

Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials

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We conducted meta-analyses to assess the impact of menopausal hormone therapy (MHT) on the risk of incident invasive breast cancer (BC) in cohort studies (CS), case-control studies (CCS) and randomized controlled trials (RCTs) published 1989–2004. We used published data providing information upon unopposed estrogen therapy (ET), estrogen-progestin therapy (EPT) or all MHT combined. Major outcomes were MHT-associated overall risk of BC and change of risk per year used. There is a linear increase of overall risk by midterm year of case ascertainment based upon data of all study types for MHT and to a larger extent for EPT, not for ET. Effects are larger in CS than in CCS. Meta-analyses stratified by <1992 versus ≥1992 as midterm year of case ascertainment indicate larger summary risks for the latter period for all MHT analysed, in particular for EPT. Annual increases in BC risk for EPT across study types are 0–9%, for ET 0–3%. In conclusion, there is evidence that relative risks for BC risks by MHT, in particular EPT, have been increasing in recent years. Given the widespread use of MHT, and often long duration, more detailed knowledge about differential BC risks of both estrogens and progestins are necessary to minimize BC risk in symptomatic women who consider MHT.

Key words: breast cancer/estrogen-progestin therapy/hormone replacement therapy/menopausal hormone therapy/unopposed estrogen therapy

Introduction

The relation between risk of breast cancer (BC) and use of menopausal hormone therapy (MHT) has been the subject of many epidemiological studies and several meta-analyses (Armstrong, 1988; Dupont and Page, 1991; Steinberg *et al.*, 1991; Grady *et al.*, 1992; Sillero-Arenas *et al.*, 1992; Colditz *et al.*, 1993; Steinberg *et al.*, 1994; Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Hemminki and McPherson, 1997; Humphrey, 2002; National Heart, Lung, and Blood Institute, 2002; U.S. Preventive Services Task Force, 2005). Most information derives from a re-analysis of individual data from 51 epidemiological studies. These results indicate that risk of BC is elevated in women using MHT, risk increases with duration of use, and decreases after cessation of therapy (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). However, results largely depend on studies with unopposed conjugated equine estrogens (CEE), and most studies were conducted in the United States. Combined estrogen-progestin therapy (EPT), a treatment modality used to reduce the excess risk of endometrial cancer associated with unopposed estrogen use, may further increase the risk of BC as suggested by some

studies (Colditz *et al.*, 1995; La Vecchia *et al.*, 1995; Magnusson *et al.*, 1999; Ross *et al.*, 2000; Schairer *et al.*, 2000; Newcomb *et al.*, 2000). Two previous meta-analyses suggested differences regarding the magnitude of risk of BC attributable to MHT, when studies from the US and few European studies were compared (Steinberg *et al.*, 1991; Colditz *et al.*, 1993). We conducted a systematic search of the literature and performed a meta-analysis of cohort studies (CS), case-control studies (CCS) and randomized controlled trials (RCTs) to assess (i) the association between specified groups of hormone regimens and overall risk of BC and (ii) the magnitude of time-dependent risk as major prespecified outcomes.

Materials and methods

Identification of studies

We conducted a topic-specific search using Medline and the Cochrane Controlled Trials Register (<http://www.cochranelibrary.com>) for the time period 1989 until August 2004; publications retrieved for the year 1989 were restricted to those not already included in a previous meta-analysis (Steinberg *et al.*, 1991). The search was

restricted to studies conducted in the United States, Canada and European countries. We used the keywords 'hormone replacement therapy', 'hormone therapy', '(o)estrogen therapy', '(o)estradiol therapy', '(o)estrogen and progest* therapy', 'HRT', 'ERT', 'breast cancer', 'case control study', 'cohort study' and 'randomized/randomised/controlled clinical trial' in several combinations. We used recent systematic reviews to potentially identify further studies (Humphrey, 2002; National Heart, Lung, and Blood Institute, 2002; Nelson *et al.*, 2002) and reference lists of pertinent studies, topic-specific reviews (mostly in English, additionally in German), editorials, supplements, conference proceedings and abstract books. In studies with multiple publications from the same population, we included only data from the most recent publication. In the case of double publication, we included only the data sets of the first publication.

We included CS, CCS and RCTs, if information upon unopposed estrogen therapy (ET), or EPT or all hormone therapy combined (MHT: including unspecified/unknown preparations) was provided. We acknowledged a large variation of reporting types of MHT; earlier studies are more likely to predominantly include ET, more recent studies to progressively include EPT. Eligible studies had to include ever/never use of MHT, risk by duration of use or increase of risk within a given time interval. Studies were eligible if confidence intervals (CIs) or standard errors of risk estimates and dates on conduct of the study were provided.

Meta-analyses

Major outcomes were (i) the association between specified groups of hormone regimens and life-time risk of BC and (ii) the magnitude of time-dependent risk. Data were abstracted and statistical analyses performed independently (C. Greiser, E. Greiser) using two different approaches. To summarize effects of MHT on BC risk irrespective of duration or dosage, point estimates and CI were used in a fixed-effects model applying the general variance-based method (Petitti, 2000). In this method, the variance for each risk parameter is derived from published CIs (for the formula used see Appendix). To estimate summary slopes to determine increase of risk per year of use, slopes for both individual studies and summary slopes were calculated using inverse variance-weighted least squares estimates as suggested (Berlin *et al.*, 1993). In studies providing both risk estimates for various time periods and annual change estimates, the latter were used assuming that they provide a more precise estimate than values derived from tables in publications. We included two studies, which provided only slope estimates (Colditz and Rosner, 1998; Ross *et al.*, 2000), in the summary slope estimations. We used midperiod time points to determine duration values for time-periods. When durations were reported as 'greater than' a specific number of months or years, we added 20% to that duration. We examined heterogeneity across studies by applying the general variance-based method (Petitti, 2000) and providing for Cochrane's Q for individual substrata and for various totals of substrata. Cochrane's Q is a measure of heterogeneity and can be tested, using the chi-square distribution. *P* values less than 0.05 indicate heterogeneity. Analyses are stratified by type of study (CS, RCT and CCS), type of hormone therapy (ET, EPT and MHT), and midterm of years of case ascertainment (before 1992 versus 1992 and later). We chose the latter stratification level to improve analysis of time trends of

MHT. We calculated weighted linear regressions with midterm date of case ascertainment as independent variable and the natural logarithm of risk parameters (odds ratio, relative risk and hazard ratio) as well as untransformed risk parameters as dependent variables. For these meta-regressions the inverse of variances were used as weights. We used SAS version 6.12 (SAS Institute) for all analyses and STATA-8 (Stata Corporation) for bubble plots.

Results

We retrieved 94 publications, 44 CCS, 37 CS, 12 RCTs and one cross-sectional study. Included studies are listed in Table I (15 CS and 6 RCTs) and Table II (21 CCS) and excluded studies are listed in Table III. Briefly, included CS and RCTs varied widely regarding number of BC cases, women-years, age, longest reported duration of MHT use, type of MHT and time of follow-up. Of 21 studies, 12 were conducted in North America. The same variation was found in CCS; 14 of 21 were conducted in the US or Canada. The majority of studies had to be excluded for a wide spectrum of reasons, apart from not meeting our inclusion criteria.

The time trend of BC risk in conjunction with MHT use (hormone or unspecified/unknown hormone therapy) accrued at date of study, is shown in Figure 1. MHT regimens show a steady linear increase of BC risk within the studied time period when CS, RCTs and CCS are combined in a linear regression. The increase amounts to 4.4% per year from 1979 onwards, where 'year' reflects the midterm year of case ascertainment for respective studies. Figure 2 shows the results of a meta-analysis to assess risks in these women stratified by study type and two case ascertainment periods. There are larger risk increases in CS and the one RCT combined than in CCS when the latter time periods are compared; there is no difference between study types for the first time period. There is major heterogeneity present except in the first time period of CS. The time trend of BC risk in conjunction with EPT is shown in Figure 3. The regression analysis of time-dependent risk change shows a larger increase than in MHT, i.e. 5.8% per year, as derived from the regression coefficient for the untransformed risk. Figure 4 shows the results of a further meta-analysis to assess risks in EPT users, stratified by study type and time periods; increasing risks after EPT are evident in the latter time periods. All effects are homogenous except for the last period in CS, where the Million Women Study results with its large weight dominate the overall effect of CS with midterm of case ascertainment year after 1991. Figure 5 shows BC risks per year in EPT users, with stratifications as before. Risk increases by year of EPT use amount to 5–9% per year in those strata where effects are not heterogenous, i.e. CCS of the second time period and CS/RCTs irrespective of time periods. The first time period in CCS (three studies only) shows a wide range from a significant decrease of 7% per year of use to a significant increase of 5% per year. Again, as in risks associated with ever use (Figure 4), effects are larger in CS than in CCS. A regression of overall risk dependent on ET by midterm year of case ascertainment in different studies provided nonsignificant regression coefficients (data not shown). Figure 6 shows stratified risks in ET users. Summary risks derived from a meta-analysis differ between CCS and CS: a nil effect in the period before 1992 in CCS compared to a 19% risk increase in CS and increased risks of 18% (CCS) versus 27% (CS) in the later time period. However, effects were heterogenous for both time

Table 1. Cohort studies and randomized controlled trials included in meta-analysis

First author (year), region	Number of cases	Women (women-years)	Age/source	Longest reported duration	Type of hormone therapy*		Time period follow-up
					Ever/never	Duration	
Mills (1989), USA	215	20 341 (115 619)	PMP† Seventh-day-Adventist women	≥10	MHT		1976 to December 1982 (6 years)
Risch (1994), Canada	742	3279 (448 716)	43–49 years in 1976 Saskatchewan Health Prescription Drug Plan	≥3	MHT, ET		1976–1990
Colditz (1995), USA	1935	69 586 (725 550)	30–55 years in 1976, PMP†, Nurses' Health Study	≥10	ET, EPT		1978–1992
Folsom (1995), USA	468	41 070 (129 149)	55–69 years in 1985, Iowa Women's Health Study	≥15	MHT		1985–1991
Schuurman (1995), The Netherlands	471	62 573 (not given)	55–69 years, Netherlands Cohort Study (NLCS)	≥15	MHT		September 1986 to December 1989 (3.3 years)
Colditz (1998), USA	2035	Not given (980 000)	PMP†, Nurses' Health Study	10	ET, EPT		16 years
Lando (1999), USA	219	5761 (73 253)	PMP†, NHANES I Epidemiologic Follow-up Study	≥10	MHT		1971–1992 (22 years)
Persson (1999), Sweden	198	10 472 (60 298)	Born after 1918, original cohort, Sweden 1977–1980 Uppsala Health Care Region	≥6	ET, EPT		1987–1993
Schairer (2000), USA	2082	46 355 (473 687)	PMP†, Breast Cancer Detection Demonstration Project	≥16	ET, EPT		1980–1995 (16 years)
Manjer (2001), Sweden	141	5755 (57 199)	PMP†, Department of Preventive Medicine at Malmö University Hospital		MHT		June 1983 to April 1997 (average 9.8 years)
Viscoli (2001), RCT, USA	10	664 (not given)	71 years‡ from 21 hospitals in USA for stroke trial	2	ET		2.8 years‡
ESPRIT Team (2002), RCT, UK	8	1017 (not given)	50–69 years, 62.5 years‡		ET		July 1996 to February 2000 (trial duration 2 years)
Hulley (2002), RCT, USA	88	2763 (17 308§)	67 years‡, PMP†, HERS and HERS II	≥10	EPT		1993–2000 (6.8 years)
de Lignières (2002), France	105	3175 (28 367)	PMP†, cohort women, attending from January 1975 to December 1987, Department of Endocrinology and Reproductive Medicine, Necker Hospital, Paris		MHT, EPT		January 1975 to December 1995
Waters (2002), RCT, USA, Canada	4	423 (3160)	65 years‡, WAVE Trial, seven clinical sites		MHT		July 1997 to January 2002 (trial duration 2 years‡)
Writing Group for the Women's Health Initiative Investigators (2002), RCT, USA	290	16 608 (85 364)	50–79 years, PMP†, 40 clinical centres		EPT		5.2 years‡
Jernström (2003), Sweden	101	6586	50–64 years, WHILA Study		MHT		December 1995 to December 2001
Million Women Study Collaborators (2003), UK	9364	828 923	50–64 years		MHT, ET, EPT		May 1996 to March 2001
Tjønneland (2004), Denmark	423	23 618	50–64 years, PMP†, Diet, Cancer and Health Study, Danish cancer society		MHT		December 1993 to December 2000
Stahlberg (2004), Denmark	244	10 874 (68 912)	>44 years PMP†		MHT ET		1993 to April 2001
Women's Health Initiative Steering Committee (2004), RCT, USA	218	10 739 (71 522)	Danish Nurse Cohort 50–79 years, PMP†, 40 clinical centres		ET		1993 to November 2003 (average follow up of 6.8 years‡)
Total	17 138	1 129 512					

HERS, Heart Estrogen/Progestin Replacement Study; NHANES, National Health and Nutrition Examination Survey; RCT, randomized controlled trial; PMP, postmenopausal; WHILA Study, Women's Health in the Lund Area Study; WAVE, Women's Angiographic Vitamins and Estrogen.

*Menopausal hormone therapy (MHT) [unspecified/unknown hormone therapy or estrogen therapy (ET) plus estrogen-progestin therapy (EPT) combined], as utilized for meta-analysis.

†Only postmenopausal women included.

‡Mean.

§Women-years derived from Grady *et al.* (2002), as Hulley *et al.* (2002) did not provide women-years.

¶Estrogen plus testosterone-like cyclical progestin.

Table II. Case-control studies included in meta-analysis period

Author (year), region	Number of cases	Number /type of controls	Age (years), Type of cancer	Longest reported duration	Type of hormone therapy*		Time period follow-up
					Ever/never	Duration	
Kaufmann (1991) USA and Canada	1686, H	2077, H	40–69 PMP†	≥15	ET, EPT	ET	January 1980 to September 1988
Palmer (1991), Canada	607, P	1214, P	<70	≥15	ET, EPT	ET	1982–1986
Harris (1992), USA	412, H	336, H	<30 to ≥80 PMP†	≥5	MHT		January 1987 to December 1989
La Vecchia (1992), Italy	3037, H	2569, H		≥3	MHT		1983–1990
Yang (1992), Canada	699, P	685, P	<75 PMP†	≥10	ET, EPT	ET	June 1988 to June 1989
Weinstein (1993), USA	837, P	860, P	<79 PMP†	≥20	MHT		January 1984 to December 1986
La Vecchia (1995), Italy	2569, H	2588, H	20–74	≥5	MHT, EPT		June 1991 to February 1994
Lipworth (1995), Greece	820, H	795, 753, H	Mean: 56.4 (cases) and 54.4 (controls) PMP†	≥3	MHT		January 1989 to December 1991
Newcomb (1995), USA	3130, P	3698, P	<75 PMP†	≥15	MHT, ET, EPT	ET, EPT	April 1989 to December 1991
Stanford (1995), USA	537, P	492, P	50–64, 16.2% <i>in situ</i>	≥20	ET, EPT	ET, EPT	January 1988 to June 1990
Levi (1996), Switzerland	230, H	507, H	24–75	≥10	MHT		January 1990 to July 1995
Persson (1997), Sweden	435, P	1770, P	40–74, 13% <i>in situ</i>	≥11	MHT, ET, EPT	ET, EPT	February 1990 to June 1995
Henrich (1998), USA	109, P	545, P	45 + PMP†, 29.4% <i>in situ</i>	≥11	MHT, ET, EPT		July 1987 to March 1992
Magnusson (1999), Sweden	2563, P	2845, P	50–74, PMP†	>10	MHT, ET, EPT	ET, EPT	October 1993 to March 1995
Moorman (2000), USA	397, P	425, P	20–74, PMP†	≥10	MHT, ET, EPT		1993–1996
Ross (2000), USA	1897, P	1637, P	55–72, PMP†	≥15		ET, EPT	March 1987 to December 1989, January 1992 to December 1992, January 1995 to April 1996
Kirsh (2002), Canada	404, P	403, P	20–74, PMP†	≥10	MHT, ET, EPT	ET, EPT	April 1995 to March 1996
Newcomb (2002), USA	5298, P	5571, P	50–79 PMP†	≥5	MHT, ET, EPT	ET, EPT	January 1992 to December 1994
Weiss (2002), USA	1870, P	1953, P	55 to <65, PMP†			ET, EPT	July 1994 to April 1998
Wirfält (2002), Sweden	237, P	673, P	>49		MHT		May 1995 to December 1992
Li (2003), USA	975, P	1007, P	65–79		ET, EPT	ET, EPT	April 1997 to May 1999
Total	28 749	33, 403					

H, hospital-based cases resp. controls; P, population-based cases resp. controls; PMP, postmenopausal.

*Menopausal hormone therapy (MHT) [unspecified/unknown hormone therapy or estrogen therapy (ET) plus estrogen-progestin therapy (EPT) combined], as utilized for meta-analysis.

†Only postmenopausal women included.

periods across study types. Figure 7 shows stratified BC risks per year in ET users. There is no risk increase per year of use in early CCS, minimal increase of risk (1–3% in CS, 0.9% in CCS in 2nd period) with major differences in effect sizes when comparing different studies.

Discussion

The main findings are that overall risk of BC is increased in ever users of MHT, in particular EPTs. This difference was evident in all types of studies assessed. There is also an apparent time trend towards larger risks in recent studies. The increasing risk of intake of EPT (ever use) is indicative of increasing periods of use in subsequent years covered by different studies, as the analyses of annual increase of risk (Figure 5) show only a moderate increase from the first to second time period. The larger risk increases we found in CS could be due to the fact that there is generally a lag time of several years between the last follow-up of exposure data and the end of follow-up for BC incidence. It can be safely assumed that in the years before publication of end results of recent major studies (Million Women Study Collaborators, 2003; Writing Group for the Womens' Health Initiative Investigators, 2002; Women's Health Initiative Steering Committee, 2004), a

majority of women using MHT will have continued use until the end of morbidity assessment.

There have been secular trends in the use of both estrogens and progestins, including type, dose, and administration. Since it was acknowledged in the 1970s that use of ET increases endometrial cancer risk, the use of EPT has increased (Wysowski *et al.*, 1995; Brett and Madans, 1997; Hemminki *et al.*, 1988). The increasing duration of progestin use, alongside the extended duration of MHT use, may contribute to our finding that risks increase in ET and EPT users according to studies conducted more recently. The progestin largely used in North America is medroxyprogesterone acetate (MPA), in European countries various progestins, apart from MPA (Sitruk-Ware, 2002), including some with the potential to increase insulin-like growth factor 1 activity are used (Warren, 2004). Differences in BC risk may be attributable to differences in the functional profile of the various estrogens and progestins, apart from many other factors including environmental, genetic and life-style factors. A recent key issue is whether (different) progestins exert (more) proliferative effects on the postmenopausal breast. In a French cohort study, there were also differences regarding risk in EPT users according to the type of progestin (Fournier *et al.*, 2005).

Our results regarding overall risk, derived from ever use of hormones, and annual change are consistent with some, but not all

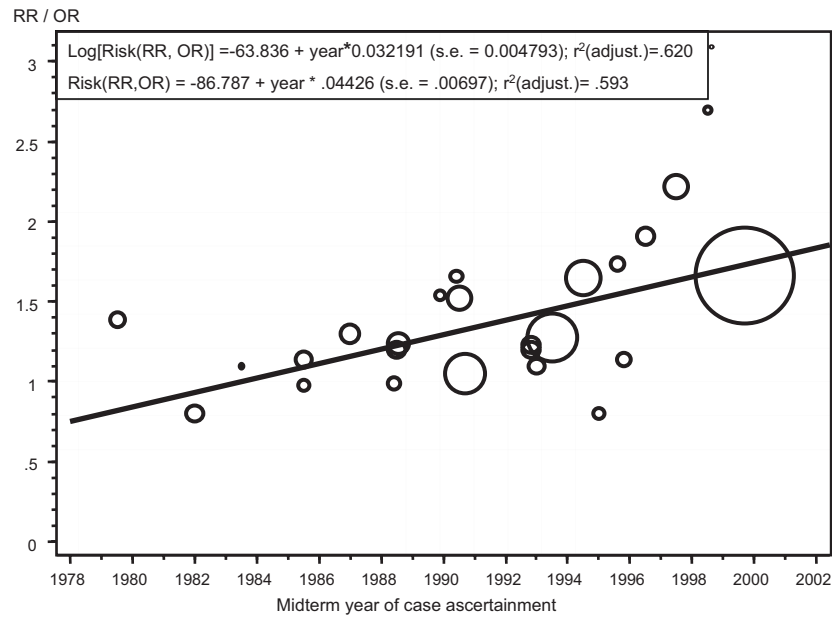
Table III. Excluded studies

Author	Year of publication	Type of study	Reason for exclusion
Bergkvist	1989	Cohort	Included in meta-analysis by Steinberg <i>et al.</i> (1991)
Dupont	1989	Cohort	Included in meta-analysis as above
Colditz	1990	Cohort	Data included in Colditz <i>et al.</i> (1995)
Colditz	1992	Cohort	Data included in Colditz <i>et al.</i> (1995)
Nachtigall	1992	RCT	Neither person-years nor CI provided
Yuen	1993	Cohort	Investigated breast cancer mortality only; same population as in Li <i>et al.</i> (2003)
Squitieri	1994	CCS	Compared breast cancer women with and without MHT
Schairer	1994	Cohort	More recent publication (Schairer <i>et al.</i> , 2000) with identical cohort included
Willis	1996	Cohort	Investigated breast cancer mortality only
Franceschi	1997	CCS	Identical study as in La Vecchia <i>et al.</i> (1995), published in Italian
Tavani	1997a	CCS	Combined results of two separate studies (La Vecchia <i>et al.</i> , 1992, 1995)
Tavani	1997b	CCS	Same data as La Vecchia <i>et al.</i> (1995) analysed with respect to attributable risk factors for breast cancer
Grodstein	1997	Cohort	End point: breast cancer mortality risk
Sellers	1997	Cohort	Restricted to women with family history of breast cancer
Bonnier	1998	CCS	Analysis restricted to women with breast cancer by stage
Brinton	1998	CCS	Included premenopausal women (<55 years) only
Sourander	1998	Cohort	Analyses restricted to past and current versus never users; lagtime until follow-up 7 years
Hulley	1998	RCT	Subsequent publication (Hulley <i>et al.</i> , 2002) with prolonged follow-up included
Fioretti	1999	CCS	Data of two previous CC studies: La Vecchia <i>et al.</i> (1987, 1995); latter study included
Newcomer	1999	CCS	Analysed for current use (within 2 years of reference date) only
Cobleigh	1999	Cohort	Only women with breast cancer included, analyses performed according to estrogen receptor status
Dupont	1999	Cohort	Restricted to women with a history of proliferative breast disease
Gapstur	1999	Cohort	No parameter suitable for meta-analysis
Lam	2000	CCS	Analysed for impact of weight increase, BMI, and breast tissue density on breast cancer risk
Li	2000a	CCS	Identical data in Stanford <i>et al.</i> (1995), analysed for impact of anthropometric variables
Li	2000b	CCS	Analysed MHT in relation to risk of lobular and ductal breast cancer, no risk coefficients by duration of use given
Newcomb	2000	CCS	Data included in more recent publication (Newcomb <i>et al.</i> , 2002)
Trentham-Dietz	2000	CCS	Data overlap with case-control study (Newcomb <i>et al.</i> , 1995), study evaluates risk factors of carcinoma <i>in situ</i> versus invasive breast cancer
Reeves	2000	CCS	Risk factors analysed in women with fatal breast cancer risk
Stallard	2000	Cross-sectional	Included women with breast cancer, analysing the effect of MHT on stage of breast cancer
Claus	2001	CCS	Evaluated risk factors of breast cancer <i>in situ</i>
Joffe	2001	Cohort	Data from the Nurses' Health Study (1988–1994) with mammography screening as potential bias (data included in Colditz <i>et al.</i> , 1995)
Olsson	2001	Cohort	No parameter suitable for this meta-analysis
Pukkala	2001	Cohort	Analyses restricted to long cycle versus monthly MHT use
Clarke	2002	RCT	One case of breast cancer in two study groups each; excluded as dates of study not provided
Chen	2002a	Cohort	Data from Nurses' Health Study with shorter observation period than in Colditz and Rosner (1998)
Chen	2002b	CCS	Restricted analyses (current/past MHT use)
Daling	2002	CCS	Analysed MHT in relation to histology
Li	2002	CCS	Reference group short-term users of MHT, not never-users
Hedblad	2002	Cohort	Identical study as Manjer <i>et al.</i> (2001), but shorter follow-up
Lumachi	2002	CCS	Control group partially self-selected
Porch	2002	Cohort	Only current users at baseline included, past users excluded
Ursin	2002	CCS	Analysed MHT in relation to histology
Cotterchio	2003	CCS	Analysed MHT in relation to estrogen/progestin receptor status
van der Klift	2003	Cohort	No data upon MHT use provided
Newcomer	2003	CCS	Analysed MHT in relation to histology
Norman	2003	CCS	Identical data as Weiss <i>et al.</i> (2002), analysed impact of OC
Olsson	2003	Cohort	No parameter suitable for meta-analysis
Feigelson	2004	Cohort	Analyses stratified exclusively by BMI

BMI, body mass index; CCS, case control study; CI, confidence interval; OC, oral contraceptives; MHT, menopausal hormone therapy; RCT, randomized controlled trial.

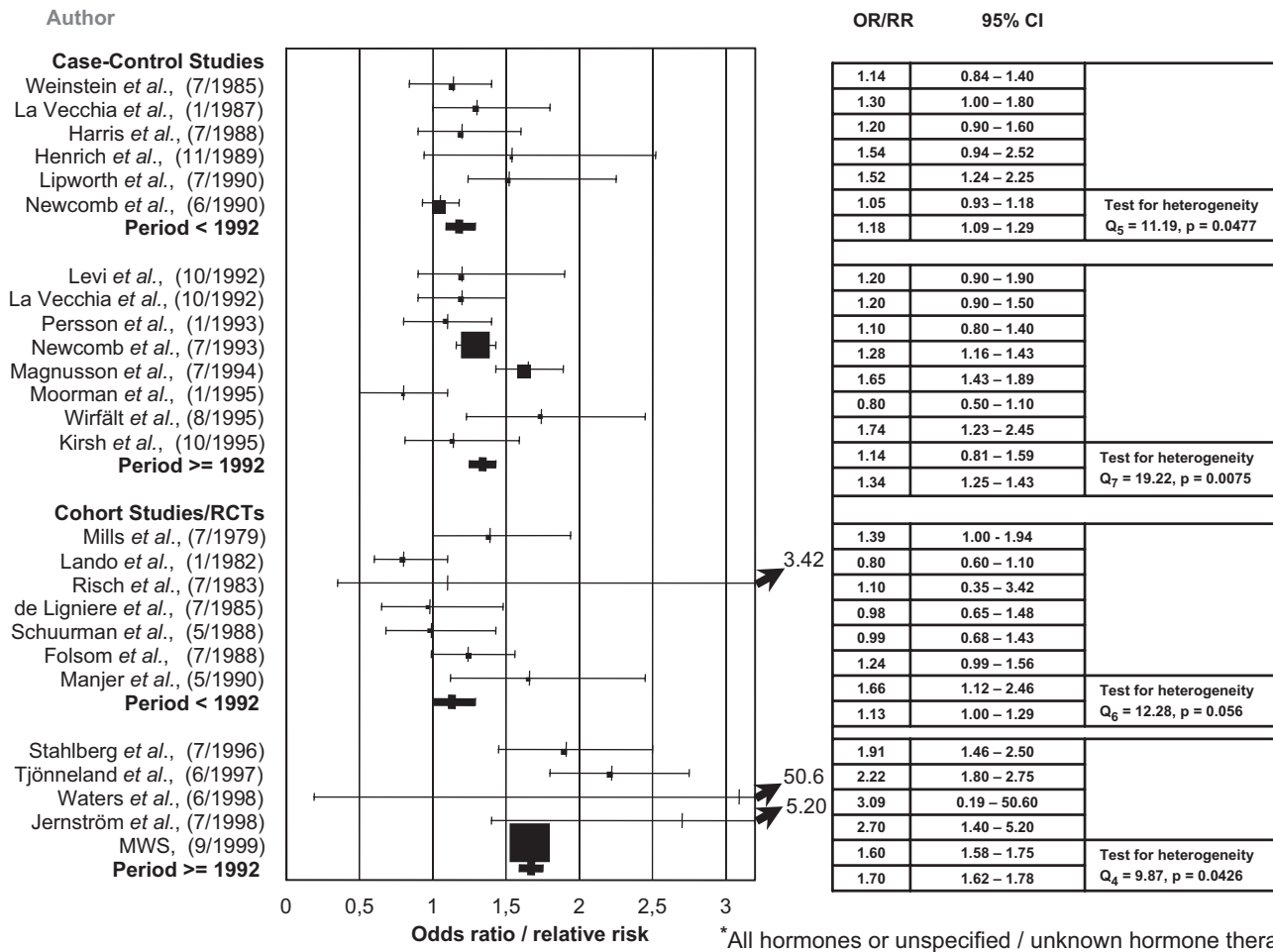
major findings of the collaborative reanalysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Our findings suggest a distinct difference between ET and EPT. This difference was also found in a French CS published outside the time frame of

our study selection (Fournier *et al.*, 2005). In the reanalysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997), in only 31% of cases and in 24% of controls, constituents of MHT could be identified. The proportion of those with EPT was appar-



* All hormones or unspecified / unknown hormone therapy

Figure 1. Risk of breast cancer after menopausal hormone therapy (all hormones or unspecified/unknown hormone therapy; ever/never) in 14 case-control studies, 11 cohort studies and 1 randomized controlled trial by midterm year of case ascertainment.



*All hormones or unspecified / unknown hormone therapy

Figure 2. Risk of breast cancer after menopausal hormone therapy (all hormones or unspecified/unknown hormone therapy; ever/never) in case-control studies, cohort studies and randomized controlled trials.

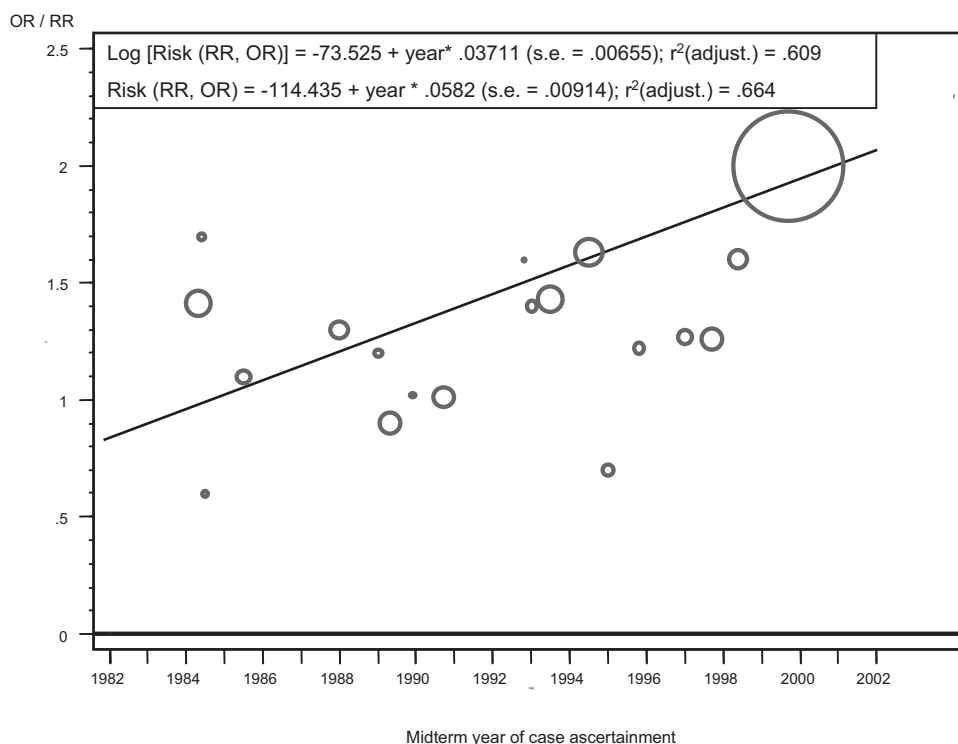


Figure 3. Risk of breast cancer after estrogen–progestin hormone therapy (ever/never) in 13 case–control studies, 4 cohort studies and 2 randomized controlled trials by midterm year of case ascertainment.

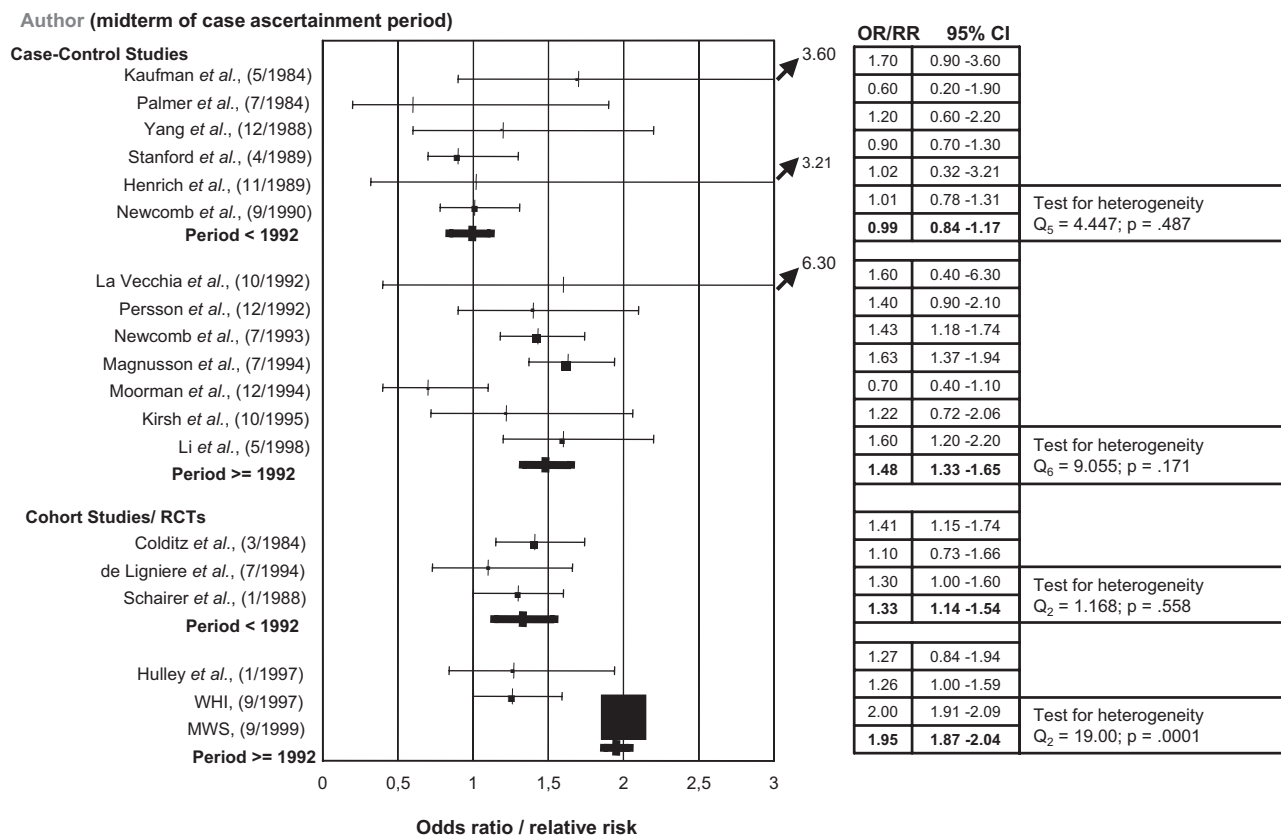


Figure 4. Risk of breast cancer after estrogen–progestin hormone therapy (ever/never) in case–control studies, cohort studies and randomized controlled trials.

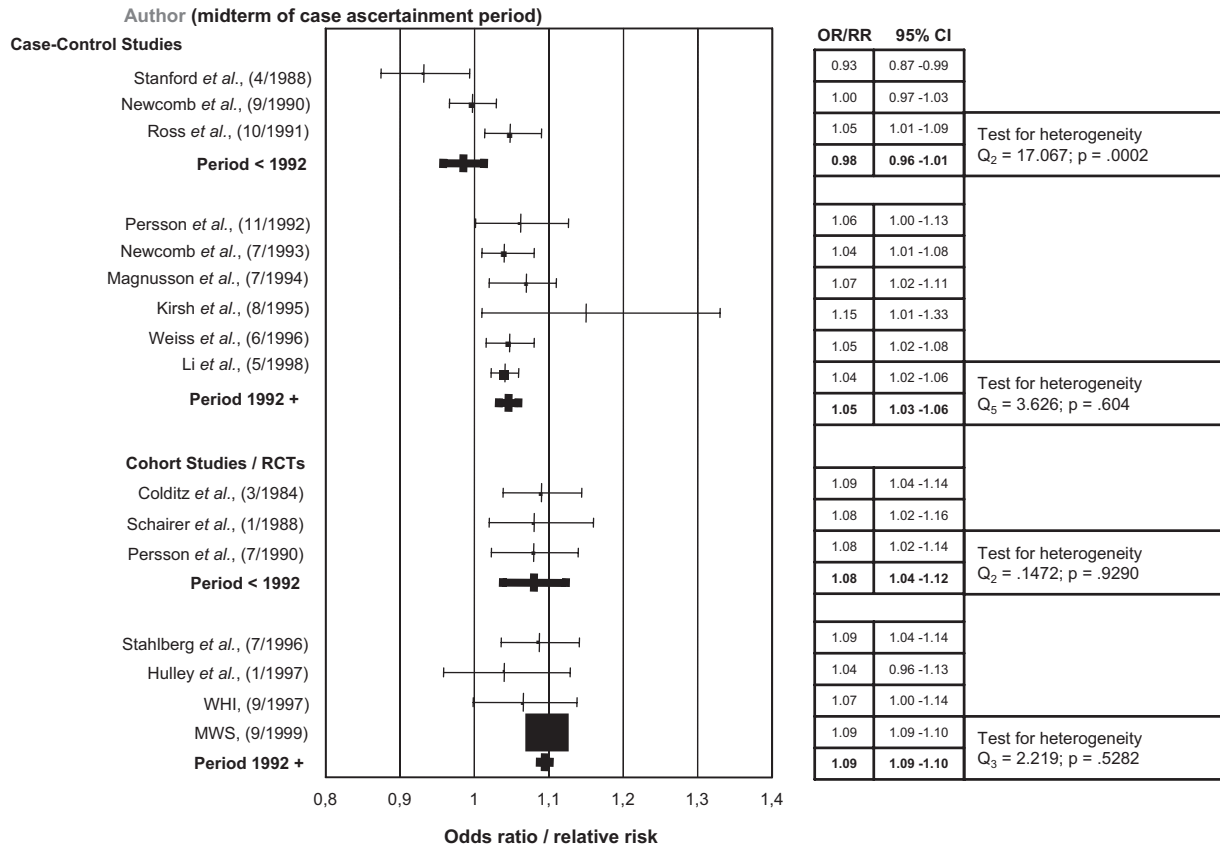


Figure 5. Increase of breast cancer risk per year of use of estrogen-progestin therapy in case-control, cohort studies and randomized controlled trials.

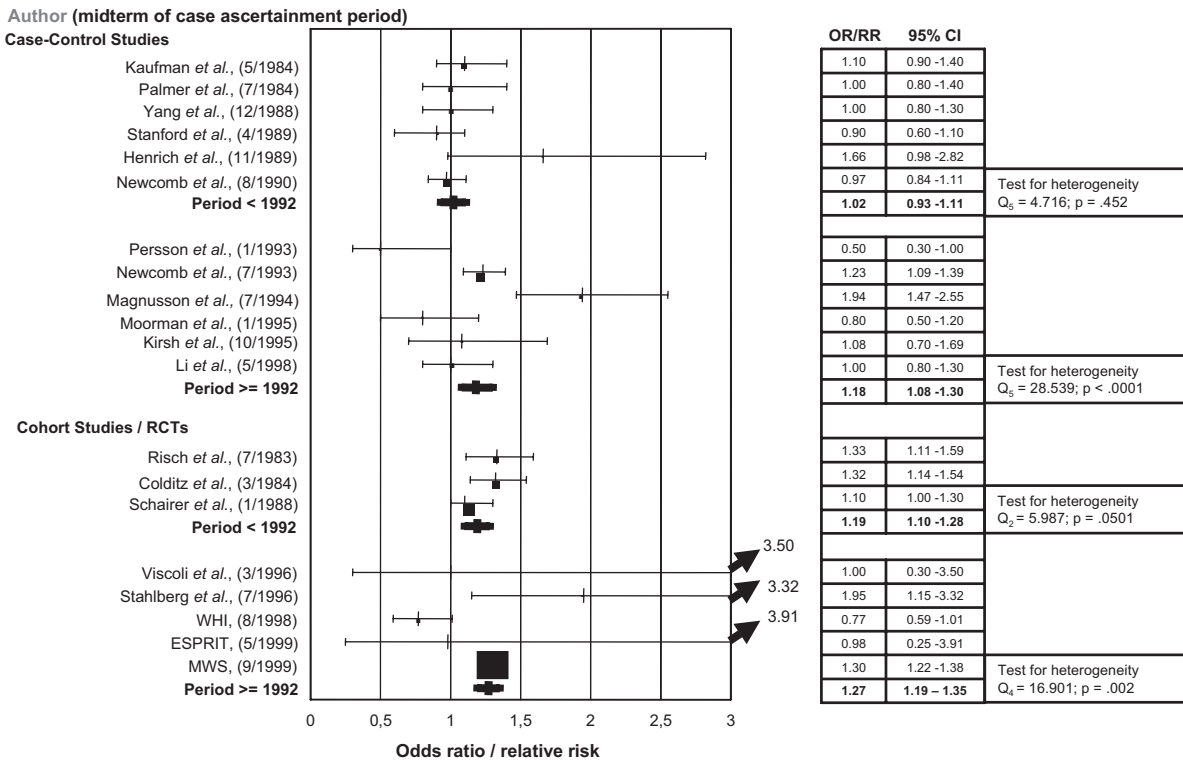


Figure 6. Increase of breast cancer risk after unopposed estrogen therapy (ever/never) in case-control, cohort studies and randomized controlled trials.

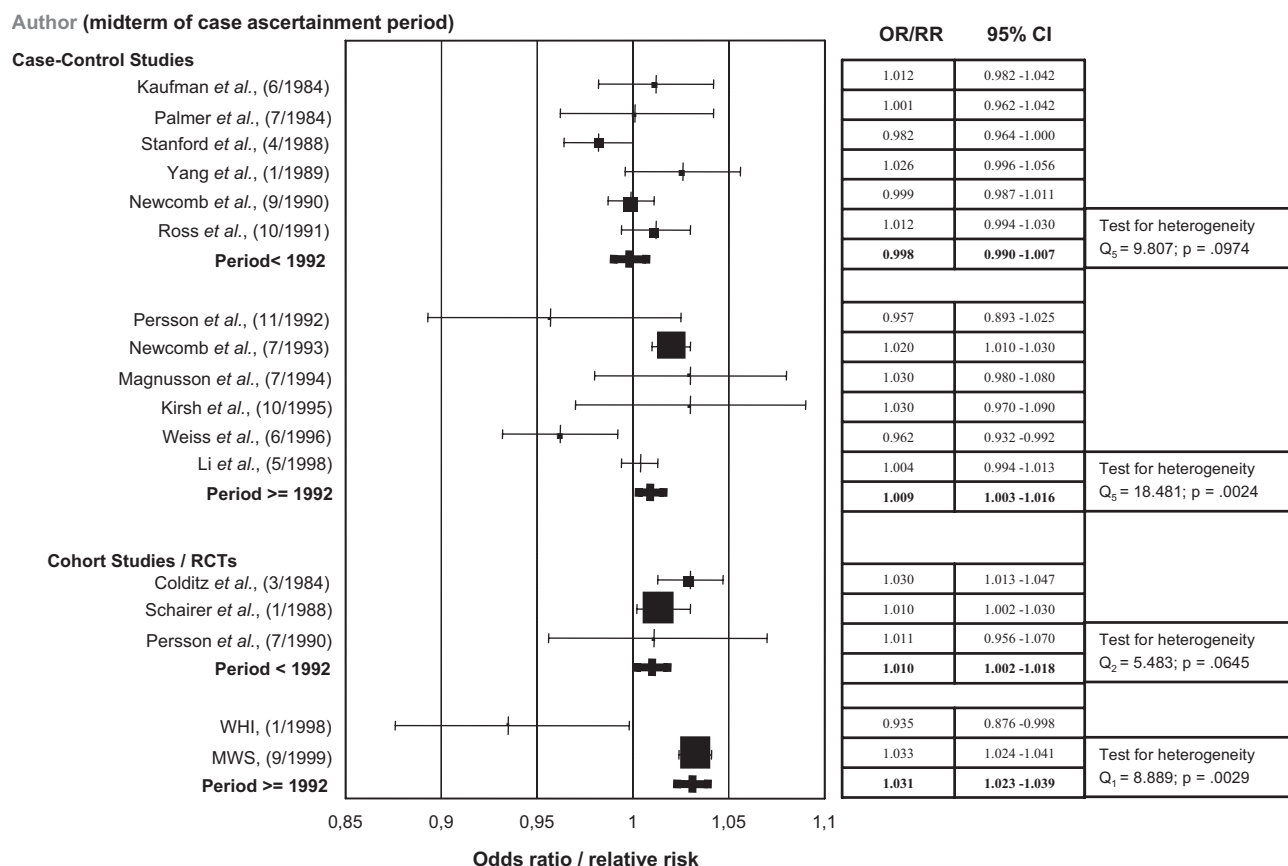


Figure 7. Increase of breast cancer risk per year of use of unopposed estrogen therapy in case-control, cohort studies and randomized controlled trials.

ently 12.5% in cases and 11% in controls (Figure 3, Table II in Collaborative Group on Hormonal Factors in Breast Cancer, 1997); this may have limited the possibility to detect differences between regimens. Thus, results are primarily based on ET with CEE as predominant constituent.

We refrained from including risk estimates for current use of hormones into our meta-analysis although several studies provided these data. In general, these risks are higher than estimates for ever use of hormones. One major recent study (Million Women Study Collaborators, 2003) found elevated risks in current users, but not in past users. Our reluctance is based on vastly differing definitions of ‘current use’, i.e. the range reaches from use within 6 months before the interview (in a case-control study) up to 8 years before last date of follow-up (in a cohort study). In our opinion this diversity could have been a source of major bias.

The same argument applies to the analysis of change of risk after discontinuation of MHT, as for such an analysis ‘current use’ should be the starting point from which a change could be estimated. Therefore we did not present a meta-analysis for risk estimates after discontinuation of MHT. The available studies, however, present an equivocal picture, as some—especially the older studies—show a remarkable decrease of risk, whereas some of the recently published major studies present figures to the contrary. The largest of recent studies, the Million Women Study, shows a statistically increased risk only within the first year after discontinuation of hormone therapy. The problem of risk change

after discontinuation is a pertinent one which might be more easily investigated in ongoing studies, as after the publication of the results of the Women’s Health Initiative RCT and the Million Women Study the proportion of women ceasing MHT has considerably increased.

In two studies risk substantially increased after cessation of MHT (Magnusson *et al.*, 1999; Newcomb *et al.*, 2002). Newcomb and coauthors (2002) calculated odds ratios for annual change of risks for ET of 0.99 (95% CI = 0.99–1.00) and for EPT of 0.98 (95% CI = 0.97–0.99). The latter result, however, seems not to be quite compatible with further risk estimates provided by the authors for different time periods after discontinuation, which show a marked increase with elapsed time after therapy was stopped [current use 1.39 (95% CI = 1.12–1.71); past use <5 years ago 1.71 (95% CI = 0.92–3.18); past use >5 years ago 2.38 (95% CI = 0.82–6.87); Table III of Newcomb *et al.*, 2002]. In a Swiss CCS (Levi *et al.*, 1996) risks remained elevated for 10–15 years after stopping MHT. In a large Swedish CCS an annual increase of 8% per year of MHT 10 and more years after discontinuation was observed. After adjustment for recency, there was no attenuation of risk increase by duration of use (Magnusson *et al.*, 1999). Ross and coauthors (2000) noted that for at least 2 years after cessation of MHT, risks for women taking EPT remained elevated. In contrast, Olsson and coauthors (2001) found increased risks for current users only and Weiss and coauthors (Weiss *et al.*, 2002) concluded that risk dissipated once use

discontinued. The discrepancy between studies which show a risk decrease shortly after discontinuation (Yang *et al.*, 1992; Stanford *et al.*, 1995; Colditz *et al.*, 1995; Weiss *et al.*, 2002) and two major recent studies (Magnusson *et al.*, 1999; Newcomb *et al.*, 2002) with no decrease of risk even after prolonged periods without use of MHT can possibly be attributed to lack of power of smaller studies. In these studies the absolute number of women who stopped for defined periods probably was too small to achieve small CIs and statistical significance.

There are several limitations of our analyses. It has to be considered, that a relevant part of heterogeneity might be due to the mix of different regimens that constitutes 'hormone therapy'. In studies conducted in earlier years with 'menopausal hormones' it is likely that predominantly ET was prescribed whereas in later years this term reflects a varying mix of ET and EPT. It was not possible to control for the varying degree of adjustment for confounding factors in the studies included. Women who use MHT differ in many ways from nonusers (Matthews *et al.*, 1996). User may be more likely to undergo mammography, possibly leading to an earlier diagnosis of BC. This argument, however, seems to be contradicted by results of the WHI randomised controlled trial, where every woman underwent screening and annual mammograms, irrespective of allocation to hormone or placebo group. We did not address the impact of body mass index and age of menopause on BC risk because of the paucity of studies providing appropriate results for pooling. Owing to the use of published, not raw data, we could not include the duration of exogenous hormone exposure into our calculations of changes of risk after cessation of MHT, as it has been done by authors of one CCS (Magnusson *et al.*, 1999). Finally, given the lack of specific information on hormonal constituents, subanalyses addressing the issue of potential differences between CEE-based and non-CEE based preparations were not possible, likewise we could not differentiate between various progestins.

In conclusion, there is evidence that relative risks for BC risks by MHT, in particular EPT, and risks have been increasing in recent years. Given the widespread use of MHT, and often long duration, more detailed knowledge about differential BC risks of both estrogens and progestins are necessary to minimize BC risk in symptomatic women who consider MHT. We think that a potential lack of decrease of risk in past users of MHT calls for a pooled reanalysis of recent major epidemiological studies.

Appendix

Formula to derive the variance and weight of a risk parameter (relative risk and odds ratio) from confidence intervals:

$$\text{Variance} = (\log(\text{RR}/\text{CIL})/1.96)^2$$

where RR is risk parameter (relative risk or odds ratio), CIL is lower bound of confidence interval of risk parameter.

Weight = 1/variance.

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