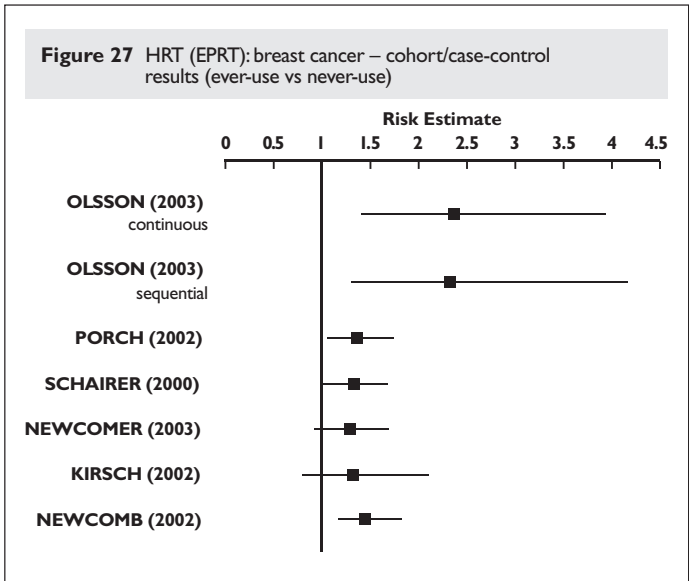
TABLE 72 HRT (EPRT): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (EVER-USE VS NEVER-USE)

Author	Study type	HRT (or case/control)	No HRT (or case/control)	Type of risk measure	Risk estimate
Olsson (2003) ^a continuous	Cohort	31/445	153/6707	HR	<i>2.33 (1.38, 3.93)</i>
Olsson (2003) ^a sequential	Cohort	19/320	153/6707	HR	<i>2.27 (1.26, 4.10)</i>
Porch (2002)	Cohort	164/32885 py	146/38762 py	RR	<i>1.37 (1.05, 1.78)</i>
Schairer (2000)	Cohort	101/17428 py	761/196666 py	RR	1.3 (1.0, 1.6)
Newcomer (2003)	Case-control	99/94	1875/2294	OR	1.2 (0.9, 1.6)
Kirsch (2002)	Case-control	48/33	272/283	OR	1.22 (0.72, 2.06)
Newcomb (2002)	Case-control	315/286	3827/4132	RR	<i>1.43 (1.18, 1.74)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; OR, odds ratio; py, person-years; RR, risk ratio.

^a Includes only women who had undergone natural menopause.



Duration of ever-use of therapy

Five studies provided evidence regarding the effect of the duration of EPRT therapy on breast cancer risk, with durations ranging from < 2 years to ≥ 10 years. A statistically significant risk was seen in the Newcomb *et al.*(2002) study for any duration of use, but this was greater in the longer duration group (ie, < 5 years and ≥ 5 years; 36% and 58% respectively). A greater than three-fold risk which approached statistical significance was seen in the study by Kirsch and Kreiger (2002), however, as this was based on very few cases/controls (12/4), this result should be interpreted with extreme caution. A significantly increased risk was seen for long-term use of continuous EPRT and short-term use of sequential EPRT in the in the Olsson *et al.* (2003). A significant reduction in risk was seen for any EPRT and sequential EPRT use of < 6 months in the Weiss study. Nevertheless, in general there is a tendency towards increased risk with increased duration of use. These results are shown in Table 73 and Figure 28.

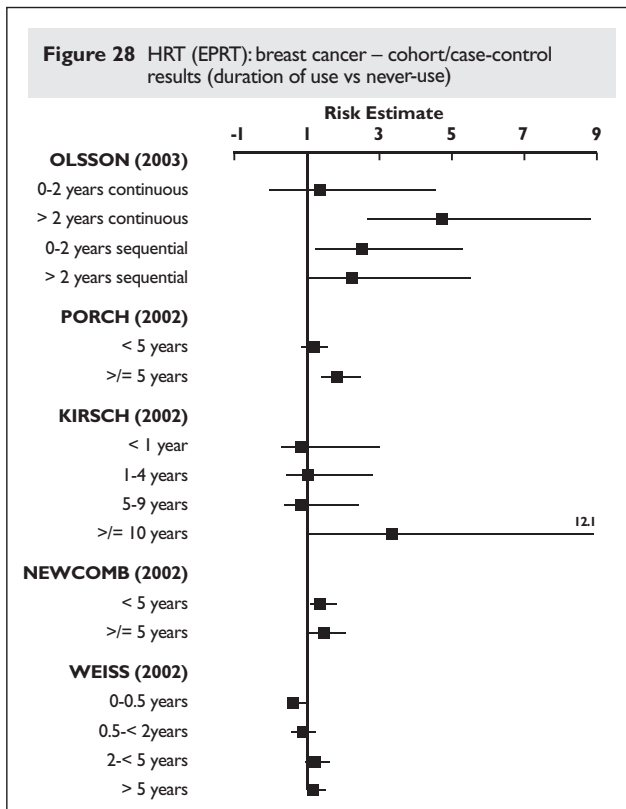
TABLE 73 HRT (EPRT): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (DURATION OF USE VS NEVER-USE)

Author	Study type	HRT (or case/control)	No HRT (or case/control)	Type of measure	Risk estimate
<i>Olsson (2003)</i> ^a					
0-2 years (continuous)	Cohort	15/272	153/6707	HR	1.37 (0.63, 3.01)
> 2 years (continuous)	Cohort	16/173	153/6707	HR	4.60 (2.39, 8.84)
0-2 years (sequential)	Cohort	13/184	153/6707	HR	2.53 (1.21, 5.28)
> 2 years (sequential)	Cohort	6/136	153/6707	HR	2.23 (0.90, 5.56)
<i>Porch(2002)</i>					
< 5 years	Cohort	85/20333 py	146/38762 py	RR	1.11 (0.81, 1.52)
≥ 5 years	Cohort	79/12343 py	146/38762 py	RR	1.76 (1.29, 2.39)
<i>Kirsch(2002)</i>					
< 1 year	Case-control	6/8	272/283	OR	0.86 (0.26, 2.82)
1-4 years	Case-control	16/10	272/283	OR	0.96 (0.39, 2.39)
5-9 years	Case-control	9/10	272/283	OR	0.84 (0.31, 2.24)
≥ 10 years	Case-control	12/4	272/283	OR	3.48 (1.0, 12.11)
<i>Newcomb (2002)</i>					
< 5 years	Case-control	198/193	3827/4132	RR	1.36 (1.07, 1.73)
≥ 5 years	Case-control	117/93	3827/4132	RR	1.58 (1.16, 2.15)
<i>Weiss (2002)</i>					
0-0.5 years	Case-control	64/98	672/655	OR	0.65 (0.46, 0.93)
0.5-<2 years	Case-control	115/130	672/655	OR	0.92 (0.69, 1.23)
2-< 5 years	Case-control	190/151	672/655	OR	1.25 (0.96, 1.63)
> 5 years	Case-control	320/252	672/655	OR	1.17 (0.92, 1.48)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; nr, not reported; OR, odds ratio; py, person-years; RR, risk ratio.

^a Results not available for overall effect of EPRT (ie, sequential and continuous). Includes only women who had undergone natural menopause.



Current-use and duration of current-use

Five studies provided data regarding the association between current-use of EPRT and risk of developing breast cancer (see Table 74 and Figure 29). Three of the four studies showed a significantly increased risk of breast cancer associated with current-use of EPRT with increased risks of 39%-49% (Chen *et al.*, 2000; Schairer *et al.*, 2000; Newcomb *et al.*, 2002). In addition, Newcomb *et al.* (2002) show that current-use of EPRT for less than 5 years increased risk by 32%, while current-use for at least 5 years increased the risk of developing breast cancer by 50%. Weiss also showed that current, long-term use of EPRT significantly increased the risk of breast cancer. This supports the increased risk associated with longer duration use observed in the ever-use EPRT results.

TABLE 74 HRT (EPRT): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (CURRENT-USE AND DURATION OF CURRENT-USE VS NEVER-USE)

Author	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of measure	Risk estimate
<i>Newcomer(2003)</i>					
Current use ^a	Case-control	62/67	1875/2294	OR	1.0 (0.7, 1.5)
<i>Newcomb(2003)</i>					
Current use ^b	Case-control	270/261	3827/4132	RR	<i>1.39 (1.12, 1.71)</i>
< 5 years duration	Case-control	163/170	3827/4132	RR	<i>1.32 (1.02, 1.70)</i>
≥ 5 years duration	Case-control	107/91	3827/4132	RR	<i>1.50 (1.09, 2.06)</i>
<i>Weiss (2002)</i>					
Current ^c	Case-control	505/390	672/655	OR	1.22 (0.99, 1.50)
0 — < 0.5 years duration	Case-control	12/23	672/655	OR	0.53 (0.26, 1.09)
0.5 — < 2 years duration	Case-control	60/56	672/655	OR	1.11 (0.75, 1.65)
2 — < 5 years duration	Case-control	139/109	672/655	OR	1.28 (0.95, 1.73)
≥ 5 years duration	Case-control	291/199	672/655	OR	<i>1.37 (1.06, 1.77)</i>
<i>Chen(2000)</i>					
Current use ^d	Case-control	112/74	243/271	OR	<i>1.49 (1.04, 2.12)</i>
<i>Schairer(2000)</i>					
Current use ^e	Cohort	77/11780 py	761/196666 py	RR	<i>1.4 (1.1, 1.9)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HRT, hormone replacement therapy; nr, not reported; OR, odds ratio; py, person-years; RR, risk ratio.

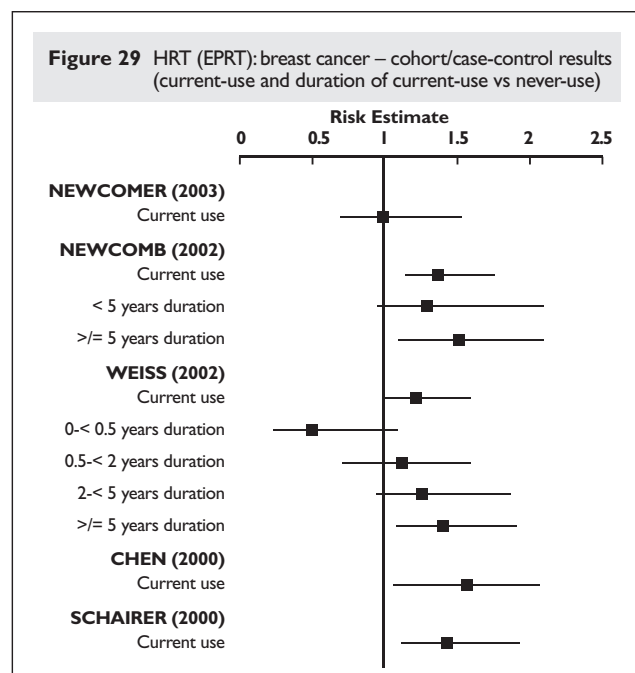
^a Defined as recent use, within two years of the reference date.

^b Defined as at least 6 months of therapy within the 12 months preceding the reference date.

^c Defined as use within 6 months prior to the reference date.

^d Defined as having had at least two prescriptions filled in the 6 months preceding the reference date.

^e Not defined.



Past-use and years since last use

Four studies assessed the association between past use of EPRT and the risk of developing breast cancer. Only one statistically significant change in breast cancer risk was seen in association with past use of EPRT, and this was a decrease (Weiss *et al.*, 2002).

Two studies examined the association between past-use of EPRT and breast cancer risk at different time points since last use. Neither study showed a significant association between past EPRT use and increased risk of breast cancer, at any of the reported time points. However, in the study with the largest number of subjects (Schairer *et al.*, 2000), there does appear to be a trend toward diminishing risk of breast cancer with increasing time since cessation of therapy. The results are summarised in Table 75 and Figure 30.

TABLE 75 HRT (EPRT): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (PAST-USE AND YEARS SINCE PAST-USE VS NEVER-USE)

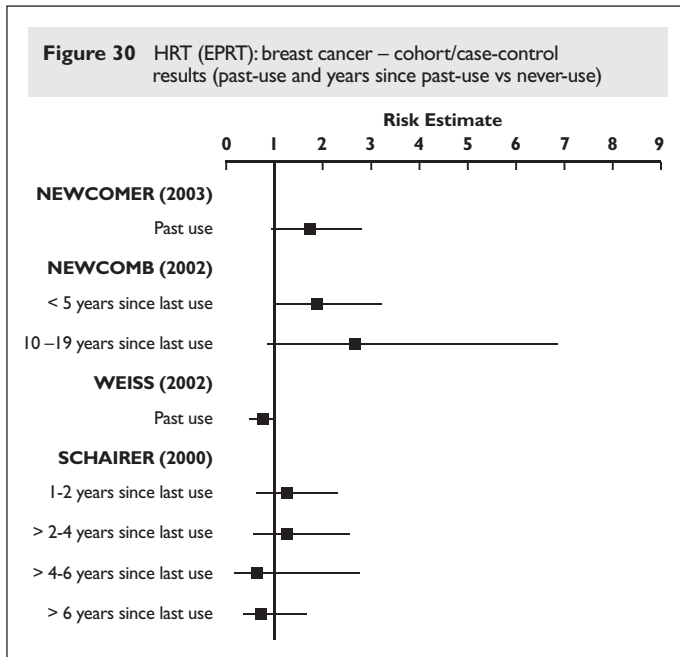
Author	Study type	HRT (n/N or case/ control)	No HRT (n/N or case/ control)	Type of measure	Risk estimate
<i>Newcomer(2003)</i>					
Past use ^a	Case-control	37/27	1875/2294	OR	1.6 (0.9, 2.7)
<i>Newcomb(2002)</i>					
< 5 years since last use	Case-control	31/19	3827/4132	RR	1.71 (0.92, 3.18)
10-19 years since last use	Case-control	14/6	3827/4132	RR	2.38 (0.82, 6.87)
<i>Weiss (2002)</i>					
Past use ^b	Case-control	189/246	672/655	OR	0.76 (0.60, 0.97)
<i>Schairer(2000)</i>					
1-2 years since last use	Cohort	9/1899 py	761/196666 py	RR	1.2 (0.6, 2.4)
>2-4 years since last use	Cohort	7/1388 py	761/196666 py	RR	1.2 (0.5, 2.5)
> 4-6 years since last use	Cohort	2/579 py	761/196666 py	RR	0.6 (0.2, 2.6)
> 6 years since last use	Cohort	6/1779 py	761/196666 py	RR	0.6 (0.3, 1.6)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HRT, hormone replacement therapy; OR, odds ratio; py, person-years; RR, risk ratio.

^a Defined as use greater than 2 years prior to the reference date.

^b Defined as use greater than 6 months prior to the reference date.



In summary, when contrasting the result for EPRT use and those for ERT use (pp 88-94) it appears that the magnitude of the risk point estimate was somewhat greater with EPRT compared with ERT. Furthermore, of the studies providing data for both ERT and EPRT, in all cases the risk estimate versus never use was higher in the women taking EPRT than ERT. However, it is important to remember that the patients receiving ERT and EPRT are different and therefore direct comparisons may not be appropriate.

Effect by HRT type: any type or type not specified

One case-control study examined the risk of breast cancer in association with the use of any type of HRT (ie, including both ERT and EPRT). There were no RCTs or cohort studies available for this analysis.

Ever-use versus never-use

A borderline statistically significant increased risk of 10% was seen in the Fernandez *et al.* (2003) study. This result is summarised in Table 76.

TABLE 76 HRT (ANY OR UNSPECIFIED): BREAST CANCER — COHORT/CASE-CONTROL RESULTS (EVER-USE VS NEVER-USE)

Author	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of measure	Risk estimate
Fernandez (2003)	Case-control	359/537	4354/6439	OR	1.1 (1.0, 1.3)

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: HRT, hormone replacement therapy; OR, odds ratio; py, person-years; RR, risk ratio.

Duration of ever-use of therapy

The use of HRT for < 2 years resulted in a borderline significant 20% increased risk of breast cancer in the Fernandez *et al.* (2003) study. A similar, non-significant point estimate was seen for HRT use of 2 years or more. These results are shown in Table 77.

TABLE 77 HRT (ANY OR UNSPECIFIED): BREAST CANCER — COHORT/CASE-CONTROL STUDIES (DURATION OF USE VS NEVER-USE)

Author	Study type	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of measure	Risk estimate
<i>Fernandez(2003)</i>					
< 2 years	Case-control	241/344	4354/6439	OR	1.2 (1.0, 1.4)
≥ 2 years	Case-control	115/180	4354/6439	OR	1.1 (0.9, 1.4)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; nr, not reported; OR, odds ratio; py, person-years; RR, risk ratio.

Women with previous breast cancer

Existing systematic reviews

Two systematic reviews were identified which examined the association between HRT and the risk of breast cancer in women who had previously had breast cancer. The review by Meurer *et al.* (2002) was considered to be of good quality. The review by Col *et al.* (2001) was considered to be of poor quality due to a lack of quality assessment of the included studies and poor reporting and therefore was not considered further. A summary of the characteristics and quality of these systematic reviews can be found in Table 78. For further details see Appendix B (Section 9.1.4).

TABLE 78 HRT: BREAST CANCER (PRIOR BREAST CANCER) — EXISTING SYSTEMATIC REVIEWS

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcome
Level III-2 evidence					
Meurer & Lena (2002)	Systematic review of observational studies (10) Good	Women with previous breast cancer	HRT Mode of administration and dose not specified	Not specified but assumed to be no therapy	Recurrence Mortality
Col <i>et al.</i> (2001)	Systematic review of observational studies (11) Poor	Women with previous breast cancer	HRT Mode of administration and dose not specified	Not specified but assumed to be no therapy	Recurrence

See Section 9.1.4.

The review by Meurer *et al.* (2002) included data from one pilot RCT and nine cohort studies. The authors classified the included studies into those of high or low quality (based on a set of quality criteria) and analysed the results of each set of studies individually. The results showed that there was no increased risk of breast cancer recurrence associated with the use of HRT in the high quality studies (OR 0.58; 0.30, 1.12), low quality studies (OR 0.85; 0.48, 1.49) or all studies combined (OR 0.72; 0.47, 1.10). Meurer and associates found that breast cancer-related mortality was significantly lower in the HRT group with significantly decreased risks of 79%, 84% and 72% for high quality, low quality and all studies respectively. However, the authors note that as their review contains primarily observational studies, the results may be subject to significant bias. In addition, they state that most studies include women who have had less severe disease and as such the results may only be generalised to this more specific population.

Original studies

There is evidence regarding the association between HRT and breast cancer incidence and mortality in women with previous breast cancer from a high quality, recent systematic review (Meurer *et al.*, 2002). Therefore, a search for original studies was conducted for the years 2001-2003 to update the evidence provided by the existing systematic review. The search identified one RCT (Vassilopoulou-Sellin *et al.*, 2002), which was considered to be of poor quality due to unclear randomisation and blinding, and the inclusion of insufficient patients in the analysis to meet the required sample size for the study. However, as this is the only additional study available it will be discussed here. For details of the characteristics and quality of this study see Table 79. For further details see Appendix B (Section 9.1.4).

TABLE 79 HRT: BREAST CANCER (PRIOR BREAST CANCER) — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcome
Level II evidence					
Vassilopoulou-Sellin <i>et al.</i> (2002)	Double-blind RCT Follow-up 5 years Poor	Postmenopausal women with previous breast cancer Mean age ~54 N=77	ERT (Premarin, Wyeth) 0.625 mg days 1-25 of month N=34	No HRT N=43	Recurrence

See Section 9.1.4.

Abbreviations: ERT; oestrogen-only therapy; RCT; randomised controlled trial.

In this study, four cases of breast cancer were seen in the ERT group compared with two cases in the no ERT group after five years ($p=0.44$). The authors conclude that disease-free survival was not compromised in this patient group however they state that larger randomised trials are required to confirm this finding as the risk of a type II error is considerable.

Endometrial cancer

Summary

There is unequivocal evidence demonstrating an increased risk of endometrial cancer when oestrogen-only HRT is used by women with an intact uterus. The magnitude of the risk elevation is large, and it is closely related to the duration of oestrogen-only HRT use. Increased risk is still significantly present amongst past users of oestrogen-only HRT. Some, but not all, studies suggest that the magnitude of risk of endometrial cancer may diminish over time.

High quality evidence from RCTs shows no indication of an increased risk of endometrial cancer amongst women with an intact uterus who used a continuous combined oestrogen/progestogen preparation. However, evidence from observational studies is less consistent, with some case-control studies reporting an elevation in risk of endometrial cancer with longer duration combined oestrogen/progestogen HRT. Nevertheless, any elevation in risk of endometrial cancer that may be present with oestrogen/progestogen combined therapy is smaller in magnitude than that observed with oestrogen alone.

Existing systematic reviews

One existing systematic review was identified by the literature search. This review by Grady and associates (1995) was considered to be of fair methodological quality. In addition, the review contains observational studies only and as such may be subject to substantial bias. The characteristics and quality of the Grady review are summarised in Table 80. For further details see Appendix B (Section 9.1.4).

TABLE 80 HRT: ENDOMETRIAL CANCER — EXISTING SYSTEMATIC REVIEWS

Study	Study type No. of studies Study quality	Population N	Intervention N	Comparator N	Outcomes
Level III-2 evidence					
(Grady <i>et al.</i> 1995)	Systematic review of observational studies 34 studies <i>Fair</i>	Postmenopausal women	HRT Mode of administration and dose not specified	No HRT	Incidence Mortality

See Section 9.1.4.

The analysis showed an increased risk of developing endometrial cancer with ERT use when considering all studies, which was still evident when the results from cohort or case-control studies were considered separately. The authors concluded that the increased risk was strongly associated with increasing dose and duration of therapy and a higher risk was also seen for conjugated oestrogen compared with synthetic oestrogens. Risk decreased with increasing time since last use, however the elevated risk was still evident after more than five years. Risk of endometrial cancer mortality was examined in three studies and was shown to be increased although this was not statistically significant. It should be noted that substantial heterogeneity was found in many of the analyses. These results are summarised in Table 81 and Figure 31.

The analysis of studies examining the use of EPRT showed no increased risk overall, however when cohort and case-control studies were analysed separately, a significantly decreased risk was seen in the cohort studies while a significantly increased risk was seen in the case-control studies. These results are summarised in Table 81.

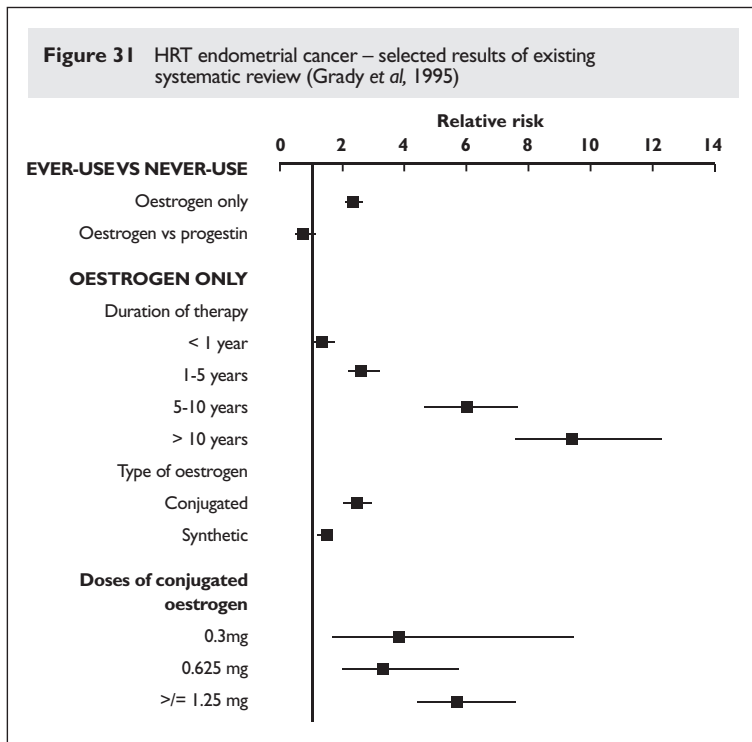
TABLE 8 | HRT: ENDOMETRIAL CANCER — RESULTS OF EXISTING SYSTEMATIC REVIEW (GRADY *ET AL*, 1995)

Comparison	Number of studies	Relative risk (95% CI)
Oestrogen only		
Ever use versus never use		
All studies	29	2.3 (2.1, 2.5) ^a
Cohort studies	4	1.7 (1.3, 2.1) ^a
Case-control studies	25	2.4 (2.2, 2.6) ^a
Duration of therapy		
< 1 year	9	1.4 (1.0, 1.8)
1-5 years	12	2.8 (2.3, 3.5)
5-10 years	10	5.9 (4.7, 7.5)
> 10 years	10	9.5 (7.4, 12.3) ^a
Type of oestrogen		
Conjugated	9	2.5 (2.1, 2.9) ^a
Synthetic	7	1.3 (1.1, 1.6) ^a
Dose of conjugated oestrogen		
0.3 mg	3	3.9 (1.6, 9.5)
0.625 mg	4	3.4 (2.0, 5.6)
≥ 1.25 mg	9	5.8 (4.5, 7.5)
Time since last use		
≤ 1 year	3	4.1 (2.9, 5.7) ^a
1-4 years	3	3.7 (2.5, 5.5)
≥ 5 years	5	2.3 (1.8, 3.1)
Mortality	3	2.7 (0.9, 8.0)
Oestrogen + progestogen		
Ever use versus never use		
All studies	5	0.8 (0.6, 1.2)
Cohort studies	2	0.4 (0.2, 0.6)
Case-control studies	3	1.8 (1.1, 3.1)
Duration of progestogen use		
< 10 days/month	1	2.0 (0.7, 5.3)
≥ 10 days/month	1	0.9 (0.3, 2.4)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: *nr*, not reported; *RR*, relative risk.

^a Statistically heterogeneous.



Original studies

A search for original studies was conducted for the years 1994 - 2003 to update the evidence provided by the Grady *et al.* (1995) systematic review. The search identified four RCTs and six case-control studies. For details of the characteristics and quality of each of the included studies see Table 82. For further details see Appendix B (Section 9.1.4). The study by Mizunuma *et al.* (2001) was considered to be subject to substantial bias and as such was deemed poor quality and was not considered further.

The study by Mizunuma *et al.* (2001) was considered to be of poor methodological quality as it included very few women on HRT and a large proportion of eligible women were excluded from the analysis.

One study (Fernandez *et al.*, 2003) was subsequently excluded from the analysis as it presented results for a combined analysis of ERT and EPRT. As ERT and EPRT are known to have differential effects on the endometrium it was not considered appropriate to present the results of a combined analysis of these types of HRT, as it was thought that this might mask the true effects of ERT on the endometrium.

TABLE 82 HRT: ENDOMETRIAL CANCER — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Cherry (2002)	RCT ESPRIT 2 years Fair	Postmenopausal women aged 50-69 with previous MI Mean age 63 years N=1017	ERT Oral oestradiol valerate 2 mg/d N=513	Placebo N=504	Incidence
Hulley <i>et al.</i> (1998); Hulley <i>et al.</i> (2002)	Double-blind RCT (HERS I) with open-label follow-up (HERS II) Mean 6.8 years follow-up Good	Postmenopausal women aged < 80 with intact uterus and existing CVD Mean age 67 N=2763	EPRT Oral CEE and MPA 0.625 mg/2.5 mg daily HERS I=1380 HERS II=1156	Placebo HERS I N=1383 HERS II=1165	Incidence
Rossouw <i>et al.</i> (2002)	Double-blind RCT WHI Mean 5.2 years follow-up Good	Postmenopausal women aged 50-79 with intact uterus Mean age 63 15% FH of BC N=16608	EPRT Oral CEE and MPA 0.625 mg/2.5 mg daily N=8506	Placebo N=8102	Incidence
Mebane-Sims <i>et al.</i> (1996)	RCT (placebo) 3 years Good	Postmenopausal women aged 45-64 with intact uterus Mean age 56 years N=596	HRT Oral (i) CEE 0.625 mg/d, N=119; (ii/iii) CEE plus MPA 0.625 mg/d + 10 mg/d for first 12 days N=118, or 0.625 mg/d + 2.5 mg/d, N=120; (iv) CEE plus micronised progesterone 0.625 mg/d + 200 mg/d for first 12 days, N=120	Placebo N=119	Incidence
Level III-2 evidence					
Fernandez <i>et al.</i> (2003)	Case-control (hospital-based) Fair	Postmenopausal women 45-75 years N=7680	HRT Mode of administration and dose not specified N=624	No HRT N=7056	Incidence
Newcomb & Trentham-Dietz (2003)	Case-control (population-based) Good	Postmenopausal women with an intact uterus 40-79 years N=2636	HRT Oral, injectable or transdermal \geq 6 months N=567	No HRT N=2069	Incidence
Mizunuma <i>et al.</i> (2001)	Case-control (hospital-based) Poor	Japanese postmenopausal women with an intact uterus Mean age ~ 62 N=2292	HRT Mode of administration not specified N=110	No HRT N=2126	Incidence
Hill <i>et al.</i> (2000)	Case-control study (population-based) Fair	Postmenopausal women with an intact uterus 45-64 years N=2294	EPRT Mode of administration and dose not specified N=1109	No HRT N=1185	Incidence
Jain <i>et al.</i> (2000)	Case-control (population-based) Fair	Women aged > 48 years Mean age 63 N=1025	HRT Mode of administration and dose not specified N=417	No HRT N=608	Incidence

See Section 9.1.4.

Abbreviations: CEE, conjugated equine oestrogens; ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen therapy; ESPRIT, oEstrogen in the Prevention of ReInfarction Trial; HERS, Heart and Estrogen/progestin Replacement Study; HRT, oestrogen \pm progestogen therapy; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

Effect by HRT type: oestrogen only

Four original studies published since 1994 were identified that examined the association between oestrogen-only therapy (ERT) and endometrial cancer risk and endometrial cancer-related mortality. Two studies were RCTs (level II evidence) and three were case-control studies (level III-2 evidence).

The results of the two RCTs examining the use of ERT in postmenopausal women are summarised in Table 83. In the 2-year ESPRIT study (Cherry, 2002), no cases of endometrial cancer were identified. In the 3-year PEPI trial (Mebane-Sims *et al.*, 1996) only one case of endometrial cancer was seen and this was in the placebo arm. These results are not unexpected given the relatively short follow-up and the small sample size of the two studies.

TABLE 83 HRT (ERT ONLY): ENDOMETRIAL CANCER — RCT RESULTS

Author	Study type	HRT n/N	No HRT n/N
Cherry (2002) ^a	RCT	0/373	0/399
Mebane-Sims (1996)	RCT	0/119	1/119

Abbreviations: RCT, randomised controlled trial.

^a Denominator includes only women with an intact uterus

Ever-use versus never-use

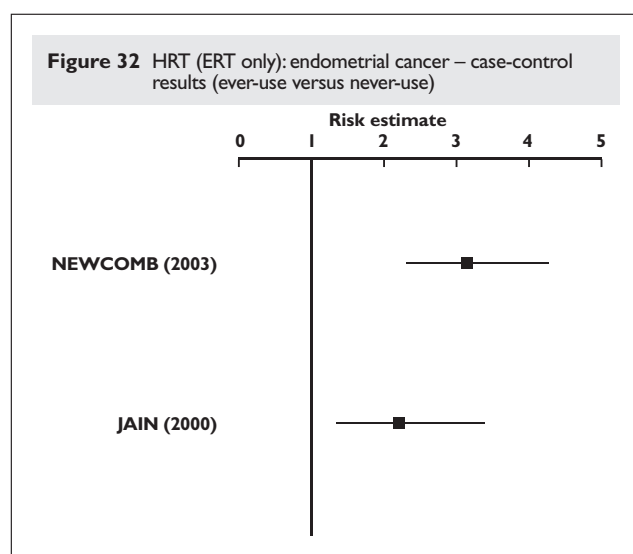
Two case-control studies provided data regarding the ever-use of ERT and its association with endometrial cancer. Both studies showed a significantly increased risk of endometrial cancer (2-3-fold) in women who had used ERT compared with those who had never used HRT. These results are summarised in Table 84 and Figure 32.

TABLE 84 HRT (ERT ONLY): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (EVER-USE VERSUS NEVER-USE)

Author	Study type	HRT (case/ control)	No HRT (case/ control)	Type of measure	Risk estimate
Newcomb (2003)	Case-control	112/165	402/1667	RR	<i>3.15 (2.37, 4.19)</i>
Jain (2000)	Case-control	77/54	292/316	OR	<i>2.23 (1.45, 3.43)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: OR, odds ratio; RR, relative risk.



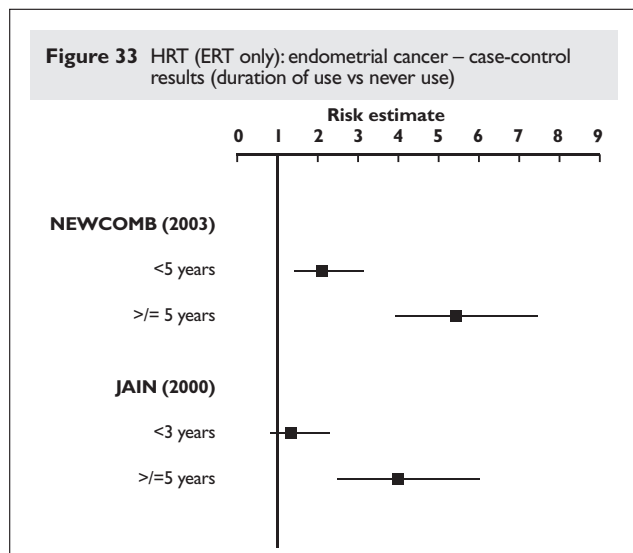
Duration of use

Data regarding the duration of ERT use and its association with endometrial cancer are summarised in Table 85 and Figure 33. These results strongly suggest that increasing duration of use of ERT results is associated with an increased risk of endometrial cancer.

TABLE 85 HRT (ERT ONLY): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (DURATION OF USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Newcomb (2003)</i>					
< 5 years	Case-control	50/98	402/1667	RR	<i>2.08 (1.41, 3.07)</i>
≥ 5 years	Case-control	62/67	402/1667	RR	<i>5.47 (3.66, 8.19)</i>
<i>Jain(2000)</i>					
< 3 years	Case-control	34/35	292/316	OR	<i>1.34 (0.77, 2.32)</i>
≥ 3 years	Case-control	43/19	292/316	OR	<i>4.12 (2.21, 7.71)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: OR, odds ratio, RR, relative risk.



Current-use

The effect of current use of ERT on endometrial cancer was assessed in one case-control study. The results indicated the risk of endometrial with current ERT use was more than six times the baseline risk (Table 86).

TABLE 86 HRT (ERT ONLY): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (CURRENT-USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
Newcomb (2003)	Case-control	56/59	402/1667	RR	<i>6.19 (4.03, 9.50)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: RR, relative risk.

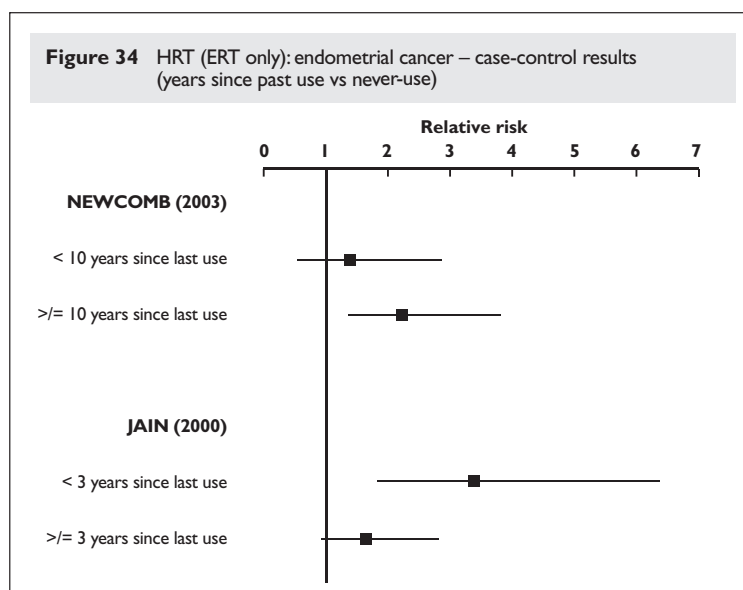
Years since past use

Two case-control studies assessed the association between years since past use of ERT and endometrial cancer risk (Table 87 and Figure 34) and show disparate results. The results of the Jain study (2000) show a decreasing risk of endometrial cancer with increasing years since last used. On the other hand, the results of the Newcomb study show an increased risk of ERT with increasing time since last use of ERT. However, both studies included only a small number of women that had taken HRT.

TABLE 87 HRT (ERT ONLY): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (YEARS SINCE PAST USE VS NEVER-USE)

Authors	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Newcomb (2003)</i>					
< 10 years since last use	Case-control	11/33	402/1667	RR	1.49 (0.72, 3.09)
≥ 10 years since last use	Case-control	44/72	402/1667	RR	2.31 (1.51, 3.54)
<i>Jain (2000)</i>					
< 3 years since last use	Case-control	38/18	292/316	OR	3.35 (1.77, 6.32)
≥ 3 years since last use	Case-control	39/36	292/316	OR	1.66 (0.97, 2.84)

Note: Risk estimates in *italics* are considered statistically significant as they do not include one. Abbreviations: OR, odds ratio; RR, relative risk.



Effect by HRT type: oestrogen plus progestogen

Eight original studies published since 1994 were identified that examined the association between oestrogen plus progestogen only therapy (EPRT) and endometrial cancer risk and endometrial cancer-related mortality. Four studies were RCTs (level II evidence) and four were case-control studies (level III-2 evidence). Where available, data regarding the differential effects of continuous and sequential EPRT will be presented separately.

The results of the four RCTs examining the use of ERT in postmenopausal women are summarised in Table 88 and Figure 35. In the 3-year PEPI trial (Mebane-Sims et al., 1996) only one case of endometrial cancer was seen and this was in the placebo arm. This result is not unexpected given the relatively short follow-up and the small sample size of the study. No summary measure of risk was calculated for the PEPI trial results. However, the HER/HERS II and WHI studies also showed no significant difference in risk despite their longer duration and follow-up (6.8 years and 5.2 years respectively).

It should be noted that since the literature search was conducted for this review an updated analysis of endometrial cancer data from the WHI study has been published. For details see Addendum A.

TABLE 88 HRT (EPRT): ENDOMETRIAL CANCER — RCT RESULTS

Author	Treatment	HRT n/N	No HRT n/N	Type of measure	Risk estimate
<i>Continuous therapy</i>					
Hulley (2002) ^a	CEE + MPA	0.4/1000 py	0.9/1000 py	RH	0.39 (0.08, 2.02)
Hulley (2002) ^b	CEE + MPA	0.2/1000 py	0.9/1000 py	RH	0.25 (0.05, 1.18)
Rossouw (2002) ^c	CEE + MPA	22/8506	25/8102	HR	0.83 (0.29, 2.32)
Mebane-Sims (1996)	CEE + MPA	0/120	1/119	-	-
<i>Sequential therapy</i>					
Mebane-Sims (1996)	CEE + MPA	0/118	1/119	-	-
Mebane-Sims (1996)	CEE + MP	0/120	1/119	-	-

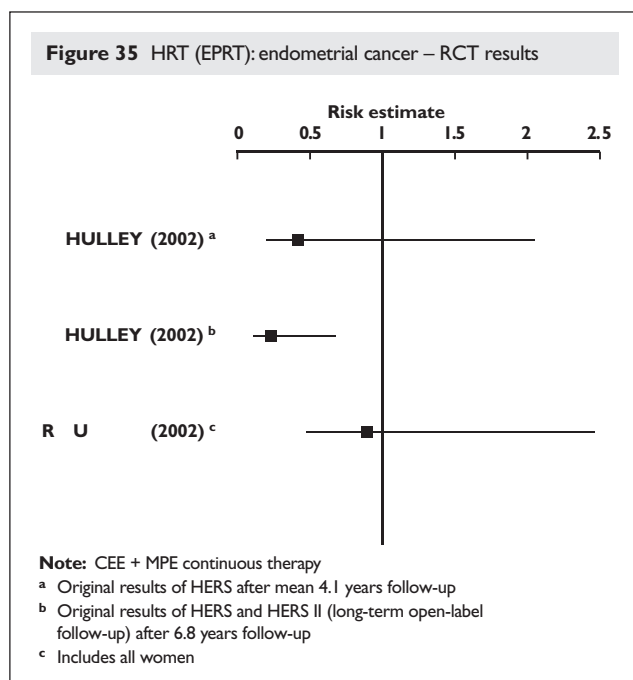
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CEE, conjugated equine oestrogen; HR, hazard ratio; MP, micronised progesterone; MPA, medroxyprogesterone acetate; py, person-years; RH, relative hazard.

^a Original results of HERS after mean 4.1 years follow-up; unadjusted results.

^b Overall results of HERS and HERS II (long-term open-label follow-up) after 6.8 years follow-up; unadjusted results.

^c Includes all women



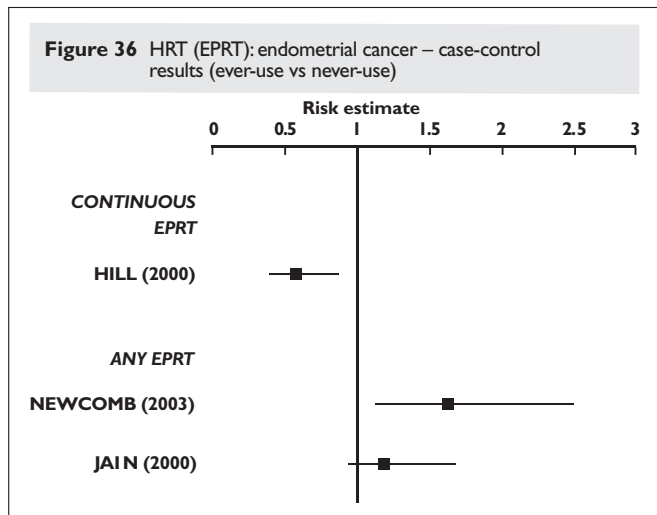
Ever-use versus never-use

The effect of ever-use versus never-use of EPRT on endometrial cancer risk was assessed in three case-control studies. In the Hill *et al.* (2000) study the use of continuous EPRT was not associated with a change in risk of endometrial cancer. A similar result was seen for any type of EPRT in the Jain *et al.* (2000) study. On the other hand, the use of any type of EPRT (continuous or sequential) was associated with a significantly increased risk of endometrial cancer in the Newcomb and Trentham-Dietz (2003) study. These results are summarised in Table 89 and Figure 36.

TABLE 89 HRT (EPRT): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (EVER-USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Continuous EPRT</i>					
Hill (2000)	Case-control	9/33	392/793	OR	0.6 (0.3, 1.3)
<i>Any EPRT</i>					
Newcomb (2003)	Case-control	48/166	402/1667	RR	<i>1.69 (1.15, 2.47)</i>
Jain (2000)	Case-control	97/111	292/316	OR	1.25 (0.88, 1.77)

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: EPRT, oestrogen + progestogen therapy; OR, odds ratio, RR, relative risk.



Newcomb and Trentham-Dietz (2003) further assessed the effect of different doses and duration of progestogen on endometrial cancer risk. These results are summarised in Table 90 and Figure 37. Although based on a small number of cases, the results suggest that a regimen with only a low dose of progestogen may have contributed to the elevated risk of endometrial cancer. The effect of the sequential regimen is less clear.

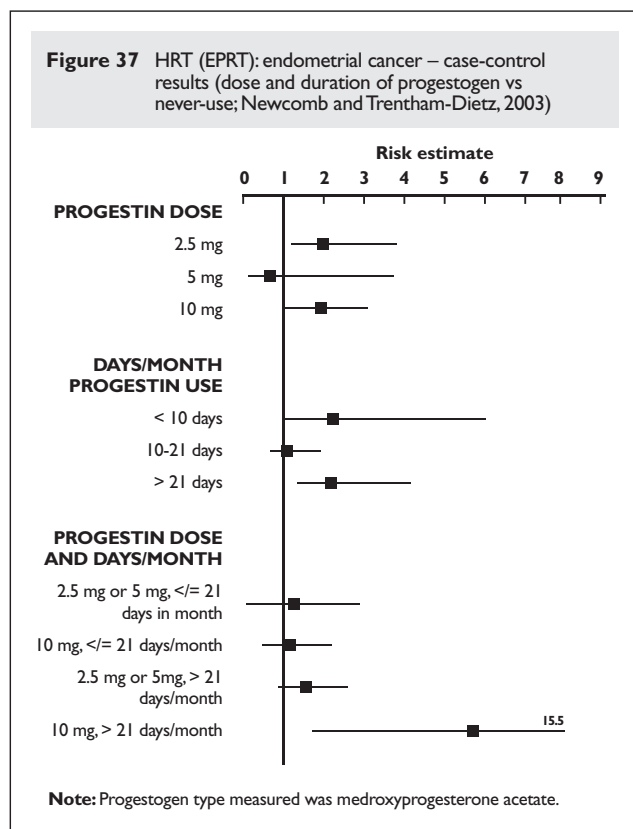
TABLE 90 HRT (EPRT): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (DOSE AND DURATION OF PROGESTOGEN VS NEVER-USE; NEWCOMB AND TRENTHAM-DIETZ, 2003)

Author	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Progestogen dose</i>				
2.5 mg	18/53	402/1667	RR	1.98 (1.09, 3.62)
5 mg	2/16	402/1667	RR	0.75 (0.16, 3.41)
10 mg	16/65	402/1667	RR	1.59 (0.87, 2.92)
<i>Days/month of progestogen</i>				
< 10 days	8/21	402/1667	RR	2.43 (1.00, 5.92)
10-21 days	14/71	402/1667	RR	1.10 (0.59, 2.07)
> 21 days	20/62	402/1667	RR	2.26 (1.27, 4.00)
<i>Progestogen dose and days/month^a</i>				
2.5 mg or 5 mg, ≤ 21 days/month	6/24	402/1667	RR	1.29 (0.49, 3.36)
10 mg, ≤ 21 days/month	10/54	402/1667	RR	1.11 (0.53, 2.32)
2.5 mg or 5 mg, > 21 days/month	12/45	402/1667	RR	1.68 (0.82, 3.43)
10 mg, > 21 days/month	5/8	402/1667	RR	5.75 (1.75, 18.9)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: RR relative risk.

^a Progestogen type measured was medroxyprogesterone acetate.



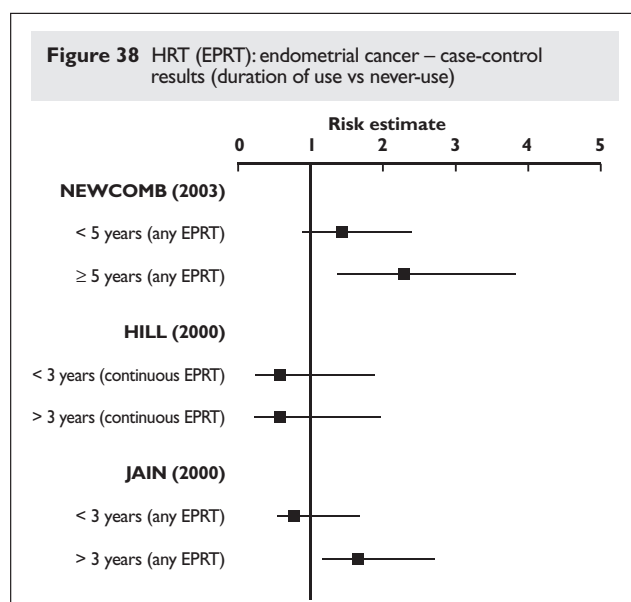
Duration of use

The effect of duration of EPRT on endometrial cancer risk was assessed in three case-control studies. Hill *et al.*(2000) showed no change in risk associated with increased duration of EPRT, however it should be noted that there were very small numbers of continuous EPRT users (cases and controls) in this analysis. On the other hand, the results of the Newcomb (2003) and Jain (2000) studies suggest an increasing risk of endometrial cancer associated with an increasing duration of EPRT. These results are summarised in Table 91 and Figure 38.

TABLE 91 HRT (EPRT): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (DURATION OF USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Newcomb (2003)</i>					
< 5 years (any EPRT)	Case-control	24/104	402/1667	RR	1.41 (0.85, 2.35)
≥ 5 years (any EPRT)	Case-control	24/62	402/1667	RR	2.25 (1.32, 3.82)
<i>Hill (2000)</i>					
< 3 years (continuous EPRT)	Case-control	4/16	392/793	OR	0.6 (0.2, 1.7)
> 3 years (continuous EPRT)	Case-control	5/17	392/793	OR	0.6 (0.2, 1.8)
<i>Jain (2000)</i>					
< 3 years (any EPRT)	Case-control	29/51	292/316	OR	0.72 (0.43, 1.21)
> 3 years (any EPRT)	Case-control	68/60	292/316	OR	1.74 (1.14, 2.64)

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: EPRT, oestrogen + progestogen therapy; OR, odds ratio; RR, relative risk.



Current-use

The effect of the current use of EPRT on risk of endometrial cancer was examined in the study by Newcomb and Trentham-Dietz (2003) only. Their result suggests that the current use of any EPRT regimen results in a significantly increased risk of endometrial cancer (Table 92). Whilst the magnitude of this risk elevation is considerable, it is substantially less than that for oestrogen only therapy reported in the same study (RR 6.19).

TABLE 92 HRT (EPRT): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (CURRENT-USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
Newcomb (2003)	Case-control	44/153	402/1667	RR	<i>1.76 (1.18, 2.64)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: RR, relative risk.

Past-use and years since past-use

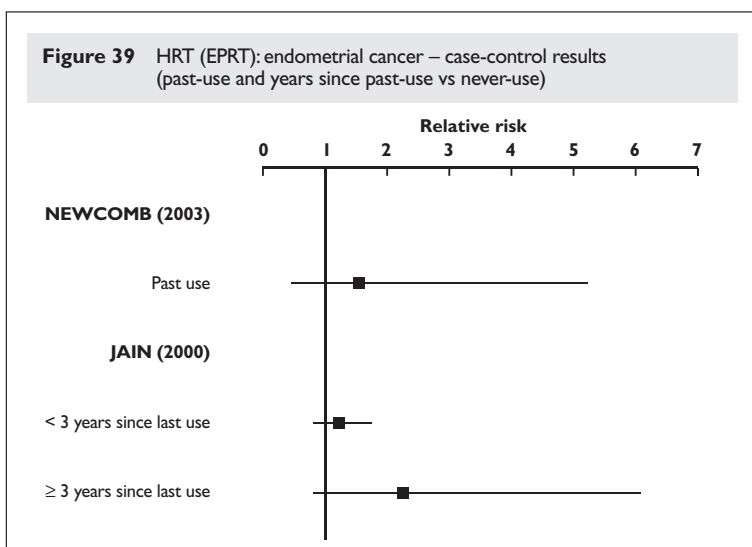
The association between past-use and years since past-use of EPRT was assessed in two case-control studies. As shown in Table 93 and Figure 39, past-use of EPRT was not associated with increased risk of endometrial cancer. However, it should be noted that very small numbers of EPRT users (cases and controls) were included in the analyses of past use (Newcomb) and more than 3 years since last use (Jain), as shown by the wide confidence intervals.

TABLE 93 HRT (EPRT): ENDOMETRIAL CANCER — CASE-CONTROL RESULTS (PAST-USE AND YEARS SINCE PAST-USE VS NEVER-USE)

Author	Study type	HRT (case/control)	No HRT (case/control)	Type of measure	Risk estimate
<i>Newcomb et al.(2003)</i>					
Past-use	Case-control	4/13	402/1667	RR	1.53 (0.45, 5.2)
<i>Jain et al.(2000)</i>					
< 3 years since last use	Case-control	86/103	292/316	OR	1.17 (0.82, 1.69)
≥ 3 years since last use	Case-control	11/8	292/316	OR	2.2 (0.84, 5.78)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: OR, odds ratio; RR, relative risk.



Ovarian cancer

Summary

At the time of the current review there was no level I or II evidence available relating to ovarian cancer risk. However, since then, ovarian cancer results from the WHI study (level II evidence) have become available showing no increased risk (see Addendum A). Previous level III-2 evidence suggested an increased risk of both ovarian cancer incidence and mortality with oestrogen-only HRT, that became more pronounced with longer duration therapy.

Existing systematic reviews

The literature search identified only one systematic review examining the association between HRT use and risk of ovarian cancer. This review contained observational studies only (one cohort study and no case-control studies) and as such constitutes level III-2 evidence. The characteristics and quality of this included systematic review are summarised in Table 94. For further details see Appendix B (Section 9.1.4).

TABLE 94 HRT: OVARIAN CANCER — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level III-2 evidence					
Garg et al. (1998)	Systematic review of observational studies (12) <i>Fair</i>	Postmenopausal women	HRT Mode of administration and dose not specified	No HRT	Incidence

See Section 9.1.4.

A meta-analysis of the case-control and cohort studies was performed for this review. This analysis showed that the increased risk of developing invasive ovarian cancer associated with 'ever-use' of HRT was 15% (RR 1.15; 1.05, 1.27). The amount of heterogeneity and the risk estimate varied when different studies were included in the analyses (ie, case-control studies or whether hospital or population-based, or studies examining different durations of use; not shown). The largest risk was seen in women undergoing greater than 10 years of HRT, although this was only of borderline statistical significance. It should be noted that when both invasive and borderline cases were included the increased risk was 14% (RR 1.14; 1.04, 1.24).

The results of the Garg *et al.* (1998) review are summarised in Table 95 and Figure 40.

TABLE 95 HRT: OVARIAN CANCER — RESULTS OF EXISTING SYSTEMATIC REVIEW* (GARG ET AL., 1998)

HRT use	No. of studies	Relative risk ^a
Invasive		
Ever-use		
All studies ^b	10	<i>1.15 (1.05, 1.27)</i> ^c
Duration of use		
< 1 year	4	1.12 (0.92, 1.36)
1-5 years	6	0.95 (0.79, 1.14)
6-10 years	6	1.02 (0.81, 1.29)
> 10 years	6	1.27 (1.00, 1.61) ^c
Invasive and borderline		
Ever-use		
All studies	12	<i>1.14 (1.04, 1.24)</i>
Duration of use		
< 1 year	5	1.13 (0.93, 1.36)
1-5 years	7	0.96 (0.80, 1.15)
6-10 years	7	1.04 (0.83, 1.29)
> 10 years	7	1.25 (0.99, 1.57) ^c

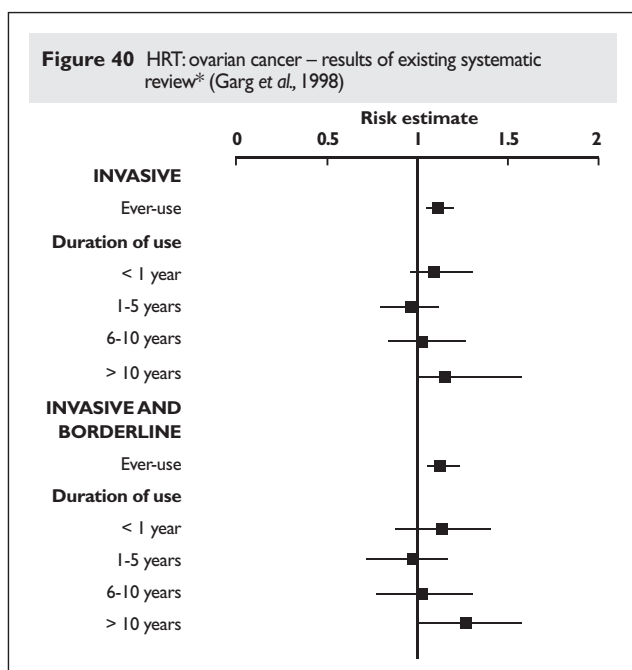
Note: Risk estimates in italics are considered statistically significant as they do not include one.

*Table modified from Garg *et al.* (1997).

^a All risk estimates obtained using the fixed effects model.

^b For details of results restricted to study type see the original paper.

^c Significantly heterogenous ($P < 0.1$).



Original studies

There is existing level III-2 evidence regarding the association between HRT and ovarian cancer in the review by Garg *et al.* (1998) which was considered to be of fair methodological quality. Therefore, a search for original studies was conducted for the years 1997-2003 to supplement and update the evidence provided by the existing systematic review.

The search identified two cohort studies (Lacey *et al.*, 2002; Rodriguez *et al.*, 2001) and one case-control study (Riman *et al.*, 2002). The study by Lacey *et al.* (2002) examined the association between ERT and EPRT and ovarian cancer risk and was considered to be a good quality cohort study. The study by Rodriguez *et al.* (2001) presents results of an extended follow-up of a cohort study already included in the Garg review. While it was considered to be a good quality study its generalisability is in question given that it is unclear whether the included subjects used ERT only or combined EPRT. Nevertheless, it will be included here as it presents results regarding mortality due to ovarian cancer and provides 14 years of follow-up. The case-control study by Riman *et al.* (2002) was considered to be only fair quality as the main analysis compared the ever-use of particular HRT regimens with never-users of that particular regimen, not never-users of HRT. However, in order to validate their results they did perform limited analyses of ever-use versus 'true' never-use of HRT and these results will be presented here. For details of the characteristics and quality of these cohort studies see Table 96. For further details see Appendix B (Section 9.1.4).

There was one additional study identified which contained duplicate data already contained in the existing systematic review (Purdie *et al.*, 1995). However, a more recent publication of this study by Purdie *et al.* (1999) did provide greater detail regarding different types of HRT. While not officially included in this review, it was examined to determine if the results concur with those of the other included studies.

It should be noted that since the literature search was conducted for this review, an analysis of ovarian cancer data from the WHI study has been published. For details see Addendum A.

TABLE 96 HRT: OVARIAN CANCER — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level III-2 evidence					
Lacey <i>et al.</i> (2002)	Cohort Mean follow-up 13.4 years Good	Postmenopausal women with at least one intact ovary Mean age at baseline 57 years N=44241	ERT, EPRT or EPRT following ERT Mode of administration and dose not specified N=256084 py	Never-use HRT N=270520 py	Incidence
Rodriguez <i>et al.</i> (2001)	Cohort Follow-up 14 years Good/Fair	Postmenopausal women with intact uterus and at least one intact ovary ~ 8% FH of OC N=211581	HRT Mode of administration and dose not specified N=46260	Never-use HRT N=165321	Mortality
Riman <i>et al.</i> (2002)	Case-control (population-based) Fair	Women aged 50-74 with at least one intact ovary Mean age ~ 63 N=4554	ERT, EPRT (sequential or continuous) Various modes of administration and doses N=965	Never-use HRT ^a N=3589	Incidence

See Section 9.1.4.

Abbreviations: EPRT, oestrogen + progestogen therapy; ERT, oestrogen-only therapy; FH, family history; HRT, oestrogen ± progestogen therapy; OC, ovarian cancer.

^a The primary analysis was carried out for ever-use of a particular regimen versus never-use of that regimen. Only results of the validation analysis of ever-use of a regimen versus never-use of any HRT will be included in this review.

Effect by HRT type: ERT only

The results of the studies by Riman *et al.* (2002) and Lacey *et al.* (2002) are summarised in Table 97 and Figure 41. They show that ever-use of ERT was associated with significantly increased risk of ovarian cancer. When duration of ERT was considered, a significantly increased risk of ovarian cancer was related to use of greater than four years with risk increasing as duration increased. This resulted in an increased RR per year of use of 0.07 (0.02, 0.13). An analysis of the effect of duration of therapy and time since last use was also performed. Recent use of greater than 20 years was associated with a two-fold increased risk of ovarian cancer. However, past use of 10-19 years was also associated with a significantly increased risk.

The results of the updated analysis by Purdie *et al.* (1999) show an increased risk, however this was not statistically significant (adjusted OR 1.27; 0.86, 1.88).

TABLE 97 HRT (ERT ONLY): OVARIAN CANCER — COHORT/CASE-CONTROL RESULTS

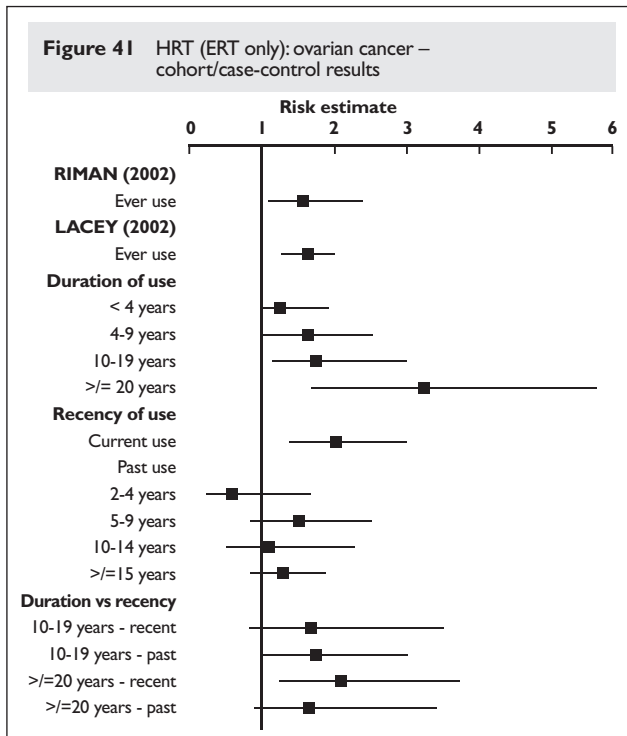
	HRT (case/control or n/py)	No HRT (case/ control or n/py)	Type of measure	Risk estimate ^a
<i>Riman et al.(2002)</i>				
Ever use	59/259	nr	OR	<i>1.58 (1.03, 2.42)</i>
<i>Lacey et al.(2002)</i>				
Ever use	116/179065	120/270520	RR	<i>1.6 (1.2, 2.0)</i>
Duration of use				
< 4 years	51/93804	120/270520	RR	1.3 (0.96, 1.9)
4-9 years	25/40451	120/270520	RR	1.6 (1.0, 2.6)
10-19 years	21/30058	120/270520	RR	<i>1.8 (1.1, 3.0)</i>
>= 20 years	16/11567	120/270520	RR	<i>3.2 (1.7, 5.7)</i>
Recency of use				
Current use ^b	-	-	RR	<i>2.0 (1.4, 3.0)</i>
Past use				
2-4 years	-	-	RR	0.64 (0.24, 1.7)
5-9 years	-	-	RR	1.5 (0.88, 2.5)
10-14 years	-	-	RR	1.1 (0.59, 2.2)
≥ 15 years	-	-	RR	1.3 (0.82, 2.1)
Duration vs recency				
10-19 years - recent	-	-	RR	1.7 (0.78, 3.5)
10-19 years - past	-	-	RR	1.8 (1.0, 3.0)
≥ 20 years - recent	-	-	RR	<i>2.1 (1.2, 3.8)</i>
≥ 20 years - past	-	-	RR	1.7 (0.9, 3.4)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: OR, odds ratio; py, person-years; RR, relative risk.

^a Multivariate-adjusted for ever-use and duration of use. It is unclear whether RRs for other analyses are adjusted as they were extracted from the text.

^b Current use or use within 2 years.



Effect by HRT type: EPRT only and EPRT following ERT only

The results of the Riman and Lacey studies are summarised in Table 98 and Figure 42. The Lacey *et al.* (2002) study shows that ever-use of EPRT, duration of use of EPRT, current use of EPRT and use of EPRT following ERT only were not significantly associated with risk of ovarian cancer. Past use of EPRT, however, was significantly associated with an almost three-fold increase in risk. This is an unexpected finding and it should be noted from the width of the confidence interval that this analysis may be based on very few patient years (not reported).

When ever-use of EPRT is broken down into sequential and continuous regimens in the Riman *et al.* (2002) study, a significantly increased risk of ovarian cancer is seen in subjects taking the sequential regimen.

It should be noted that the results shown in an updated analysis of the Australian study by Purdie (excluded from this review as it was included in the Garg systematic review) concur with those of the Lacey study. An increased risk of ovarian cancer is seen in subjects taking EPRT compared with never-use of HRT (adjusted OR 1.34; 0.83, 2.17), however this is not statistically significant.

TABLE 98 HRT (EPRT AND EPRT FOLLOWING ERT): OVARIAN CANCER — COHORT/CASE-CONTROL RESULTS

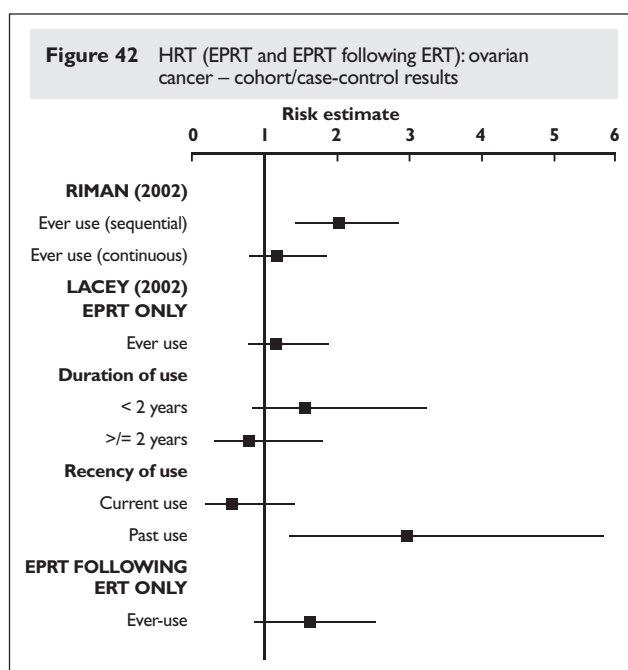
Author	HRT (case/control or n/py)	No HRT (case/control or n/py)	Type of measure	Risk estimate ^a
<i>Riman et al.(2002)</i>				
Ever-use (sequential only)	87/348	nr	OR	<i>1.98 (1.40, 2.78)</i>
Ever-use (continuous only)	55/280	nr	OR	1.11 (0.71, 1.74)
<i>Lacey et al.(2002)</i>				
EPRT only				
Ever use	18/42400	120/270520	RR	1.1 (0.64, 1.7)
Duration of use				
< 2 years	8/12809	120/270520	RR	1.6 (0.78, 3.3)
>= 2 years	6/19521	120/270520	RR	0.8 (0.35, 1.8)
Recency of use				
Current use ^b	-	-	RR	0.62 (0.27, 1.4)
Past use	-	-	RR	<i>2.8 (1.4, 5.7)</i>
EPRT following ERT only				
Ever-use	21/34619	120/270520	RR	1.5 (0.91, 2.4)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: EPRT, oestrogen + progestogen therapy; ERT, oestrogen-only therapy; OR, odds ratio; RR, relative risk.

^a Multivariate adjusted for ever-use and duration of use. Unclear whether RRs for other analyses are adjusted as they were extracted from the text.

^b current use or use within 2 years.



Effect by HRT type: any type

The results of the Rodriguez study are summarised in Table 99 and Figure 43.

They show that ever-use of HRT and use of HRT at baseline were associated with a significantly increased risk of ovarian cancer-related mortality. When HRT was broken down into duration of use, significantly increased risk of death due to ovarian cancer was significantly related to use of greater than 10 years duration only.

TABLE 99 HRT (ANY): OVARIAN CANCER — COHORT RESULTS (EVER-USERS MORTALITY; RODRIGUEZ ET AL., 2001)

Author	HRT (deaths per person-years)	No HRT (deaths per person-years)	Type of measure	Risk estimate ^a
Level III-2 evidence				
Ever-users	255/625984	689/2185876	RR	<i>1.23 (1.06, 1.43)</i>
Baseline ^b	62/151800	689/2185876	RR	<i>1.51 (1.16, 1.96)</i>
Former ^c	193/474103	689/2185876	RR	1.16 (0.99, 1.37)
< 10 years				
Baseline	31/110379	689/2185876	RR	1.14 (0.79, 1.65)
Former	158/416823	689/2185876	RR	1.1 (0.92, 1.31)
≥ 10 years				
Baseline	31/41396	689/2185876	RR	<i>2.2 (1.53, 3.17)</i>
Former	35/57281	689/2185876	RR	<i>1.59 (1.13, 2.25)</i>
Former-users	158/416823	689/2185876	RR	1.10 (0.92, 1.31)

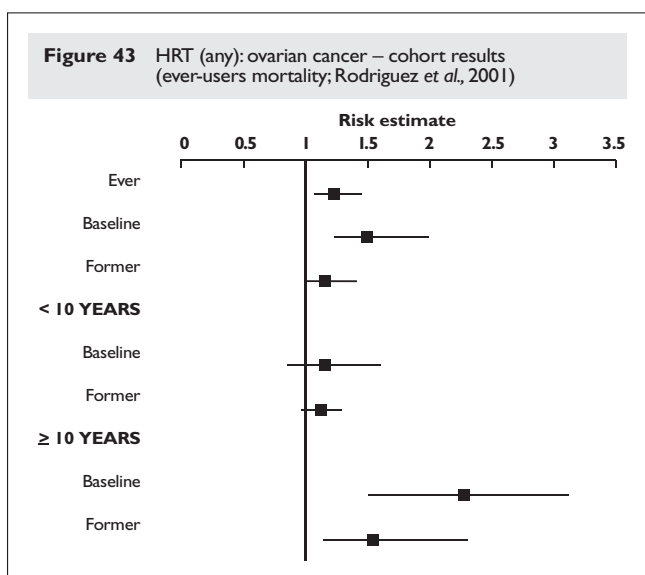
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: RR, relative risk.

^a The most adjusted data was used preferentially. Data was adjusted for age, race, duration of OC use, number of live births, age at menopause, BMI, age at menarche and tubal ligation.

^b Baseline users were defined as women who either said they were still using oestrogen or whose total years of use, added to their age at first use, was within 1 year of their age at baseline.

^c Formers users were defined as women whose total years of use added to their age at first use was less than their age at enrolment.



When former-users of HRT were compared with never-users, the results showed that use for longer than 10 years within the last 15 years was associated with a 59% increased risk of ovarian cancer mortality. These results are summarised in Table 100 and Figure 44.

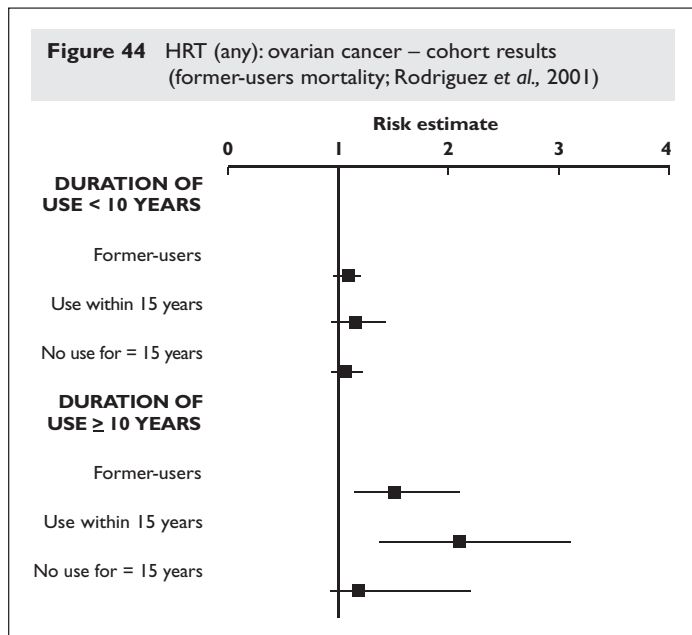
TABLE 100 HRT (ANY): OVARIAN CANCER — COHORT RESULTS (FORMER-USERS MORTALITY; RODRIGUEZ ET AL., 2001)

Author	HRT (deaths per person years)	No HRT (deaths per person/years)	Type of measure	Risk estimate ^a
Level III-2 evidence				
<i>Duration of use < 10 years</i>				
Former-users	158/416823	689/2185876	RR	1.10 (0.92, 1.31)
Use within 15 years	45/160278	689/2185876	RR	1.17 (0.85, 1.60)
No use for ≥ 15 years	113/256545	689/2185876	RR	1.07 (0.87, 1.32)
<i>Duration of use ≥ 10 years</i>				
Former users	35/57281	689/2185876	RR	1.59 (1.13, 2.25)
Use within 15 years	19/30887	689/2185876	RR	2.05 (1.29, 3.25)
No use for ≥ 15 years	16/26394	689/2185876	RR	1.31 (0.79, 2.17)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: RR, relative risk.

^a The most adjusted data was used preferentially. Data was adjusted for age, race, duration of OC use, number of live births, age at menopause, BMI, age at menarche and tubal ligation.



Cardiovascular risk

The following sections present the current evidence relating to the association between the use of HRT and various cardiovascular risks. The evidence is divided under the following outcomes:

1. **'cardiovascular disease (CVD)'**, an overall composite outcome which can include the following; stroke, coronary artery disease (CAD), sudden cardiac death, congestive heart failure (CHF), peripheral vascular disease, coronary artery bypass graft surgery (CABG), and percutaneous transluminal coronary angioplasty (PTCA).
2. **'coronary artery disease (CAD)'**, a composite outcome generally limited to non-fatal myocardial infarction or coronary death, but which sometimes includes unstable angina (UA), and coronary revascularisation procedures (ie, CABG and PTCA).
3. **'stroke'**, typically defined as stroke or cerebrovascular accident, which can include ischaemic as well as haemorrhagic stroke. Also included are studies which only report a composite outcome of stroke or transient ischaemic attack (cerebral).
4. **'venous thromboembolism (VTE)'**, defined as deep vein thrombosis (DVT) or pulmonary embolism (PE). Any studies which included superficial phlebitis or similar outcomes within their definition of VTE were excluded from the current review.

The evidence for each of these cardiovascular sections is presented separately for two populations of women: (i) women in general and (ii) women with existing cardiovascular disease. Where a particular study is restricted to women without prior cardiovascular disease, this fact is noted in the text or tables, and the study is included in the 'women in general' sub-section.

The results will be further subdivided by type of HRT: (i) oestrogen only (ERT), (ii) oestrogen combined with progestogen (EPRT) and (iii) any type, defined as analyses where the type of HRT being examined is not limited or specified.