<table>
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<tr>
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<th>Relative risk (95% CI)*</th>
<th>Adjustment for potential confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colditz &amp; Rosner (2000) USA Nurses’ Health Study 1980–1994</td>
<td>58,520 women aged 30–55 years in 1980, followed through June 1, 1994 in the Nurses’ Health Study. 1,761 incident invasive breast cancer cases were identified. Followed 1980–94</td>
<td>Mailed questionnaire</td>
<td>invasive breast cancer</td>
<td>Postmenopausal hormone use</td>
<td>None 5977</td>
<td>1.0 ref</td>
<td>Age of menarche, menopause, pregnancy history, BBD, postmenopausal hormone use, body mass index, height, alcohol use, and family history of breast cancer</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ERT 7322</td>
<td>1.23 (1.06–1.42)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>HRT 9988</td>
<td>1.67 (1.18–2.36)</td>
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<tr>
<td>Schairer et al., (2000) Breast Cancer Detection Demonstration Project, USA 1973–1995</td>
<td>46,355 postmenopausal women (mean age at start of followup, 58 years) identified from 29 screening centers throughout the United States. participants in the Breast Cancer Detection Demonstration Project (BCDDP); 2082 breast cancer cases identified during follow-up; follow-up between 1979–84</td>
<td>Mailed questionnaire or telephone interview</td>
<td>Incident breast cancer</td>
<td>Estrogen only</td>
<td>Ever use 805</td>
<td>1.1 (1.0–1.3)</td>
<td>Age, education, BMI, age at menopause, mammographic screening</td>
<td>Increases in risk with estrogen only were restricted to use within the previous 4 years (RR, 1.2 [95% CI, 1.0–1.4]; the relative risk increased by 0.01 [95% CI, 0.002–0.03] with each year of estrogen-only use. The primary type of estrogen used was conjugated estrogens (Premarin).</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>with progestin unknown Years since last use Current 243</td>
<td>1.1 (1.0–1.3)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–2 77</td>
<td>1.4 (1.1–1.8)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;2–4 55</td>
<td>1.2 (0.9–1.6)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;4–6 35</td>
<td>0.9 (0.6–1.3)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;6 309</td>
<td>1.1 (0.9–1.2)</td>
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</table>
Table 2.1 Cohort studies of estrogen-only menopausal therapy and breast cancer

<table>
<thead>
<tr>
<th>Reference, location, name of study</th>
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<th>No. of cases/deaths</th>
<th>Relative risk (95% CI)*</th>
<th>Adjustment for potential confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beral et al. (2003) UK Million Women Study, 1996–2001</td>
<td>1 084 110 UK women aged 50–64 years were recruited between 1996 and 2001 and were followed up for cancer incidence and death.</td>
<td>Mailed questionnaire</td>
<td>ICD C50</td>
<td>Oestrogen only</td>
<td>991</td>
<td>1.30 (1.22–1.38)</td>
<td>Age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.</td>
<td>Users of oestrogen-only preparations were further subdivided according to the specific oestrogen constituent of the HRT (equine oestrogen or oestradiol), its dose, and whether it was administered as an oral, transdermal, or implanted formulation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration of current use (yrs)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 1</td>
<td>25</td>
<td>0.81 (0.55–1.20)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1-4</td>
<td>251</td>
<td>1.25 (1.10–1.41)</td>
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<td></td>
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<td></td>
<td></td>
<td>5-9</td>
<td>416</td>
<td>1.32 (1.20–1.46)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>≥10</td>
<td>277</td>
<td>1.37 (1.22–1.54)</td>
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<td></td>
<td></td>
<td></td>
<td>By constituent and dose</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>All equine oestrogen</td>
<td>426</td>
<td>1.29 (1.16–1.43)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤0·625 mg</td>
<td>288</td>
<td>1.25 (1.11–1.41)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0·625 mg</td>
<td>135</td>
<td>1.36 (1.14–1.61)</td>
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<tr>
<td></td>
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<td></td>
<td>All ethinyloestradiol</td>
<td>454</td>
<td>1.24 (1.12–1.37)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤1 mg ethinyloestradiol</td>
<td>367</td>
<td>1.25 (1.12–1.40)</td>
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<td></td>
<td></td>
<td></td>
<td>&gt;1 mg ethinyloestradiol</td>
<td>47</td>
<td>1.19 (0.89–1.58)</td>
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<td>By formulation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral</td>
<td>606</td>
<td>1.32 (1.21–1.45)</td>
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<td></td>
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<td></td>
<td></td>
<td>Transdermal</td>
<td>324</td>
<td>1.24 (1.11–1.39)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Implanted</td>
<td>54</td>
<td>1.65 (1.26–2.16)</td>
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<tr>
<td>Olsson et al., (2003), Sweden Swedish registry data, 40 000 women aged 25–65, randomly selected from the South Swedish Health Care Region, followed until 2001; 556 malignant tumors developed during the follow-up period</td>
<td>Questionnaire Interviews</td>
<td>Malignant breast cancer</td>
<td>Time to breast carcinoma in relation to the type of HRT use</td>
<td>Estradiol only</td>
<td>NR</td>
<td>0.81 (0.34–1.96)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estradiol</td>
<td>NR</td>
<td>0.71 (0.40–1.26)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td>Type and duration of HRT</td>
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<td></td>
<td></td>
<td></td>
<td>Women who ever used only one type of HRT</td>
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<td></td>
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<td>Estradiol only</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Never user of HRT</td>
<td>NR</td>
<td>1.00</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–48mos</td>
<td>NR</td>
<td>1.56 (0.38–6.38)</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>48+mos</td>
<td>NR</td>
<td>1.00</td>
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### Table 2.1 Cohort studies of estrogen-only menopausal therapy and breast cancer

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<tr>
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<td></td>
</tr>
<tr>
<td>1–48mos</td>
<td>48+mos</td>
<td>Women who used different types of HRT</td>
<td>Estradiol only</td>
<td>NR</td>
<td>1.44 (0.63–3.28)</td>
<td>2.29 (0.93–5.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never user of HRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–48mos</td>
<td>48+mos</td>
<td>Estradiol</td>
<td></td>
<td>NR</td>
<td>1.40 (0.56–3.48)</td>
<td>1.05 (0.25–4.26)</td>
<td></td>
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</tr>
<tr>
<td>Never user of HRT</td>
<td></td>
<td>Estriol</td>
<td></td>
<td>NR</td>
<td>1.44 (0.59–3.53)</td>
<td>2.27 (0.99–5.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type and duration of HRT</td>
<td>Estradiol only</td>
<td>1–48mos</td>
<td></td>
<td>526 (13)</td>
<td>0.77 (0.38–1.57)</td>
<td>0.58 (0.22–1.55)</td>
<td>For other types of HRT exposures and for year of interview.</td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>48+mos</td>
<td>Estradiol</td>
<td></td>
<td>300 (8)</td>
<td>0.87 (0.41–1.85)</td>
<td>1.98 (1.04–3.79)</td>
<td>Adjusted for year of interview. Adjusted for family history, age at first full-term pregnancy, nulliparity, and age at menarche</td>
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</tr>
<tr>
<td>Gestagen also considered</td>
<td></td>
<td>Reference category not clear</td>
<td>For estradiol use: it is clearly mentioned “estradiol only”, for estriol it is only mentioned “estriol”</td>
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<th>Relative risk (95% CI)*</th>
<th>Adjustment for potential confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakken et al. (2004) Norway, The Norwegian Women and Cancer (NOWAC) study 1996-1998</td>
<td>A representative, national, population-based prospective cohort study. 31 451 postmenopausal women, aged 45–64 years, with complete information; follow-up information based on linkage to the Cancer Registry of Norway</td>
<td>HRT Postal questionnaire</td>
<td>Incident breast cancer</td>
<td>Estrogen only HRT</td>
<td>&lt; 5 years 13 2.5 (1.4–4.5)</td>
<td>1.0 (0.4–2.5) p trend = 0.2</td>
<td>Age, time since start of menopause, age at menarche, ever use of OCs, BMI, history of breast cancer in mother, regions with a screening program, age at first delivery and parity</td>
<td></td>
</tr>
</tbody>
</table>
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<th>Adjustment for potential confounders</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewertz et al. (2005) Denmark 1989–2002</td>
<td>From the files of the CPR, we identified 83 873 women identified from the Central population register, 40–66 years of age; linked to the Danish Cancer Registry and the Pharmaco-Epidemiological Prescription Database to identify cases of breast cancer and assess HRT exposure occurring through 2002.</td>
<td>Pharmaco-Epidemiologic Prescription Database</td>
<td>Breast cancer</td>
<td>Oestrogen only HRT</td>
<td>50</td>
<td>1.35 (1.01–1.80)</td>
<td>Calendar period, number of children, and age at first birth</td>
<td>Since women with only 1 prescription may never have actually taken the drug, they were classified as nonexposed.</td>
</tr>
<tr>
<td>Fournier et al., France, (2005) E3N Study, 1990–2000</td>
<td>98 997 women born between 1925 and 1950, after exclusions: 54 548 postmenopausal women followed for an average of 5.8y until 2000, 948 primary invasive breast cancer</td>
<td>24-month intervals: self administered questionnaires, from 1992</td>
<td>Invasive breast cancer</td>
<td>Estrogen used alone Transdermal/percutaneous route Oral route</td>
<td>29</td>
<td>1.2 (0.8–1.7)</td>
<td>Time since menopause, BMI, age at menopause parity and age at first full-term pregnancy, familial history of breast cancer, personal history of benign breast disease, use of oral progestogens before, ever use of oral contraceptives and previous mammography</td>
<td>The referent group consisted of women who indicated that they had either never used any form of HRT or had started taking HRT less than 1 year before the end of follow-up</td>
</tr>
<tr>
<td>Reference, location, name of study</td>
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<td>No. of cases/deaths</td>
<td>Relative risk (95% CI)*</td>
<td>Adjustment for potential confounders</td>
<td>Comments</td>
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<tr>
<td><strong>Lee et al; (2006)</strong> Hawaii and California MultiEthnic Cohort, 1993–96</td>
<td>A cohort study among 55,371 African-American, Native Hawaiian, Japanese-American, Latina and White postmenopausal women aged 45–75 years old enrolled the Multiethnic Cohort Study between 1993–96. A total of 1,615 incident invasive breast cancer cases were identified over an average of 7.3 years, followed until 2002.</td>
<td></td>
<td>Breast</td>
<td>Current ET&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Time on study</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0 to &lt;5 years</td>
<td>18</td>
<td>1.02 (0.62–1.66)</td>
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<td></td>
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<td></td>
<td></td>
<td>5 to &lt;10 years</td>
<td>60</td>
<td>1.35 (1.01–1.80)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>10+ years</td>
<td>183</td>
<td>1.55 (1.25–1.92)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Per 5 years of use</td>
<td>180</td>
<td>1.10 (1.05–1.16)</td>
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<td></td>
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<td></td>
<td>Past ET&lt;sup&gt;1&lt;/sup&gt;</td>
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<td></td>
<td>&gt;0 to &lt;5 years</td>
<td>31</td>
<td>0.95 (0.66–1.37)</td>
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<td></td>
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<td>5 to &lt;10 years</td>
<td>26</td>
<td>0.89 (0.59–1.33)</td>
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<td></td>
<td>10+ years</td>
<td>0.99 (0.88–1.11)</td>
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<tr>
<td><strong>Rosenberg et al (2006a), USA 1995–2003</strong></td>
<td>Biennial questionnaires from 1995 through 2003 in the Black Women’s Health Study, 32,559 women 40 years or older, 615 cases of breast cancer were reported.</td>
<td></td>
<td>Breast</td>
<td>Estrogen alone</td>
<td>134</td>
<td>1.10 (0.85–1.41)</td>
<td>Age, menopausal status, and age at menopause or hysterectomy</td>
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<td>Stratified by BMI</td>
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<td>BMI&lt;25</td>
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<td>1.41 (0.85–2.33)</td>
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<td>Duration (y)</td>
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<td>Estrogen (&lt;5)</td>
<td>14</td>
<td>1.30 (0.69–2.42)</td>
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<td>Estrogen (5–9)</td>
<td>6</td>
<td>1.15 (0.46–2.85)</td>
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<td></td>
<td>Estrogen (≥10)</td>
<td>13</td>
<td>2.71 (1.31–5.59)</td>
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<td>BMI 25–29</td>
<td>54</td>
<td>1.17 (0.77–1.78)</td>
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<td>Duration (y)</td>
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<td>Estrogen (&lt;5)</td>
<td>18</td>
<td>0.97 (0.56–1.68)</td>
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<td>Estrogen (5–9)</td>
<td>14</td>
<td>1.50 (0.80–2.82)</td>
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<td>Estrogen (5–9)</td>
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<td>Estrogen (≥10)</td>
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<sup>1</sup> Each subject may contribute to more than one category of use. Analyses are simultaneously adjusted for the other categories of hormone therapy use.
<table>
<thead>
<tr>
<th>Reference, location, name of study</th>
<th>Cohort description</th>
<th>Exposure assessment</th>
<th>Organ site (ICD code)</th>
<th>Exposure categories</th>
<th>No. of cases/deaths</th>
<th>Relative risk (95% CI)*</th>
<th>Adjustment for potential confounders</th>
<th>Comments</th>
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<tr>
<td>Rosenberg et al (2008), Sweden 1993–95</td>
<td>3979 cases from a population-based case–control study; women born in Sweden aged 50–74 years at first diagnosis of breast cancer; cases identified although the Swedish Cancer Register followed until 2003</td>
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