2. Studies of Cancer in Humans

The use of oestrogen by post-menopausal women is referred to in the following text as ‘oestrogen therapy’ when oestrogen alone is specified or assumed and as ‘oestrogen plus progestogen therapy’ when the combination has been specified. The term ‘hormone replacement therapy’ is not used because none of the currently prescribed regimens offers physiological hormone replacement.

2.1 Breast cancer

Most of the established risk factors for breast cancer seem to operate through hormonal pathways. The fundamental importance of ovarian hormones in the etiology of breast cancer is evident from the established associations with early age at menarche, late age at first full-time pregnancy and late age at menopause (Kelsey *et al*., 1993). Of particular relevance for the assessment of risk after hormonal therapy is the effect of age when menopause or oestrogen deficiency occurs. Re-analyses of individual data from 51 epidemiological studies on breast cancer showed that the risk for breast cancer increased by about 3% per year the later a woman began menopause in the absence of hormonal therapy (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Because the serum concentrations of hormones among post-menopausal women taking oestrogen therapy are increased to those of pre-menopausal women, it is reasonable to hypothesize *a priori* that

such treatment can cause a similar increase in risk as delay of natural menopause (Colditz, 1996).

2.1.1 *Descriptive studies*

The sales of orally administered non-contraceptive hormones have surged during recent years in the United States (see section 1.2.1), and analyses of age-adjusted trends in breast cancer incidence in some areas of the United States (Devesa *et al*., 1987) have revealed an increase that might be compatible with increasing exposure to hormonal therapy. The trends in incidence, which were related mainly to birth cohorts (Holford *et al*., 1991), could, however, have other explanations, such as increasing intensity of mammography screening, changes in reproductive behaviour and life-style factors.

With the increased use of hormonal therapy in Sweden (see section 1.2.1), the nation-wide age-standardized incidence of breast cancer has increased linearly, by an average of 1.3% since the 1960s up through the mid-1980s (Persson *et al.*, 1993). Thereafter, transient, period-related increases were seen in women aged 50–69 years, which are probably associated with the implementation of population-based mammography screening in Sweden from the late 1980s (Persson *et al.*, 1998). These ecological relationships between use of hormonal therapy and breast cancer incidence are, however, difficult to interpret.

2.1.2 *Analytical cohort and case–control studies*

Owing to concern in the 1970s that oestrogen therapy might increase the risk for breast cancer, numerous epidemiological studies have been conducted to evaluate possible relationships. Most explored the risk associated with intake of conjugated oestrogens, as predominantly practised in the United States; a few late studies also addressed the risk associated with oestradiol compounds, mainly prescribed in Europe. These studies are summarized in Tables 3a and 3b.

The Collaborative Group on Hormonal Factors in Breast Cancer (1997) reanalysed the original data from 51 out of 61 epidemiological studies with relevant data. Tables 3a and 3b give the relative risks found in those studies and those derived in this reanalysis. The study covered a total of 52 705 cases of breast cancer and 108 411 control subjects. The key results showed that use of hormonal therapy at the time the breast cancer was diagnosed or that had ceased within five years of the diagnosis was associated with a 2.3% (95% confidence interval [CI], 1.1–3.6%) increase in the relative risk for breast cancer for each year of intake (Figure 2). The relative risk reached 1.3 (95% CI, 1.2–1.5) after five to nine years and 1.6 (95% CI, 1.3–1.8) after 15 years of intake for current or recent users. No excess risk was seen five years after discontinuation of treatment. Further, the effect of current or recent long-term treatment was greater in lean than in overweight women (Figure 3) and seen chiefly for clinically less advanced tumours.

The results of selected, large, published studies are reviewed in more detail, and abstracted information from these 15 cohort and 23 case–control studies is given in Tables 4 and 5, respectively. The risk relationships with regard to any use, duration, recency, latency, dose, type of oestrogen, regimens and route of administration are reviewed for

Table 3a. Prospective studies of post-menopausal oestrogen therapy and breast cancer

Reference, country	Original data or reanalysis[a]	No. of cases	Any use	
			Relative risk	95% CI
Hoover *et al*. (1976), USA	Original	49	1.3	1.0–1.7
Hunt *et al*. (1987), UK	Original	50	1.6	1.2–2.1
Miller *et al*. (1992), Canada	Reanalysis	448	1.0	[0.78–1.2]
Schairer *et al*. (1994), USA	Original	1 185	1.0	0.9–1.2
Risch & Howe (1994), Canada	Original	742	NR	
Colditz *et al*. (1995), USA	Original	1 935	1.3	1.1–1.5
Schuurman *et al*. (1995), Netherlands	Original	471	0.99	0.68–1.4
Folsom *et al*. (1995), USA	Reanalysis	468	1.2	[0.94–1.5]
Thomas *et al*. (1982), USA; Hiatt *et al*. (1984), USA; Alexander *et al*. (1987), UK; Wang *et al*. (1987), UK; Kay & Hannaford (1988), UK; Bergkvist *et al*. (1989), Sweden; Mills *et al*. (1989), USA; Vessey *et al*. (1989), UK; Willis *et al*. (1996), USA; Goodman *et al*. (1997a), Japan	Grouped reanalysis	667	0.62	[0.24–1.0]
Persson *et al*. (1997b), Sweden	Original	435	1.1	0.8–1.4

[a] Reanalyses by the Collaborative Group on Hormonal Factors in Breast Cancer (1997)
NR, not reported

cohort and case–control studies together. Some comments on methods are given in the tables.

(*a*) *Use of any type of oestrogen for any length of time*

Most studies give risk estimates reflecting 'ever use', i.e. use of any type of compound for any amount of time. Most of the relative risks are close to 1.0, and only a few significantly exceed that value (La Vecchia *et al*., 1986; Hunt *et al*., 1987; Mills *et al*., 1989; Colditz *et al*., 1995; Lipworth *et al*., 1995). Comparisons of any use of hormones with no use are not, however, very informative, since most use has been short.

(*b*) *Duration of intake*

Long-term use was linked to an increased incidence of breast cancer in seven cohort studies and six case–control studies (Ross *et al*., 1980; Hoover *et al*., 1981; Brinton *et al*., 1986; La Vecchia *et al*., 1986; Hunt *et al*., 1987; Ewertz, 1988; Bergkvist *et al*., 1989;

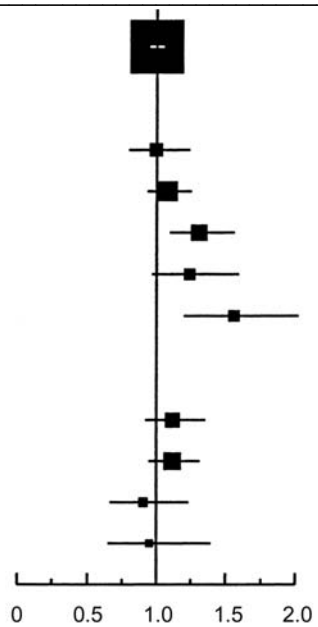
Table 3b. Case–control studies of post-menopausal oestrogen therapy and breast cancer

Reference, country	Original data or reanalysis[a]	No. of cases/ no. of controls	Any use	
			Relative risk	95% CI
Hoover *et al*. (1981), USA	Original	345/611	1.4	1.0–2.0
Kaufman *et al*. (1984), USA and Canada	Original	1 610/1 606	1.0	0.8–1.2
Brinton *et al*. (1986), USA	Original	1 960/2 258	1.0	0.9–1.2
Wingo *et al*. (1987), USA	Original	1 369/1 645	1.0	0.9–1.2
Hislop *et al*. (1986), Canada	Reanalysis	361/366	1.2	[0.67–1.6]
Siskind *et al*. (1989), Australia	Reanalysis	265/544	1.3	[0.64–2.0]
Ewertz (1988), Denmark	Original	1 486/1 336	1.3	0.96–1.7
Kaufman *et al*. (1991), USA	Original	1 686/2 077	1.2	1.0–1.6
Harris *et al*. (1992a), USA	Original	604/520	NR	
Weinstein *et al*. (1993), USA	Original	1 436/1 419	1.1	0.86–1.4
Newcomb *et al*. (1995), USA	Original	3 130/3 698	1.1	0.9–1.2
Yang *et al*. (1992), Canada	Original	699/685	1.0	0.8–1.3
Stanford *et al*. (1995), USA	Original	537/492	0.9	0.6–1.1
Ross *et al*. (1980), USA; Nomura *et al*. (1986), USA; Lee *et al*. (1987), Costa Rica; Rohan & McMichael (1988), Australia; Paul *et al*. (1990), New Zealand; Palmer *et al*. (1991), Canada; Ursin *et al*. (1992), USA; Rookus *et al*. (1994), Netherlands; White *et al*. (1994), USA; Brinton *et al*. (1995), USA	Grouped reanalysis	1 080/1 640 (with population controls)	0.96	[0.66–1.3]
Morabia *et al*. (1993), USA	Reanalysis	184/322	1.4	[0.67–2.2]
Vessey *et al*. (1983); McPherson *et al*. (1987), UK	Original	416/462	1.2	[0.53–1.9]
La Vecchia *et al*. (1992a), Italy	Reanalysis	1 615/1 450	1.7	[1.2–2.2]
Lipworth *et al*. (1995), Greece	Reanalysis	446/840	1.2	[0.55–1.8]
La Vecchia *et al*. (1995), Italy	Original	2 569/2 588	1.2	0.9–1.5
Talamini *et al*. (1985), Italy; Marubini *et al*. (1988), Italy; Ravnihar *et al*. (1988), Slovenia; Hulka *et al*. (1982), USA; WHO Collaborative Study (1990) (multinational); Ngelangel *et al*. (1994), Philippines; Levi *et al*. (1996), Italy	Grouped reanalysis	1 470/5 144 (with hospital controls)	1.0	[0.75–1.3]

[a] Reanalyses by the Collaborative Group on Hormonal Factors in Breast Cancer (1997)
NR, not reported

Figure 2. Relative risks (RR) for breast cancer by duration of use within categories of time since last use of post-menopausal hormonal therapy

Duration of use and time since last use	No. of cases/ no. of controls	RR (FSE)[a]	RR and 99% FCI[a]
No use	12 467/23 568	1.0 (0.021)	
Last use < 5 years before diagnosis (including current use)			
< 1 year	368/860	0.99 (0.085)	
1–4 years	891/2 037	1.1 (0.06)	
5–9 years	588/1 279	1.3 (0.079)	
10–14 years	304/633	1.26 (0.11)	
≥ 15 years	294/514	1.6 (0.13)	
Last use ≥ 5 years before diagnosis			
< 1 year	437/890	1.1 (0.079)	
1–4 years	566/1 256	1.1 (0.068)	
5–9 years	151/374	0.90 (0.12)	
≥ 10 years	93/233	0.95 (0.14)	



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1997)
FSE, floated standard error; FCI, floated confidence interval
[a] Relative to no use, stratified by study, age at diagnosis, time since menopause, body-mass index, parity and age when first child was born

Mills *et al*., 1989; Yang *et al*., 1992; Risch & Howe, 1994; Schairer *et al*., 1994; Colditz *et al*., 1995; Persson *et al*., 1997b). At least six case–control studies (Hulka *et al*., 1982; Kaufman *et al*., 1984; Wingo *et al*., 1987; Kaufman *et al*., 1991; Newcomb *et al*., 1995; Stanford *et al*., 1995) and one cohort study (Schuurman *et al*., 1995) found no statistically significant association with years of oestrogen intake. In two European studies (Ewertz, 1988; Bergkvist *et al*., 1989), the excess risks seemed to be higher with shorter periods of intake, the relative risk estimates exceeding 2.0 after six years of intake, than in studies in the United States (Brinton *et al*., 1986; Colditz *et al*., 1995). The American cohort studies gave increases in risk that are best explained by current intake rather than duration (Mills *et al*., 1989; Colditz *et al*., 1992, 1995), although there seemed to be duration-dependent effects in these data for current hormone takers (see Table 4).

Two recent, large population-based case–control studies in the United States (Newcomb *et al*., 1995; Stanford *et al*., 1995), the latter with considerable power to examine risk after long-term use, reported no effect of exposure of any duration.

Figure 3. Relative risks for breast cancer according to use of post-menopausal hormonal therapy by women with various characteristics

Last use < 5 years before diagnosis and duration of use < 5 years			
Characteristic	No. of cases/ no. of controls	RR (SE)	RR and 99% CI
Age at diagnosis			
< 60 years	1 042/2 341	1.1 (0.065)	
≥ 60 years	217/556	0.94 (0.11)	
Family history			
No	1 029/2 530	1.1 (0.061)	
Yes	163/230	0.9 (0.21)	
Ethnic group			
White	954/2 311	0.98 (0.06)	
Other	105/317	1.3 (0.29)	
Education			
< 13 years	593/1 237	1.0 (0.088)	
≥ 13 years	636/1 608	1.1 (0.078)	
Height			
< 165 cm	602/1 360	1.1 (0.086)	
≥ 165 cm	545/1 091	1.1 (0.093)	
Weight			
< 65 kg	676/1 416	1.1 (0.080)	
≥ 65 kg	444/993	1.0 (0.099)	
Body-mass index			
< 25.0 kg/m^2	786/1 626	1.1 (0.071)	
≥ 25.0 kg/m^2	331/774	1.0 (0.10)	
Age at menarche			
< 13 years	512/1 125	0.99 (0.092)	
≥ 13 years	721/1 702	1.1 (0.076)	
Parity			
Nulliparous	196/321	1.1 (0.16)	
Parous	1 058/2 568	1.0 (0.057)	
Age at first birth			
< 25 years	566/1 490	1.1 (0.084)	
≥ 25 years	466/1 042	1.0 (0.088)	
Use of COC in past 10 years			
No	948/2 129	1.0 (0.060)	
Yes	153/342	1.0 (0.26)	
Alcohol			
< 50 g/week	609/1 296	1.1 (0.082)	
≥ 50 g/week	284/457	1.1 (0.14)	
Smoking history			
Never	494/992	1.1 (0.097)	
Ever	566/1 187	1.1 (0.089)	
Type of menopause			
Natural	829/1 923	1.0 (0.062)	
Bilateral oophorectomy	430/974	0.92 (0.14)	

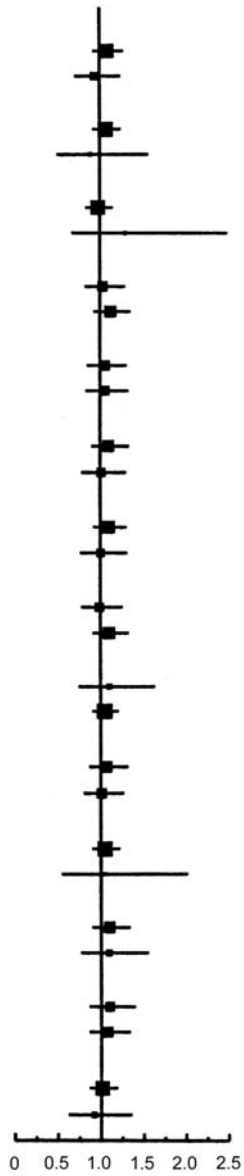


Figure 3 (contd)

Last use < 5 years before diagnosis and duration of use ≥ 5 years			
Characteristic	No. of cases/ no. of controls	RR (SE)	RR and 99% CI
Age at diagnosis			
< 60 years	612/1 390	1.3 (0.088)	
≥ 60 years	574/1 036	1.4 (0.085)	
Family history			
No	902/2 058	1.4 (0.070)	
Yes	188/246	1.1 (0.20)	
Ethnic group			
White	947/2 013	1.2 (0.067)	
Other	60/220	1.2 (0.30)	
Education			
< 13 years	522/960	1.2 (0.097)	
≥ 13 years	622/1 398	1.5 (0.092)	
Height			
< 165 cm	601/1 231	1.4 (0.094)	
≥ 165 cm	519/893	1.5 (0.11)	
Weight			
< 65 kg	721/1 228	1.6 (0.095)	
≥ 65 kg	362/839	1.1 (0.10)	
Body-mass index			
< 25.0 kg/m^2	797/1 412	1.5 (0.083)	
≥ 25.0 kg/m^2	280/651	1.0 (0.11)	
Age at menarche			
< 13 years	486/1 003	1.2 (0.10)	
≥ 13 years	682/1 408	1.4 (0.088)	
Parity			
Nulliparous	219/364	1.4 (0.16)	
Parous	962/2 043	1.3 (0.066)	
Age at first birth			
< 25 years	519/1 149	1.4 (0.10)	
≥ 25 years	434/877	1.3 (0.099)	
Use of COC in past 10 years			
No	996/2 023	1.4 (0.066)	
Yes	63/128	1.4 (0.40)	
Alcohol			
< 50 g/week	575/1 049	1.4 (0.096)	
≥ 50 g/week	288/371	1.7 (0.19)	
Smoking history			
Never	458/890	1.3 (0.11)	
Ever	561/962	1.6 (0.11)	
Type of menopause			
Natural	480/873	1.3 (0.090)	
Bilateral oophorectomy	706/1 553	1.3 (0.13)	

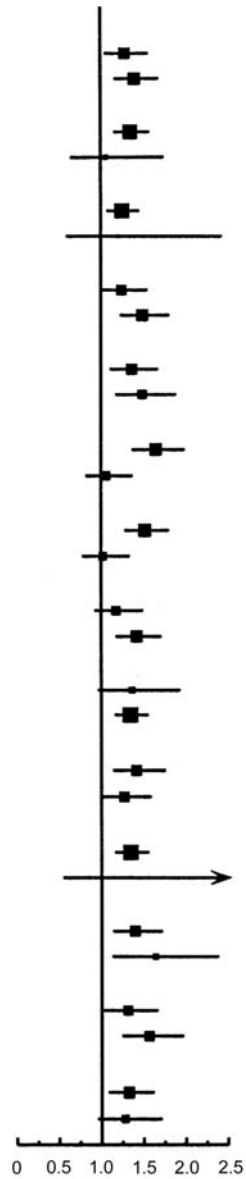
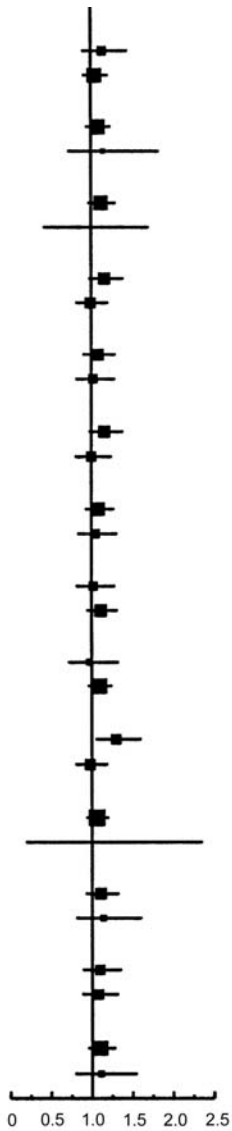


Figure 3 (contd)

Characteristic	Last use ≥ 5 years before diagnosis: No. of cases/ no. of controls	RR (SE)	RR and 99% CI
Age at diagnosis			
< 60 years	342/829	1.1 (0.10)	
≥ 60 years	905/1 824	1.05 (0.059)	
Family history			
No	973/2 340	1.1 (0.057)	
Yes	215/315	1.2 (0.20)	
Ethnic group			
White	911/2 005	1.1 (0.06)	
Other	64/262	0.8 (0.25)	
Education			
< 13 years	726/1 318	1.16 (0.076)	
≥ 13 years	501/1 378	0.99 (0.077)	
Height			
< 165 cm	696/1 435	1.1 (0.074)	
≥ 165 cm	475/1 001	1.0 (0.092)	
Weight			
< 65 kg	666/1 352	1.2 (0.075)	
≥ 65 kg	480/1 056	1.0 (0.087)	
Body-mass index			
< 25.0 kg/m^2	737/1 538	1.09 (0.066)	
≥ 25.0 kg/m^2	403/863	1.0 (0.092)	
Age at menarche			
< 13 years	464/1 083	1.0 (0.091)	
≥ 13 years	771/1 644	1.1 (0.069)	
Parity			
Nulliparous	202/429	0.97 (0.12)	
Parous	1 042/2 313	1.1 (0.055)	
Age at first birth			
< 25 years	503/1 167	1.3 (0.094)	
≥ 25 years	530/1 135	0.98 (0.076)	
Use of COC in past 10 years			
No	1168/2 585	1.1 (0.052)	
Yes	16/60	0.67 (0.40)	
Alcohol			
< 50 g/week	642/1 284	1.1 (0.075)	
≥ 50 g/week	294/422	1.1 (0.14)	
Smoking history			
Never	519/964	1.1 (0.087)	
Ever	569/1 138	1.1 (0.083)	
Type of menopause			
Natural	827/1 721	1.1 (0.062)	
Bilateral oophorectomy	420/1 032	1.1 (0.14)	



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1997)
RR, relative risk; CI, confidence interval; SE, standard error
Family history, mother or sister with breast cancer; COC, combined oral contraceptives
[a] Relative to no use, stratified by study, age at diagnosis, time since menopause, body-mass index, parity and age when her first child was born.

Table 4. Summary of cohort studies on post-menopausal oestrogen therapy and breast cancer

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Hoover *et al*. (1976)	Records of private practice, Kentucky, USA, 1969–72	Retrospective cohort, 1 891 women; follow-up through individual contacts and medical records for 12 years; 22 717 person–years; comparison with external incidence rates	**Incidence**: 49 cases observed Conjugated oestrogens: Any use: RR, 1.3 (95% CI, 1.0–1.7) Time since inclusion: increasing trend, ≥ 15 years, RR, 2.0 (95% CI, 1.1–3.4) Increasing risk with increasing dose and number of prescriptions Similar risk relationships for age at start and ovarian status	Confounding difficult to assess Proxy variables of dose–response relationship
Buring *et al*. (1987)	Nurses in 11 US states, 1976–80, 30–55 years	Cohort, 33 335 women; follow-up questionnaires sent after 4 years	**Incidence**: 221 new cases Any use: RR, 1.1 (95% CI, 0.8–1.4) Current: RR, 1.0 (95% CI, 0.7–1.4) Past: RR, 1.3 (95% CI, 0.9–1.8) Duration: < 1 year: RR, 1.0 (95% CI, 0.6–1.7) 1–< 3 years: RR, 1.0 (95% CI, 0.7–1.6) 3–5 years: RR, 1.0 (95% CI, 0.6–1.6) > 5 years: RR, 1.3 (95% CI, 0.9–2.1)	Only exposure at baseline Short follow-up
Hunt *et al*. (1987)	Menopause clinics in UK, 1978–82, counsel for menopausal symptoms	Cohort of 4 544 women who used hormones ≥ 1 year; 17 830 person–years; follow-up through contact letters and medical records; exposure data from baseline interview	**Incidence**: 50 cases. **Mortality**: 12 deaths Various kinds of hormones Any use - incidence: RR, 1.6 (95% CI, 1.2–2.1) - mortality: SMR, 0.6 (95% CI, 0.3–1.0) Time since first intake: trend for incidence ≥ 10 years: RR, 3.1 (95% CI, 1.5–5.6)	Possible selection bias in study of mortality Heterogeneous exposure regimens

Table 4 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Bergkvist *et al*. (1989)	Six counties in Sweden 1977–83, women prescribed hormones	Population-based cohort; 23 244 ≥ 35 years; 133 375 person–years; follow-up through record linkage with national cancer registry; exposure data from prescriptions; questionnaire data in a random sample; cohort, case–cohort and case–control analyses	**Incidence**: 253 cases Hormone regimens prevalent in Sweden: Any use: RR, 1.1 (95% CI, 1.0–1.3) Duration of intake: - all compounds; ≥ 9 years: RR, 1.7 (95% CI, 1.1–2.7) - oestradiol: trend, ≥ 9 years: RR, 1.8 (95% CI, 0.7–4.6) - conjugated oestrogens: no trend, ≥ 6 years: RR, 1.3 (95% CI, 0.6–2.9) Regimens, duration ≥ 9 years - oestrogens alone: RR, 1.8 (95% CI, 1.0–3.1)	Adjustment for confounders led to higher risk estimates Low power to examine conjugated oestrogens
Mills *et al*. (1989)	Seventh-day Adventists, California, USA, 1976–82, Caucasians	Cohort of 20 341 women; internal comparisons; 115 619 person-years; individual follow-up through registry linkage; baseline questionnaire in 1976	**Incidence**: 6 years follow-up, 215 cases Conjugated oestrogens: Any use: RR, 1.7 (95% CI, 1.2–2.4) - current: RR, 2.5 (95% CI, 1.6–4.0) - former: RR, 1.4 (95% CI, 1.0–2.2) Duration: - significant trend, after 6–10 years: RR, 2.8 (95% CI, 1.7–4.6) Effect modification: - previous COC intake: RR, 1.4 (95% CI, 0.7–2.9)	Data on exposure duration incomplete (only baseline)

Table 4 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Colditz *et al*. (1992)	Nurses' Health Cohort, USA, 1976–88, 30–55 years at entry	Cohort, 118 300 nurses at post-menopausal ages; 480 665 person-years; individual follow-up through questionnaires, 95% complete for incidence and 98% for deaths; internal comparisons; baseline questionnaire 1976; up-date questionnaires every 2 years	**Incidence**: 12 years' follow-up, 1015 cases Conjugated oestrogens, combinations with progestogens: - any use: RR, 0.9 (95% CI, 0.8–1.1) - current use: RR, 1.3 (95% CI, 1.1–1.6) - previous use: RR, 0.9 (95% CI, 0.8–1.0) Duration, current intake 5–< 10 years: RR, 1.6 (95% CI, 1.3–2.1) Effect modification: - none with other risk factors - previous COC-intake: RR, 1.5	Mainly relationship with current intake, possibly also duration effect: current use: 2–< 5 years: RR, 1.3 (95% CI, 1.0–1.7) 5–10 years: RR, 1.6 (95% CI, 1.25–2.06) > 10 years: RR, 1.5 (95% CI, 1.1–2.0)
Yuen *et al*. (1993)	Uppsala health care region, Sweden, 1977–80; women prescribed hormonal therapy	See Bergkvist *et al*. above. Follow-up through record-linkages with causes of death registry; comparison with external, *corrected* mortality rates; exposure data from prescriptions	**Mortality**, 12 years' follow-up, 73 deaths Various hormone regimens Any use: SMR, 0.8 (95% CI, 0.6–1.0) Prescribed compounds: - oestradiol and/or conjugated oestrogens: SMR, 0.8 (95% CI, 0.2–1.1) - other oestrogens: SMR, 0.9 (95% CI, 0.5-1.3)	Exposure data only from prescriptions Correction for possible bias due to healthy drug use (population rates corrected for prevalent cases)
Schairer *et al*. (1994)	Populations in 27 cities in the USA, breast cancer screening programme, 1980–89	Cohort of 49 017 participants; 313 902 person–years; follow-up through interviews and questionnaires; information on exposure and risk factors through questionnaires	**Incidence**, both in-situ and invasive tumours, 1 185 cases Conjugated oestrogens, combinations with progestogens Any use: - oestrogens only: RR, 1.0 (95% CI, 0.9–1.2) In-situ tumours: - oestrogens only: RR, 1.4 (95% CI, 1.0–2.0) Duration: 10–14 years, oestrogens only/ in-situ tumours: RR, 2.1 (95% CI, 1.2–3.7)	Detection bias minimized Risk relationship limited to in-situ tumours Low power to assess long-term duration of oestrogen plus progestogen regimens

Table 4 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Risch & Howe (1994)	Inhabitants of Saskatchewan, Canada, 43–49 years, start in 1976	Registry-based cohort, 32 790 women followed-up through linkage to cancer registry; 448 716 person–years; exposure data from prescription roster	**Incidence**: 742 cases Conjugated oestrogens, added progestogens Oestrogens only: increasing RR 7% per year (RR, 1.07; 95% CI, 1.02–1.13)	Limited power to look at long-term treatment
Colditz *et al*. (1995)	Nurses' Health Cohort (see above)	Cohort of 121 700 nurses; 725 550 person-years; baseline questionnaire in 1976, biannual questionnaires, up-dates on exposure and outcome (follow-up)	**Incidence**: 16 years' follow-up, 1 935 cases Conjugated oestrogens and added progestogens Current intake: - oestrogens alone: RR, 1.3 (95% CI, 1.1–1.5) - 5–9 years' oestrogens: RR, 1.5 (95% CI, 1.2–1.7) - oestrogen plus progestogen: RR, 1.4 (95% CI, 1.2–1.7) By age at diagnosis/≥ 5 years' current hormones: - 50–54 years: RR, 1.5 (95% CI, 0.91–2.3) - 55–59 years: RR, 1.5 (95% CI, 1.2–2.0) - 60–64 years: RR, 1.7 (95% CI, 1.3–2.2) **Mortality**: 359 deaths: Current use, ≥ 5 years: RR, 1.4 (95% CI, 1.0–2.1)	No relationship with past use Detection bias unlikely as explanation First study to show an increased risk of death with post-menopausal oestrogen therapy
Schuurman *et al*. (1995)	The Netherlands, random selection from 204 muni-cipal population registries, age 55–69 years	62 573 women responding to mailed questionnaire; record linkage follow-up; case–cohort approach (subcohort, 1 812 women)	**Incidence**, 3.3 years' follow-up, 471 cases 'Replacement hormones': Any use: RR, 1.0 (95% CI, 0.7–1.4) Duration: no trend Any use of COC and post-menopausal oestrogen therapy: RR, 1.0 (95% CI, 0.51–1.9)	Low power in duration categories No data on compounds or regimens Short latency

Table 4 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Folsom *et al*. (1995)	Iowa 'Women's Health Study', USA, 55–69 years, 1986–92	41 070 post-menopausal women; 129 149 person–years; record linkage for incident cases	**Incidence**, 6 years' follow-up: 468 cases 'Replacement hormones': Former use: RR, 0.96 (95% CI, 0.81–1.1) Current use: RR, 1.2 (95% CI, 0.99–1.6) ≤ 5 years: RR, 1.4 (95% CI, 1.0–2.1) > 5 years: RR, 1.2 (95% CI, 0.92–1.6)	General cancer mortality: RR, 1.1 (95% CI, 0.81–1.5) Insufficient power for cause-specific mortality No data on duration of compounds or regimens
Willis *et al*. (1996)	Women volunteers in 50 states in the USA, 1982–91	422 373 post-menopausal women; follow-up through record linkage for cause-specific deaths; data in baseline questionnaires; fatal breast cancers	**Mortality**, 9 years' follow-up: 1469 breast cancer deaths Oestrogens: Any use: RR, 0.84 (95% CI, 0.75–0.94) Recent use: RR, 0.90 (95% CI, 0.75–1.1) Duration: ≥ 11 years: RR, 0.93 (95% CI, 0.75–1.2) (no trend)	Exposure data only at baseline No specific data on exposure Mortality only
Persson *et al*. (1996)	See Yuen *et al*. above	22 597 women with registered hormone prescriptions; record linkage follow-up of incidence and mortality; risk factors from questionnaire survey	**Incidence**, 13 years' follow-up, 634 cases Prescriptions for various regimens Any post-menopausal oestrogen therapy: RR, 1.0 (95% CI, 0.9–1.1) Oestradiol or conjugated oestrogens: RR, 0.9 (95% CI, 0.8–1.1) **Mortality**: 102 deaths Any post-menopausal oestrogen therapy: RR, 0.5 (95% CI, 0.4–0.6)	No direct adjustment for covariates 'Healthy drug user' bias in mortality analyses

Table 4 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Persson *et al*. (1997b)	Participants in mammography screening, Uppsala, Sweden, 1990–95, 46–74 years	Cohort of 30 982 women participating in two screening rounds; follow-up through screening and in diagnostic registry of pathology department; questionnaires at visits; nested case–control approach	Five-year follow-up: 435 cases (87% invasive), 1 740 controls Any post-menopausal oestrogen therapy: odds ratio, 1.1 (95% CI, 0.8–1.4) Duration ≥ 11 years: odds ratio, 2.1 (95% CI, 1.1–4.0) Oestradiol or conjugated oestrogen ≥ 11 years: odds ratio, 1.3 (95% CI, 0.5–3.7)	Duration of intake significantly associated Low power in regimen subgroups

SMR, standardized mortality ratio; COC, combined oral contraceptives

Table 5. Summary of case–control studies of post-menopausal oestrogen therapy and breast cancer

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Ross *et al*. (1980)	Los Angeles, USA, retirement community, 1971–77, Caucasians, age 50–74	Population-based; 131 cases, 262 controls; data from interviews, pharmacy and medical records	Conjugated oestrogens: Any use: RR, 1.1 (95% CI, 0.8–1.9) Cumulative dose > 1 500 mg: RR, 1.9 (95% CI, 1.0–3.3) Ovaries retained: RR, 2.5 (95% CI, 1.2–5.6)	Dose and duration could not be separated
Hoover *et al*. (1981)	Portland, USA, members of insurance programme (prepaid health plan), 1969–75	Population-based; 345 cases, 611 controls; data from medical records, e.g. number of prescriptions	Conjugated oestrogens: Any use: RR, 1.4 (95% CI, 1.0–2.0) ovaries retained: RR, 1.3 ovaries removed: RR, 1.5 No. of prescriptions: trend, highest RR, 1.8 Dose: trend, highest RR, 1.8 Duration: trend, highest RR, 1.7 Effect modification: higher risk if family history	Only medical record data Adjustment only for type of menopause
Brinton *et al*. (1981)	Multicentre screening programme, 29 centres in the USA, age 35–74 years	Population-based; 881 cases, 863 controls; interviews	Conjugated oestrogens: Any use: RR, 1.2 (95% CI, 1.0–1.5) Oophorectomy: Any use: RR, 1.5 (95% CI, 0.9–2.8) ≥ 10 years: RR, 1.7 (NS)	Higher risks with higher-dose compounds Possible interaction with nulliparity, family history and benign breast disease
Hulka *et al*. (1982)	North Carolina, USA, city hospitals, 1977–78, post-menopausal women	Population- and hospital-based; 199 cases, 451 and 852 controls; data from interviews	Oestrogens: Any use: RR, 1.2 (NS) - natural menopause: RR, 1.8 (95% CI, 1.2–2.7) - surgical menopause: RR, 1.3 (NS) No relationship to duration or timing of exposure	Two control groups Speculations on higher risk with injectable oestrogens

Table 5 (contd)

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Hiatt *et al*. (1984)	Kaiser Foundation Health Plan, oophorecto-mized women, 1971–79	Population-based; 119 cases, 119 controls (matched); medical records	Oestrogens: Any use: RR, 0.7 (95% CI, 0.3–1.6) ≥ 5 notations: RR, 2.1 (95 % CI, 1.2–3.6) (significant trend)	No effect modification No trend with years of use
Kaufman *et al*. (1984)	Large cities, USA and Canada, 1976–81, < 70 years	Hospital-based; 1 610 cases, 1 606 controls; data from interviews	Conjugated oestrogens: Any use: RR, 1.0 (95% CI, 0.8–1.2) Duration: ≥ 10 years: RR, 1.3 (0.6–2.8) (no trend) Subgroup analysis: no risk relationships	Discussion on selection bias due to hospital controls
La Vecchia *et al*. (1986)	Northern Italy, 1983–85, age 26–74	Hospital-based; 1 108 cases, 1 281 controls; data from interviews	Non-contraceptive oestrogens: Any use: RR, 1.8 (95% CI, 1.3–2.7) Duration - ≤ 2 years: RR, 1.7 (95% CI, 1.1–2.6) - > 2 years : RR, 2.0 (95% CI, 1.0–4.1) Recency, latency: no relationship	Low prevalence of exposure in population
Brinton *et al*. (1986)	Nationwide screening programme, USA, 1977–80, Caucasians, post-menopausal; extension of study reported by Brinton *et al*. (1981), see above	Population-based; 1 960 cases, 2 258 controls (random); interviews	Conjugated oestrogens: Any use: RR, 1.0 (95% CI, 0.9–1.2) Duration: significant trend of increase; ≥ 20 years: RR, 1.5 (95% CI, 0.9–2.3) By menopause types: similar relationships Effect modification: benign breast disease, RR, 3.0 (95% CI, 1.6–5.5) for hormone use of ≥ 10 years Tumour stage: highest risk for in-situ and small tumours	Large study Diagnostic bias unlikely

Table 5 (contd)

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Nomura *et al*. (1986)	Patients in Hawaiian hospitals, 1975–80, age 45–74	Hospital and neighbourhood controls; 183/183 Japanese; 161/161 Caucasians	Oestrogen use: Caucasians/Japanese analysed separately: Any use: - Caucasians: RR, 0.9 (95% CI, 0.5–1.3) - Japanese, RR, 1.1 (95% CI, 0.7–1.6) Duration: no trend	Low response rates among cases Low power in subgroup analyses
Wingo *et al*. (1987)	Large cities, USA, 1980–82, age 25–54	Population-based; 1 369 cases, 1 645 controls; random-digit dialling; interviews	Conjugated oestrogens: Any use: RR, 1.0 (95% CI, 0.9–1.2) - natural menopause: RR, 0.8 (95% CI, 0.6–1.1) - 'surgical menopause': RR, 1.3 (95% CI, 0.9–1.9) Duration, latency, recency: no pattern	Limited to early post-menopausal women Low power for long-term treatment
Rohan & McMichael (1988)	Adelaide, Australia, 1982–84, post-menopausal women, < 74 years	281 cases, 288 controls; interviews	Exogenous oestrogens: Any use: RR, 1.0 (95% CI, 0.6–1.7) Duration, latency, recency: no pattern	Small numbers in duration categories
Ewertz (1988)	Denmark, nationwide, 1983–84, > 70 years	Population-based; 1 486 cases, 1 336 controls (random); self-administered, mailed questionnaire	Oestradiol and oestradiol-progestogen combinations: Any use: RR 1.0–1.3 (NS) depending on menopause status Duration: trend with increasing years of intake: RR, 0.9–2.3 after 3–13 years ($p > 0.002$)	Chiefly exposure to oestradiol compounds

Table 5 (contd)

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Kaufman *et al*. (1991)	Large cities, east coast, USA, 1980–86, post-menopausal women, 40–69 years	Hospital-based; 1 686 cases, 2 077 controls; interviews	Mostly conjugated oestrogens: Any use: RR, 1.2 (95% CI, 1.0–1.6) Duration: > 15 years RR, 0.9 (95% CI, 0.4–2.1) - conjugated oestrogens, current intake: RR, 1.2 (95% CI, 0.8–1.8) Dose: no pattern	Low power for long-term treatment
Palmer *et al*. (1991)	Toronto, Canada, one cancer hospital, 1982–86, < 70 years	Population-based; 607 cases, 1 214 controls; interviews	Conjugated oestrogens: Any use: RR, 0.9 (95% CI, 0.6–1.2) Duration ≥ 15 years: RR, 1.5 (95% CI, 0.6–3.8) (no significant trend) Current use and ≥ 5 years use: RR, 0.9 (95% CI, 0.4–1.9)	Low power in long duration categories Response rate of controls, 65%
Yang *et al*. (1992)	British Columbia, Canada, 1988–89, post-menopausal women < 75 years	Population-based; 699 cases, 685 controls; mailed questionnaire	Mainly conjugated oestrogens: Any use: RR, 1.0 (95% CI, 0.8–1.3) Current intake: RR, 1.4 (95% CI, 1.0–2.0) Duration ≥ 10 years: RR, 1.6 (95% CI, 1.1–2.5) Effect modification: highest risk after oophorectomy: RR, 1.9 (95% CI, 0.8–5.3)	Low response rate
Harris *et al*. (1992a)	New York city area, USA, 1987–89	Hospital-based; 604 cases, 520 controls; interviews in hospitals	'Use of oestrogens': lean, post-menopausal women: odds ratio, 2.0 (95% CI, 1.1–3.5) (body mass index, < 22) - < 5 years: odds ratio, 2.0 (95% CI, 1.0–3.8) - ≥ 5 years: odds ratio, 2.2 (95% CI, 0.8–5.6)	Risk increase with high body mass index and weight gain Few subjects with long duration of hormone therapy

Table 5 (contd)

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Weinstein *et al*. (1993)	Long Island, New York, USA, 1984–86	Population-based; 1 436 cases, 1 419 controls; telephone interviews	'Use of oestrogens': Any use: RR = 1.1 (0.86–1.4) No trend with duration. Current use: RR = 1.3 (0.76–2.3) Former use: no trend	Interaction with body mass index
La Vecchia *et al*. (1995)	Six areas in northern Italy, 1991–94, ≤ 74 years	Hospital-based; 2 569 cases, 2 588 controls; structured questionnaire at interview	'Conjugated and other oestrogens': Trend with duration: odds ratios, 1.0, 1.3 and 1.5 for < 1 year, 1–4 and > 5 years of intake (NS) Recency < 10 years: odds ratio, 2.0 (95% CI, 1.3–2.9)	Low power in long-duration categories
Stanford *et al*. (1995)	13 counties, Washington State, USA, 1998–90, cancer survey system, Caucasian, 50–64 years	Population-based; 537 cases, 492 controls (random-digit dialling); personal interviews	Any use: Oestrogen alone: RR, 0.9 (95% CI, 0.6–1.1) Oestrogen with progestogen: RR, 0.9 (95% CI, 0.7–1.3) Duration, recency: no association	Response rate 81% for cases and 73% for controls Low power for long-term use
Newcomb *et al*. (1995)	Four states in northern and eastern USA, tumour registries, 1988–91, age 65–74	Population-based; 3 130 cases, 3 698 controls; personal interviews	'Non-contraceptive hormones, oestrogens and progestogen combinations': Any use: RR, 1.1 (95% CI, 0.9–1.2) Duration: > 15 years: RR, 1.1 (95% CI, 0.9–1.4)	Response rates 81% for cases and 84% for controls Reasonable power for long-duration categories No effects in subgroups

Table 5 (contd)

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Levi *et al*. (1996)	Vaud, Switzerland, 1990–95, < 75 years	Hospital-based; 230 cases, 507 controls; interviews in hospitals	'Hormonal therapy': Any use: odds ratio, 1.2 (95% CI, 0.8–1.8) Recency < 10 years: odds ratio, 1.7 (95% CI, 1.1–2.9) Duration ≥ 10 years: odds ratio, 1.0 (95% CI, 0.4–2.4)	No information on participation rates Power limitations
Tavani *et al*. (1997)	Greater Milan area 1983–91, six areas in northern Italy, 1991–94, age 15–74	Two hospital-based studies; 5 984 cases, 5 504 controls; interviews	'Hormonal therapy': Any use: odds ratio, 1.2 (95% CI, 1.0–1.4) Duration > 5 years: odds ratio, 1.3 (95% CI, 0.8–2.0) Significant trend with duration Any use, age at diagnosis: trend of increasing risk with increasing age	Pooled data Low prevalence of any use of hormones Low power for long-duration categories
Lipworth *et al*. (1995)	Residents of greater Athens area, Greece, 4 major hospitals, 1989–91, all ages	Hospital-based; 820 cases, 795 orthopaedic patients; 753 healthy visitors; data from interviews in hospital	'Menopausal oestrogens': Any use: RR, 1.5 (95% CI, 1.2–2.3) Duration: - ≤ 11 months: RR, 1.8 (95% CI, 1.0–3.0) -12–35 months: RR, 1.3 (95% CI, 0.6–2.5) - ≥ 36 months: RR, 1.4 (95% CI, 0.6–3.3) (no trend)	No information on details of exposure, oestrogen–progestogen use rare Low prevalence of hormone use

NS, not significant

The pooled analysis of individual data showed a relationship of increasing risk with increasing duration only for women with current use or use ended within the previous four years. There was no significant variation in results across the individual studies (Collaborative Group on Hormonal Factors in Breast Cancer, 1997).

(*c*) *Recency of intake*

Several of the studies suggest that recency of exposure is the most important determinant of risk (Mills *et al*., 1989; Colditz *et al*., 1992, 1995; Folsom *et al*., 1995; La Vecchia *et al*., 1995; Levi *et al*., 1996). The investigators in the Nurses' Health Study in particular reported that their finding of a 50% increase in risk is best explained in this way (Colditz *et al*., 1995); however, numerous other studies found no relationship between excess risk and current or recent intake (Hulka *et al*. 1982; Kaufman *et al*., 1984; Wingo *et al*., 1987; Ewertz, 1988; Rohan & McMichael, 1988; Kaufman *et al*., 1991; Palmer *et al*., 1991; Stanford *et al*., 1995). Several of the studies did not include an analysis by recency of intake. The main results of the pooled analysis of individual data was an excess risk related to current use or use terminated within five years

(*d*) *Latency of intake*

Most studies showed no independent association with the number of years since first use (Hulka *et al*., 1982; Hiatt *et al*., 1984; Kaufman *et al*., 1984; Nomura *et al*., 1986; Wingo *et al*., 1987; Rohan & McMichael, 1988; Palmer *et al*., 1991; La Vecchia *et al*., 1995; Stanford *et al*., 1995; Brinton, 1997).

(*e*) *Compound, dose and route of administration*

Studies in the United States reflect use almost exclusively of conjugated oestrogens, while studies in Europe give results of exposure mainly to the other oestrogens, such as oestradiol valerate, oestradiol and, to a minor extent, the synthetic oestrogen ethinyloestradiol. In the European studies (Hunt *et al*., 1987; Ewertz, 1988; Bergkvist *et al*., 1989; La Vecchia *et al*., 1995), the infrequent use of conjugated oestrogens provided insufficient power for comparative analyses. Oestradiol compounds and conjugated oestrogens seem to have similar oestrogenic effects on the target organs, e.g. with regard to endometrial cancer (Persson *et al*., 1989; Beresford *et al*., 1997) and breast cancer in studies in Europe and the United States (Bergkvist *et al*., 1989; Colditz *et al*., 1995). Neither the pooled analysis of individual data nor studies in the United States (Hulka *et al*., 1982; Hiatt *et al*., 1984; Kaufman *et al*., 1984; Brinton *et al*., 1986; Wingo *et al*., 1987; Stanford *et al*., 1995) showed a difference in risk with dose of conjugated oestrogens (i.e. 0.625 versus 1.25 mg).

Data on risk by type of administration are scarce. No pattern of risk has been related to cyclic versus continuous intake of oestrogens (Hulka *et al*., 1982; Brinton *et al*., 1986). Vaginal application of oestrogen was not related to the risk for breast cancer (Colditz *et al*., 1992), whereas parenteral administration was linked to an increased risk in one study (Hulka *et al*., 1982).

(*f*) *Susceptibility factors*

In epidemiological research, interest has focused on whether certain sub-groups of women are more likely to develop breast cancer after post-menopausal hormonal therapy. Such analyses are often hampered by lack of power. In the pooled analysis of individual data, the only significant effect modifier was body mass index: the adverse effect of hormone treatment was greater for women with a body mass index < 25 kg/m^2. Other types of factor addressed in individual studies are described below.

(i) *Type of menopause*

Since oophorectomy and time of natural menopause are powerful determinants of breast cancer, menopausal status has been examined as a modifier of the risk associated with hormonal therapy. The association in oophorectomized women has been found to be strong in some studies (Hoover *et al*., 1981; Wingo *et al*., 1987; Yang *et al*., 1992; Stanford *et al*., 1995), whereas in other studies, higher risks have been noted for women who had a natural menopause and have intact ovaries (Ross *et al*., 1980; Hulka *et al*., 1982; Ewertz, 1988); some studies found no difference in effect with ovarian status (Kaufman *et al*., 1991; Palmer *et al*., 1991; Newcomb *et al*., 1995).

(ii) *Age at diagnosis*

In the Nurses' Health Study, the increased risk with current intake became progressively more pronounced with increasing age at diagnosis (Colditz *et al*., 1995). An effect of age at diagnosis has also been suggested in some case–control studies (Brinton *et al*., 1981; Wingo *et al*., 1987; Kaufman *et al*., 1991; Palmer *et al*., 1991; La Vecchia *et al*., 1992a). One difficulty in interpreting the data is that the effect of age could be mixed with duration of intake.

(iii) *Body build*

The relative contribution of treatment to post-menopausal oestrogen concentrations is likely to be greater in lean than obese women, since endogenous oestrogen production is enhanced by the amount of fat tissue (Siiteri, 1987). The findings of some epidemiological studies corroborate this hypothesis by showing stronger or unique associations in lean women (Kaufman *et al*., 1991; Palmer *et al*., 1991; Colditz *et al*., 1992; Harris *et al*., 1992a; Newcomb *et al*., 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1997); conversely, in other studies, the effect was more marked in obese women (Mills *et al*., 1989; La Vecchia *et al*., 1992a).

(iv) *Previous use of combined oral contraceptives*

Current and recent use of combined oral contraceptives has been linked to an increased risk for breast cancer (see the monograph on 'Oral contraceptives, combined'). Few studies have yet been able to address whether the risk associated with hormonal therapy is modified by previous use of combined oral contraceptives, especially for women who have taken high-dose pills. There is no evidence of such an interaction;

however, few data are available (Mills *et al*., 1989; Colditz *et al*., 1992; Schuurman *et al*., 1995; Stanford *et al*., 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Since cohorts of women who were commonly exposed to combined oral contraceptives are increasingly being treated with hormonal therapy, the possibility of a combined effect becomes an important issue.

(v) *Hereditary breast cancer*

Inherited breast cancer has been studied through the proxy variable of family history, i.e. according to closeness of relationship and age at onset. Further, the share of cancers caused by dominant inheritance is lower for post-menopausal women than for women with breast cancer before the menopause. These circumstances may explain why the findings on the joint effect of family history and hormone use are inconsistent: about as many studies show an increased risk (Hoover *et al*., 1981; Hulka *et al*., 1982; Nomura *et al*., 1986; Wingo *et al*., 1987; Kaufman *et al*., 1991; Newcomb *et al*., 1995) as show an absence of an effect modification (Kaufman *et al*., 1984; Brinton *et al*., 1986; Rohan & McMichael, 1988; Mills *et al*., 1989; Palmer *et al*., 1991; Yang *et al*., 1992; Stanford *et al*., 1995).

(vi) *Benign breast disease*

Women with a history of so-called benign breast disease may have a higher risk of developing breast cancer after post-menopausal hormonal therapy (Ross *et al*., 1980; Brinton *et al*., 1986; Nomura *et al*., 1986; Mills *et al*., 1989), but numerous other studies do not support the association (Hoover *et al*., 1981; Hulka *et al*., 1982; Kaufman *et al*., 1984; Wingo *et al*., 1987; Rohan & McMichael, 1988; Kaufman *et al*., 1991; Palmer *et al*., 1991; Yang *et al*., 1992; La Vecchia *et al*., 1995; Newcomb *et al*., 1995; Stanford *et al*., 1995). Many uncertainties hamper the interpretation of the data, e.g. whether a risk-increasing effect applies to specific types of benign lesions (hyperplasia or atypia) or whether it is use of post-menopausal hormonal therapy before or after diagnosis that is important.

(vii) *Alcohol, reproductive factors*

A few studies have shown an increased risk in association with heavy alcohol consumption (Colditz *et al*., 1992; Gapstur *et al*., 1992). Studies of the combined effects of hormonal therapy and age at menarche, age at first birth, parity and age at menopause have generally yielded null results (Kaufman *et al*., 1984; Nomura *et al*., 1986; Palmer *et al*., 1991; Yang *et al*., 1992; Stanford *et al*., 1995), whereas a few others found stronger associations among users who were older at the time of the birth of their first child (Colditz *et al*., 1992), with multiparity (La Vecchia *et al*., 1992a) and with late menopause (Wingo *et al*., 1987; Ewertz, 1988; Mills *et al*., 1989).

(*g*) *Tumour characteristics*

More intense surveillance of users of hormonal therapy may lead to earlier detection and bias with regard to latency. There is evidence of an increased risk for breast cancer after hormone treatment in two studies performed in a population of women participating in a

breast cancer screening programme in the United States, in which the impact of detection bias should be low. Thus, in a case–control study (Brinton *et al*., 1986), the positive duration-dependent relationship was significant and strongest for in-situ or small (≤ 1 cm) tumours. In a subsequent follow-up study (Schairer *et al*., 1994), a doubling of the relative risk with oestrogen use for more than 10 years was limited to in-situ tumours. Further, in a Swedish record-linkage study, the odds ratio of having a small tumour (≤ 2 cm) and spread to axillary lymph nodes was lower for women prescribed oestrogens (in combination with progestogens), even when adjustment was made for mode of detection (mammography screening or examinations because of symptoms) (Magnusson *et al*., 1996).

In the pooled analysis of individual data, the adverse effect of hormone use was stronger for women with cancers localized to the breast than for those with cancers that had spread beyond the breast (Collaborative Group on Hormonal Factors in Breast Cancer, 1997).

(*h*) *Survival and mortality*

Mortality rates due to breast cancer were analysed during a 12-year follow-up, after correction for the comparative external mortality rates for prevalent breast disease (Yuen *et al*., 1993). The standardized mortality ratio estimates were still slightly below baseline (0.8). A reduction in the rate of mortality from breast cancer among women using hormone treatment as compared with those who were not has been found in other cohort studies (Petitti *et al*., 1987; Hunt *et al*., 1990; Henderson *et al*., 1991; Willis *et al*., 1996). In the Nurses' Health Study, the relative risks for death from breast cancer were 0.76 (95% CI, 0.56–1.02) for current use and 0.83 (95% CI, 0.63–1.1) for past use, but rose to 1.4 (95% CI, 0.82–2.5) for current use for 10 or more years (Grodstein *et al*., 1997). These data should be interpreted cautiously.

In summary, the preponderence of evidence suggests an increase in risk for breast cancer with increasing duration of use of post-menopausal oestrogen therapy for current and recent users.

2.2 Endometrial cancer

2.2.1 *Descriptive studies*

In the United States, use of oestrogens at menopause increased during the 1960s. With increasing evidence of an association between post-menopausal oestrogen therapy and endometrial cancer, the United States Food and Drug Administration issued a warning to physicians in 1976. A decline in post-menopausal oestrogen therapy use ensued and was later followed by an increase in the use of post-menopausal oestrogen–progestogen therapy (Austin & Roe, 1982; Standeven *et al*., 1986; Gruber & Luciani, 1986; Ross *et al*., 1988). The incidence of uterine corpus cancer (as a proxy for endometrial cancer) began to rise in the 1960s, reached a peak in the mid-1970s and then declined until the 1990s (Persky *et al*., 1990). The increased incidence was found primarily among post-menopausal women and followed and then paralleled the increase in the use of post-menopausal oestrogen therapy.

2.2.2 *Cohort studies*

The impact of post-menopausal oestrogen therapy on the occurrence of endometrial cancer has been investigated in eight cohort studies (Table 6). Six of the studies (Hammond *et al*., 1979; Gambrell *et al*., 1980; Vakil *et al*., 1983; Lafferty & Helmuth, 1985; Hunt *et al*., 1987; Ettinger *et al*., 1988) showed an elevated risk associated with any use of post-menopausal oestrogen therapy, without specifying the risk by duration or dose, while two others (Paganini-Hill *et al*., 1989; Persson *et al*., 1989) also provided risk estimates related to the duration of use. Women who had ever used post-menopausal oestrogen therapy were more likely to develop endometrial cancer than non-users in all these studies (relative risk, 1.3–10). In three cohort studies (Hammond *et al*., 1979; Hunt *et al*., 1987; Persson *et al*,. 1989), the increased risk was significant; in two reports (Paganini-Hill *et al*., 1989; Persson *et al*., 1989) described in detail below, the risk estimates for duration of use were given.

In the study of Paganini-Hill *et al*. (1989), the risk for endometrial cancer increased from 5.2 [95% CI not provided] for ≤ 2 years of use to 20 for ≥ 15 years of use (95% CI, 7.2–54; p for trend, < 0.0001). A sustained increase in risk was noted after the cessation of therapy. Women who had stopped post-menopausal oestrogen therapy 15 or more years previously still had a nearly sixfold increase in risk (5.8; 95% CI, 2.0–17) relative to women who had never used them. In an analysis of oestrogen dose in this study, the risk for women using higher doses (≥ 1.25 mg; relative risk, 11.0 [95% CI not provided]) did not differ from that of women using lower doses (≤ 0.625 mg; relative risk, 15.0 [95% CI not provided]).

In the case–cohort study of Persson *et al*. (1989), the risk increased with increasing duration of use, from 1.1 (95% CI, 0.5–2.5) among users for six months or fewer to 1.8 (95% CI, 1.1–3.2) among women who had used post-menopausal oestrogen therapy for 73 months or more. Use of either conjugated oestrogen or oestradiol was associated with an increase in risk, with a relative risk of 1.7 (95% CI, 1.1–2.7) for conjugated oestrogen and 2.1 (95% CI, 1.4–3.0) for oestradiol.

2.2.3 *Case–control studies*

Over 30 studies have been conducted to investigate the association between post-menopausal oestrogen therapy and endometrial cancer (Table 7); all except one (Salmi, 1980) reported an elevated risk for women with any use of post-menopausal oestrogen therapy relative to those who had never used it (relative risks, 1.3–12.0), and in 22 studies the excess was statistically significant. Both qualitative reviews (Herrinton & Weiss, 1993) and a meta-analysis of the published results (Grady *et al*., 1995) have found an overall excess, with increasing risk with increasing duration of use.

The risk for endometrial cancer has been evaluated in relation to the duration of use, the time since last use (recency), oestrogenic potency (dose), type (conjugated, synthetic) and regimen (continuous versus cyclic with breaks) of therapy.

Over 20 studies that provide information on the duration of post-menopausal oestrogen therapy showed that duration is one of the strongest determinants of risk; the risk continues to increase with continuing duration of use (Ziel & Finkle, 1975; Mack *et al*.,

Table 6. Cohort studies on use of unopposed post-menopausal oestrogen therapy and risk for endometrial cancer

Reference, country	Age at beginning of follow-up (years)	Study group of source population	Comparison group	Approximate duration of follow-up (years)	No. of observed cases	No. of expected cases or person–years	Relative risk or SIR	95% CI
Hammond *et al*. (1979), USA	NR	301 women attending hospital clinic, use of OT ≥ 5 years	Rates from Third National Cancer Survey	NR	11	1.18	9.3	4.7–17
Gambrell *et al*. (1980), USA	NR	Women attending medical centre, any use of OT	Women attending medical centre, no use of OT	≤ 11	NR	NR	[1.6]	NR
Vakil *et al*. (1983), Canada	32–62	1 483 women attending gynaecology clinics	Rates from Ontario	≤ 17	8	6.2	1.3	NR, NS
Lafferty & Helmuth (1985), USA	45–60	61 women attending a private clinic, use of OT ≥ 3 years	63 women attending a private clinic, no OT use	3–16	NR	NR	[2.7]	NR
Hunt *et al*. (1987), UK	NR	4 544 women attending 21 menopause clinics	Rates from Birmingham Cancer Registry	5	12	4.2	2.8	1.5–5.0
Ettinger *et al*. (1988)	≥ 53	181 members of health maintenance organization with ≥ 5 years of OT	220 members with ≤ 1 year use of OT	≤ 24	5 years of use: 18; ≤ 1 year of use: 3	2 705 person–years 4 197 person–years	[9.3]	NR
Paganini-Hill *et al*. (1989), USA	44–100	5 160 women in a retirement community	Internal comparison	5	Never use: 45 Any use: 5	11 281 person–years 12 472 person–years	10	NR

Table 6 (contd)

Reference, country	Age at beginning of follow-up (years)	Study group of source population	Comparison group	Approximate duration of follow-up (years)	No. of observed cases	No. of expected cases or person–years	Relative risk or SIR	95% CI
Persson *et al*. (1989), Sweden	≥ 35	23 244 women with ≥ 1 prescription for any OT use	Rates from the Uppsala health care region	6	48	34.3	1.5	1.1–1.9

SIR, standardized incidence ratio; CI, confidence interval; NR, not reported; OT, oestrogen therapy; NS, not significant

Table 7. Case–control studies on any use of oestrogen alone and the risk for endometrial cancer

Reference, country	Age (years)	No. of cases/ no. of controls	Proportion (%) of cases/controls exposed	Odds ratio (95% CI)	Longest duration of OT use (years)	Odds ratio (95% CI) for longest duration of OT use
Smith *et al*. (1975), USA	≥ 48	317/317	48/17	4.5 [3.1–6.6]	NR	NR
Ziel & Finkle (1975), USA	57	94/188	57/15	7.6 [4.7–11]	≥ 7	14 (NR)
Mack *et al*. (1976), USA	≥ 52	63/252	NR/43	5.6 (2.8–11)	≥ 8	8.8 (NR)
Gray *et al*. (1977), USA	57	205/205	16/6	3.1 (1.5–6.8)	≥ 10	12 (1.5–240)
McDonald *et al*. (1977), USA	≥ 25	145/580	27/28	0.9 (0.6–1.4)	≥ 3	7.9 (2.9–21)
Horwitz & Feinstein (1978), USA	62	119/119	29/3	12 (4.0–48)	NR	NR
Hoogerland *et al*. (1978), USA	NR	587/587	18/9	2.2 (1.6–3.2)	≥ 10	6.7 (NR)
Antunes *et al*. (1979), USA	NR	451/888	17/4	5.5 (2.3–13)	≥ 5	15 (4.9–45)
Weiss *et al*. (1979), USA	50–74	322/289	69/25	[6.3] (NR)	≥ 20	8.3 (2.8–25)
Hulka *et al*. (1980), USA	61	256/861	33/35[a]	1.4 (0.9–2.1)	≥ 9.5	5.5 (1.9–16)[a]
Jelovsek *et al*. (1980), USA	58	431/431	12/6	2.4 (1.4–3.9)	≥ 10	2.6 (1.1–5.9)
Salmi (1980), Finland	35–60	282/282	6/15	0.4[b] (0.2–0.7)	NR	NR
Spengler *et al*. (1981), Canada	40–74	88/177	45/22	2.9 (1.7–5.1)	≥ 5	8.6 (3.2–23)
Stavraky *et al*. (1981), Canada	40–80	206/199[c]	47/29	4.8 (2.7–8.4)	≥ 10	14 (5.0–42)
Kelsey *et al*. (1982), USA	45–74	167/903	36/19	1.6 (1.3–2.0)[c]	≥ 10	2.7 (NR)
Henderson *et al*. (1983), USA	≤ 45	127/127	12/7	[1.8] (NR)	≥ 2	3.1 (NR)
La Vecchia *et al*. (1984), Italy	33–74	283/566	25/17	2.3 (1.6–3.2)	NR	'Trend'
Ewertz *et al*. (1984), Denmark	NR	115/115	18/13	4.9 (2.0–12)	≥ 1	1.7 (0.4–6.9)
Shapiro *et al*. (1985), USA/Canada	50–69	425/792	31/15	3.5 (2.6–4.7)	NR	NR
Petterson *et al*. (1986), Sweden	34–90	254/254	16/12	1.3 (0.8–2.1)	≥ 4	4.3 (1.3–14)
Buring *et al*. (1986), USA	40–80	188/428	39/20	2.4 (1.7–3.6)	≥ 10	7.6 (NR)
Ewertz (1988), Denmark	44–89	149/154	56/21	4.7 (2.9–7.7)	NR	NR
Koumantaki *et al*. (1989), Greece	40–79	83/164	10/6	2.0 (0.8–5.1)	NR	NR
Rubin *et al*. (1990), USA	20–54	196/986	24/14	1.9 (1.3–2.8)	≥ 6	3.5 (1.7–7.4)
Voigt *et al*. (1991), USA	40–64	158/182	19/7	3.1 (1.6–5.8)	> 3	5.7 (2.5–13)
Jick (1993), USA	50–64	172/172	75/49	6.5 (3.1–13)	≥ 5	22 (6.5–74)
Levi *et al*. (1993a), Switzerland	32–74	158/468	38/20	2.7 (1.7–4.1)	≥ 5	5.1 (2.7–9.8)

Table 7 (contd)

Reference, country	Age (years)	No. of cases/ no. of controls	Proportion (%) of cases/controls exposed	Odds ratio (95% CI)	Longest duration of OT use (years)	Odds ratio (95% CI) for longest duration of OT use
Brinton *et al*. (1993), USA	20–74	300/207	24/14	3.0 (1.7–5.1)	≥ 5	6.0 (2.7–13)
Finkle *et al*. (1995), USA	29–85	NR	54/44	5.0 (2.9–9.8)	NR	NR
Green *et al*. (1996), USA	45–74	661/865	49/21	[2.0] [1.7–2.5]	> 12	16 (10–26)
Beresford *et al*. (1997), USA	45–74	832/1 114	15/13	2.7 (1.9–4.0)	NR	NR
Goodman *et al*. (1997b), USA	18–84	332/511	50/32	2.6 (1.8–3.8)	≥ 3	3.6 (2.2–6.0)
Pike *et al*. (1997), USA	50–74	833/791	51/33	2.2[d] (1.9–2.5)	NR	NR
Cushing *et al*. (1998), USA	45–64	484/780	30/12	5.4 (2.3–13)	> 8	8.4[e] (4.0–18)

CI, confidence interval; OT, oestrogen therapy; NR, not reported

[a] Only for 321 community controls

[b] Risk for oestriol use; risk for conjugated oestrogen use, 5.0 [CI not reported]

[c] Controls without gynaecological disorders

[d] Risk per five years of use

[e] > 1.25 mg/day

1976; Gray *et al*., 1977; McDonald *et al*., 1977; Hoogerland *et al*., 1978; Antunes *et al*., 1979; Hulka *et al*., 1980; Jelovsek *et al*., 1980; Shapiro *et al*., 1980; Spengler *et al*., 1981; Stavraky *et al*., 1981; Kelsey *et al*, 1982; La Vecchia *et al*., 1984; Shapiro *et al*., 1985; Buring *et al*., 1986; Rubin *et al*., 1990; Brinton *et al*., 1993; Pike *et al*., 1997). Use for less than six months was found not to increase the risk in four studies (McDonald *et al*., 1977; Hoogerland *et al*., 1978; Hulka *et al*., 1980; Spengler *et al*., 1981), while two studies that included the risk of use for six months to one year (McDonald *et al*., 1977; Hoogerland *et al*., 1978) found increased risks in this category of duration also. In the meta-analysis of the published results (Grady *et al*., 1995), the overall relative risk was 2.3 (95% CI, 2.1–2.5) for oestrogen users when compared with non-users. The summary relative risk for less than one year of use was 1.4 (95% CI, 1.0–1.8), whereas that for use for more than 10 years was 9.5 (95% CI, 7.4–12).

In some studies, but not all (Brinton *et al*., 1993; Finkle *et al*., 1995), that addressed the risk associated with recency of post-menopausal oestrogen therapy, the risk for endometrial cancer remained higher than in non-users even 10 years after cessation (Shapiro *et al*., 1985; Levi *et al*., 1993a; Finkle *et al*., 1995; Green *et al*., 1996). Women with the longest durations of post-menopausal oestrogen therapy had especially high excess risks after discontinuation of use (Rubin *et al*., 1990; Green *et al*., 1996). In the meta-analysis of the published results (Grady *et al*., 1995), the summary relative risk was largest for the group of women who had ceased use within one year or less (relative risk, 4.1; 95% CI, 2.9–5.7) but remained elevated (2.3; 95% CI, 1.8–3.1) five years or more after cessation.

An elevated risk for endometrial cancer is associated with all commonly prescribed doses of conjugated oestrogens (Gray *et al*., 1977; Antunes *et al*., 1979; Weiss *et al*., 1979; Hulka *et al*., 1980; Stavraky *et al*., 1981; Jick *et al*., 1993; Cushing *et al*., 1998). Four studies that addressed the effect of a low dose (0.3 mg/day) on the risk for endometrial cancer (Gray *et al*., 1977; Weiss *et al*., 1979; Jick *et al*., 1993; Cushing *et al*., 1998) yielded consistent results: the risk of women using low doses did not differ from that of women using high doses (0.625 mg). In the meta-analysis of the published studies (Grady *et al*., 1995), the summary relative risks were 3.9 (95% CI, 1.6–9.5) for any use of low doses (0.3 mg), 3.4 (95% CI, 2.0–5.6) for intermediate doses (0.625 mg) and 5.8 (95% CI, 4.5–7.5) for high doses (≥ 1.25 mg), but these values did not differ significantly.

Use of oestrogens other than conjugated ones (e.g. oestradiol) was commoner in Europe than in the United States (Persson *et al*., 1989). Other oestrogens have been shown to be related to an increased risk for endometrial cancer in most (Mack *et al*., 1976; Weiss *et al*., 1979; Antunes *et al*., 1979; Buring *et al*., 1986) but not all (Shapiro *et al*., 1980) studies of the type of post-menopausal oestrogen therapy. In the meta-analysis of the published results (Grady *et al*., 1995), users of conjugated oestrogens had greater risk for endometrial cancer (relative risk, 2.5; 95% CI, 2.1–2.9) than users of other oestrogens (1.3; 95% CI, 1.1–1.6).

Most cases of endometrial cancer related to post-menopausal oestrogen therapy have been of the well-differentiated histological type and at an early clinical stage (McDonald

et al., 1977; Antunes *et al*,. 1979; Buring *et al*., 1986; Rubin *et al*., 1990). Myometrial invasion has been reported in only a few cases (Mack *et al*., 1976; McDonald *et al*., 1977; Antunes *et al*., 1979; Weiss *et al*., 1979; Jelovsek *et al*., 1980; Buring *et al*., 1986). In the meta-analysis of the published results (Grady *et al*., 1995), the summary relative risk for early-stage (0–1) cancer was higher (4.2; 95% CI, 3.1–5.7) than that for later stages (2–4) (1.4; 95% CI, 0.8–2.4). Similarly, the summary risk estimate for non-invasive cancer was higher (6.2; 95% CI, 4.5–8.4) than that for invasive cancer (3.8; 95% CI, 2.9–5.1) (Grady *et al*., 1995). Post-menopausal oestrogen therapy was related to the risk for death from endometrial cancer in four studies (Lafferty & Helmuth, 1985; Petitti *et al*., 1987; Ettinger *et al*., 1988; Paganini-Hill *et al*., 1989) and in the meta-analysis (Grady *et al*., 1995). Each of these studies reported at least a doubling of the risk for death from endometrial cancer among women who had ever used post-menopausal oestrogen therapy as compared with those who had never done so.

An increased risk for endometrial cancer has been associated with both continuous and cyclic oestrogen use (Mack *et al.*, 1976; McDonald *et al.*, 1977; Antunes *et al.*, 1979; Weiss *et al.*, 1979; Hulka *et al.*, 1980; Buring *et al.*, 1986) as well as with intermittent regimens (McDonald *et al.*, 1977; Antunes *et al.*, 1979). There were no differences in the summary relative risk estimates for the continuous regimen (2.9; 95% CI, 2.2–3.8) and intermittent and cyclic regimens (3.0; 95% CI, 2.4–3.8) in the meta-analysis (Grady *et al.*, 1995).

Weight and smoking have been reported to modify the relationship between post-menopausal oestrogen therapy and the risk for endometrial cancer. Some studies (Kelsey *et al.*, 1982; Ewertz *et al.*, 1984; La Vecchia *et al.*, 1984; Ewertz *et al.*, 1988; Levi *et al.*, 1993a) indicate that the effects of obesity and oestrogen use are not multiplicative; leaner women have a higher risk for endometrial cancer than women with higher body mass indices (La Vecchia *et al.*, 1982a). Smoking modified the relationship between post-menopausal oestrogen therapy and endometrial cancer in three case–control studies (Franks *et al.*, 1987; Koumantaki *et al.*, 1989; Levi *et al.*, 1993a). Franks *et al.* (1987) presented risks for endometrial cancer stratified by smoking: post-menopausal non-smoking women using oestrogen therapy had a higher relative risk (3.8; 95% CI, 1.7–8.2) than smokers using such therapy (1.0; 95% CI, 0.4–2.6). Levi *et al.* (1993a) and Koumantaki *et al.* (1989) reported similar risk estimates. [Although the effect of smoking is biologically plausible, it cannot be regarded as protective against endometrial cancer.]

2.3 Cervical cancer

2.3.1 *Methodological considerations*

The methodological issues that arise in studies of oral contraceptives and cervical cancer also apply to studies of post-menopausal oestrogen therapy and this disease (see section 2.3 of the monograph on 'Oral contraceptives, combined'). Briefly, exogenous oestrogens may affect various stages in the development of cervical cancer, and epidemiological studies of intraepithelial lesions and invasive lesions should therefore be considered separately. There are also two main histological types of invasive disease, squamous-cell

carcinoma and adenocarcinoma, and ideally these also should be considered separately. In assessing associations between exogenous oestrogens and cervical cancer, the potentially confounding effects of sexual factors and infection by oncogenic strains of the human papillomavirus should be considered. Finally, the influence of Papanicolaou (Pap) smear screening should be considered, as women on post-menopausal hormonal therapy may be more likely to have Pap smears than women not on this therapy.

In the study of Persson *et al*. (1997a) in Sweden, women taking post-menopausal hormonal therapy tended to be of lower parity, older at the birth of their first child and have a higher prevalence of hysterectomy or oophorectomy than women who did not receive such therapy. In addition, a higher level of education was associated with long-term exposure to post-menopausal hormonal therapy, as were heavy physical exercise and diets rich in fibre. Women who had used oral contraceptives were more likely to use oestrogens both with and without progestogen than women who had not used oral contraceptives. These observations serve to demonstrate the importance of considering potentially confounding variables when assessing observed relationships between post-menopausal hormonal therapy and the risks for various neoplasms.

2.3.2 *Cohort studies*

The risk for cervical carcinoma in relation to post-menopausal hormonal therapy has been considered in two cohort studies. Adami *et al.* (1989) reported results for a cohort of 23 244 Swedish women who had been given prescriptions for such therapy. The cohort was assembled between 1977 and 1980 and followed through to the end of 1984. The observed numbers of women with various cancers were compared with expected numbers based on the incidence rates in the population from which the cohort members were accrued. Women who had ever used post-menopausal oestrogen therapy had a relative risk for cervical cancer of 0.8 (95% CI, 0.5–1.2) in comparison with women who had never used oestrogens (27 observed and 34.05 expected cases). The risk in relation to duration of use was not calculated. The risk was lower for women who had used conjugated oestrogens or oestradiol (0.6; 95% CI, 0.3–1.0) than for women who had used other compounds, mainly oestriol (1.3; 95% CI, 0.7–2.3), although oestriol is a less potent oestrogen than conjugated oestrogens or oestradiol. Women who were under 60 years of age at entry into the cohort had a relative risk of 0.6 (95% CI, 0.4–1.0) when compared with older women, whose relative risk was 1.2 (95% CI, 0.6–2.3). This difference was observed for use of either conjugated oestrogens or oestradiol and for use of oestriol. The risk was also somewhat lower for women who were followed for more than five years than for women who were followed for a shorter period: the relative risk of women followed from 0–4 years was 0.9 (95% CI, 0.6–1.3) and that for women followed for five or more years was 0.6 (95% CI, 0.2–1.3). The investigators were unable to control for sexual variables, prior Pap smear screening or human papillomavirus infection. An updated report of the same study (Schairer *et al*., 1997) gave a relative risk for dying of cervical cancer in relation to use of post-menopausal hormonal therapy of 1.2 (95% CI, 0.8–1.7), based on 23 deaths after follow-up through the end of 1986.

In a study in Britain (Hunt *et al*., 1990), 4544 women who had received continuous post-menopausal hormone treatment for at least one year were recruited from 21 pre-menopause clinics around the country between 1974 and 1982, and were followed through 1988. During this period, two women died of cervical cancer, whereas the expected number was 6.8 on the basis of mortality rates for England and Wales. This gave a rate ratio of 0.3 (95% CI, 0.0–1.1).

2.3.3 *Case–control studies*

The results of only one case–control study of post-menopausal oestrogen therapy and cervical cancer have been published (Parazzini *et al*., 1997). In this hospital-based study conducted in northern Italy, 645 women with invasive cervical cancer were compared with 749 women admitted to the same hospitals with acute conditions. After adjustment for age, calendar year of interview, number of sexual partners, parity, oral contraceptive use, lifetime number of cervical smears, social class, smoking and menopausal status, the relative risk for women who had ever used post-menopausal oestrogen therapy was estimated to be 0.5 (95% CI, 0.3–0.8). The risk of women who had used post-menopausal oestrogen therapy for fewer than 12 months was 0.6 (95% CI, 0.4–1.1) and that for women who had used it for 12 or more months was 0.5 (95% CI, 0.2–1.0) (p value for trend, < 0.01). Consistent with the results of Adami *et al*. (1989) described above, the risk of women who had last used post-menopausal oestrogen therapy more than 10 years previously was 0.4 (95% CI, 0.2–0.7), whereas that for women who had last used these products within the past 10 years was 0.9 (95% CI, 0.5–1.7); the risk was lower for women who had first used these products before the age of 50 (0.4; 95% CI, 0.2–0.7) than for women who had first used them at a greater age (0.8; 95% CI, 0.4–1.5).

2.4 Ovarian cancer

2.4.1 *Descriptive studies*

Over the last few decades, no major or systematic trend in incidence or mortality rates has been observed for ovarian cancer in elderly women (Adami *et al.*, 1990; La Vecchia *et al.*, 1992b; Koper *et al.,* 1996; La Vecchia *et al.*, 1998). Consequently, descriptive data on the incidence of and mortality from ovarian cancer do not indicate an effect of post-menopausal oestrogen therapy.

2.4.2 *Cohort studies*

The main findings of cohort studies on post-menopausal oestrogen therapy and ovarian cancer risk are given in Table 8.

In a 13-year follow-up for mortality, between recruitment in 1968–72 and 1983, in a study in the United States on contraception use in 16 638 women aged 18–59, six deaths from ovarian cancer were observed among women who had ever used post-menopausal oestrogen therapy (relative risk, 0.9; 95% CI, 0.3–2.8) (Petitti *et al.,* 1987).

The relationship between post-menopausal oestrogen therapy and ovarian cancer was also analysed in the data from the American Cancer Society's cancer prevention study (II)

Table 8. Selected cohort studies on post-menopausal oestrogen therapy and ovarian cancer, 1980–97

Reference, country	Outcome	No. of cases	Relative risk for any use (95% CI)	Comments
Petitti *et al.* (1987), USA	Mortality	6	0.9 (0.3–2.8)	13-year mortality follow-up of the study on contraception
Rodriguez *et al.* (1995), USA	Mortality	436	1.2 (0.9–1.4)	Significant: direct relationship with duration ($p = 0.03$). RR, 1.4 (95% CI, 0.9–2.1) for 6–10 years and RR, 1.7 (95% CI, 1.1–2.8) for ≥ 11 years of use
Adami *et al.* (1989), Sweden	Incidence	64	1.0 (0.7–1.2)	Cohort of 23 246 women prescribed post-menopausal oestrogen therapy, followed for an average of 6.7 years
Schairer *et al.* (1997), Sweden	Mortality	52	1.0 (0.8–1.3)	Same cohort as Adami *et al.* (1989); follow-up for mortality, 8.6 years

CI, confidence interval; RR, relative risk

for 240 073 peri- and post-menopausal women enrolled in 1982; 436 deaths from ovarian cancer were registered over seven years of follow-up (Rodriguez *et al.*, 1995). The relative risk was 1.2 (95% CI, 0.9–1.4) for any use of oestrogen and rose to 1.4 (95% CI, 0.9–2.1) for 6–10 years of use and to 1.7 (95% CI, 1.1–2.8) for ≥ 11 years of use. This elevated risk was not explained by allowance for other known or likely risk factors for ovarian cancer.

In a Swedish record-linkage prospective study of 23 246 women who were prescribed menopausal oestrogens, recruited between 1977 and 1980 and followed-up for an average of 6.7 years (Adami *et al.,* 1989), 64 cases of ovarian cancer were observed versus 66.64 expected (relative risk, 1.0; 95% CI, 0.7–1.2). After 8.6 years of follow-up (Schairer *et al.*, 1997), 52 deaths from ovarian cancer were observed versus 52.7 expected (relative risk, 1.0; 95% CI, 0.8–1.3).

2.4.3 *Case–control studies*

At least 12 case–control studies published after 1979 and a pooled analysis of individual data from 12 studies of ovarian cancer have provided data on post-menopausal oestrogen therapy (Table 9). Of these, seven studies, including an investigation of 205 cases in the United States (Weiss *et al.*, 1982), a multicentre case–control study of 377 cases in various areas of Canada, Israel and the United States (Kaufman e*t al.*, 1989), a population-based case–control investigation of 367 cases and 564 controls in Ontario,

Table 9. Selected case–control studies on post-menopausal oestrogen therapy and ovarian cancer, 1980–97

Reference, country	Type of study	No. of cases	Age (years)	Relative risk for any use (95% CI)	Comments
Hildreth *et al.* (1981), USA	Hospital-based	62	45–74	0.9 (0.5–1.6)	
Weiss *et al.* (1982), USA	Population-based	205	36–75	1.3 (0.9–1.5)	Stronger association for endometrioid ovarian cancer (3.1; 95% CI, 1.0–9.8)
Franceschi *et al.* (1982), Italy	Hospital-based	161	19–69	[1.0]	No effect
Tzonou *et al.* (1984), Greece	Hospital-based	150	All	1.6 (post-menopausal)	Not significant
Harlow *et al.* (1988), USA	Population-based	116	20–79	0.9	Ovarian neoplasms of borderline malignancy
Kaufman *et al.* (1989), Canada, Israel, USA	Hospital-based	377	18–69	1.1 (0.8–1.6)	Unopposed oestrogens only. No association with combined treatment (RR, 0.7; 95% CI, 0.2–1.8) or with specific histotypes
Booth *et al.* (1989), UK	Hospital-based	225	< 65	1.5 (0.9–2.6)	No association with specific histotypes
Polychronopoulou *et al.* (1993), Greece	Hospital-based	189	< 75	1.4 (0.4–4.9)	Based on 6 exposed cases and 4 controls only
Parazzini *et al.* (1994), Italy	Hospital-based	953	23–74	1.6 (1.2–2.4)	Adjusted for major covariates, including combined oral contraceptive use
Purdie *et al.* (1995), Australia	Population-based	824	18–79	1.0 (0.8–1.3)	Adjusted for major covariates, including oral contraceptive use
Risch *et al.* (1996), Ontario, Canada	Population-based	367	35–79	1.3 (0.9–2.0)	Multivariate RR, 2.0 (95% CI, 1.0–4.0) for serous and 2.8 (95% CI, 1.2–6.9) for endometrioid for ≥ 5 years of use. No association with mucinous tumours

Table 9 (contd)

Reference, country	Type of study	No. of cases	Age (years)	Relative risk for any use (95% CI)	Comments
Hempling *et al.* (1997), USA	Hospital-based	491	NR	0.9 (0.6–1.2)	Other cancers as controls
Re-analysis of original data					
Whittemore *et al.* (1992), USA	Pooled analysis of 12 US hospital- and population-based case-control studies	2 197	All	0.9 (0.7–1.3) (hospital-based) 1.1 (0.9–1.4) (population-based)	Invasive cancers. No trend in risk with duration. RR per year of use, 1.0 for both hospital- and population-based studies
Harris *et al.* (1992b), USA	Pooled analysis of same 12 studies as Whittemore *et al.* (1992) but for tumours of low malignant potential	327	All	1.1 (0.7–1.9)	Ovarian neoplasms of borderline malignancy. No difference between hospital-based and population-based studies. No trend in risk with duration

CI, confidence interval; RR, relative risk; NR, not reported

Canada (Risch, 1996), and four European studies, from the United Kingdom (Booth *et al*., 1989), Greece (Tzonou *et al*., 1984; Polychronopoulou *et al*., 1993) and Italy (Parazzini *et al*., 1994), reported relative risks between 1.2 and 1.6. Other case–control studies, including the pooled analysis of individual data from the United States studies (Whittemore *et al*., 1992), however, showed no consistent association.

Hildreth *et al.* (1981) provided data on 62 cases of ovarian cancer and 1068 controls in seven hospitals in Connecticut, United States, between 1977 and 1979. The response rate was 71% for both cases and controls. The relative risk for any use of post-menopausal oestrogen therapy was 0.9 (95% CI, 0.5–1.6).

Weiss *et al.* (1982) considered 205 cases of epithelial ovarian cancer diagnosed between 1975 and 1979 and 611 population controls in Washington State and Utah, United States. The overall relative risk for any use of post-menopausal oestrogen therapy was 1.3 (95% CI, 0.9–1.8), and there was no consistent time–risk relationship; however, the relative risk was 3.1 (95% CI, 1.0–9.8) for the 17 endometrioid tumours. Allowance was made for age, state of residence and hysterectomy.

Franceschi *et al.* (1982) reported data on 161 cases and 561 population controls interviewed in 1979–80 in greater Milan, northern Italy. Any use of non-contraceptive oestrogens was reported by 17% of cases and 17% of controls, corresponding to an age-adjusted relative risk of [1.0]. The duration of use was also similar in cases and controls.

In a hospital-based case–control investigation of 150 case and 250 control women interviewed in 1980–81 in Athens, Greece (Tzonou *et al.,* 1984), the relative risk for any use of post-menopausal oestrogen therapy was 1.6 (not significant). No information was available on duration of use or other time factors.

Harlow *et al.* (1988) considered 116 cases of ovarian cancer of borderline malignancy and 158 hospital controls in western Washington, United States, diagnosed between 1980 and 1985. The response rate was 68% for cases and 74% for controls. The relative risk for any use of post-menopausal oestrogen therapy was 0.9, in the absence of a consistent duration–risk relationship.

Kaufman *et al.* (1989) conducted a multicentre case–control study in Canada, Israel and the United States on 377 cases of epithelial ovarian cancer and 2030 hospital controls interviewed between 1976 and 1985. The multivariate relative risk for any use of post-menopausal oestrogen therapy was 1.1 (95% CI, 0.8–1.6), after allowance for socio-demographic factors, age at menarche, parity, menopausal status, age at menopause and oral contraceptive use, but it rose to 1.6 (95% CI, 0.8–3.2) for ≥ 10 years of use. The trend in risk with duration was not significant. No appreciable heterogeneity was observed across different histological types.

A study of 235 cases and 451 hospital controls conducted between 1978 and 1983 in London and Oxford, England (Booth *et al.,* 1989), gave a multivariate relative risk for any use of post-menopausal oestrogen therapy of 1.5 (95% CI, 0.9–2.6) after adjustment for age and social class. No data were available on duration of use.

A study of 189 cases and 200 controls conducted in 1989–91 in greater Athens, Greece (Polychronopoulou *et al.,* 1993) gave a relative risk for any use of post-menopausal

oestrogen therapy of 1.4 (95% CI, 0.4–4.9). No information was given on duration or other time–risk relationships. The response rate of cases was almost 90%. Allowance was made for age, education, weight, age at menarche, parity and age at the birth of the first child.

A study of 953 cases diagnosed between 1983 and 1992 in northern Italy and 2503 hospital controls (Parazzini *et al.,* 1994) found a multivariate relative risk (after allowance for socio-demographic factors, parity, age at menarche, type of menopause, age at menopause and oral contraceptive use) of 1.6 (95% CI, 1.2–2.4) for any use of post-menopausal oestrogen therapy. The relative risk for ≥ 2 years of use was 1.7 (95% CI, 0.9–3.4).

Purdie *et al.* (1995) provided data on 824 cases diagnosed between 1990 and 1993 and 860 population controls in three Australian states. The response rate was 90% for cases and 73% for controls. The multivariate relative risk (adjusted for socio-demographic factors, family history of cancers, talc use, smoking and reproductive and hormonal factors) for any use of post-menopausal oestrogen therapy was 1.0 (95% CI, 0.8–1.3). No information was given on duration of use or any other time–risk relationship.

Risch (1996) reported data on post-menopausal oestrogen therapy for 367 patients with invasive epithelial ovarian cancer and 564 population controls in Ontario, Canada, interviewed during 1989–92. The response rate was 71% for cases and 65% for controls. The relative risk for any use of post-menopausal oestrogen therapy was 1.3 (95% CI, 0.9–2.0) for non-mucinous neoplasms and 0.7 (95% CI, 0.2–2.1) for mucinous ones. The association was apparently strongest (1.9; 95% CI, 1.0–3.5) for endometrioid neoplasms, with a significant duration–risk relationship. Allowance was made in the analysis for age, parity, lactation, combined oral contraceptive use, tubal ligation, hysterectomy and family history of breast cancer.

In a study based on data collected between 1982 and 1995 at the Roswell Park Cancer Institute, United States (Hempling *et al.*, 1997), 491 patients with epithelial ovarian cancer were compared with 741 women admitted for non-hormone-related malignancies. The overall relative risk for any use of post-menopausal oestrogen therapy was 0.9 (95% CI, 0.6–1.2); there was no significant trend with duration of use. The relative risk was 0.6 (95% CI , 0.3–1.4) for ≥ 10 years of use. Further, there was no appreciable heterogeneity across histological types. Allowance was made for age, parity, combined oral contraceptive use, smoking, family history of ovarian cancer, age at menarche, menopausal status and socio-demographic factors.

A pooled analysis of individual data from 12 studies of 2197 white cases of invasive epithelial ovarian cancer and 8893 white controls in the United States (Whittemore *et al.*, 1992) gave a pooled multivariate relative risk for invasive ovarian cancer associated with any use of post-menopausal oestrogen therapy for more than three months of 0.9 (95% CI, 0.7–1.3) for hospital-based studies and 1.1 (95% CI, 0.9–1.4) for population-based studies; there was no consistent duration–risk relationship. The relative risk for use for > 15 years was 0.5 (95% CI, 0.2–1.3) for hospital-based and 1.5 (95% CI, 0.8–3.1) for population-based studies. The overall trend per year of use was 1.0 for both types of

study; neither risk estimate was significant. Allowance was made in the analysis for age, study, parity and combined oral contraceptive use.

In a similar pooled analysis of individual data on 327 cases of epithelial ovarian tumours of borderline malignancy, the relative risk for any use of post-menopausal oestrogen therapy was 1.1 (95% CI, 0.7–1.9) (Harris *et al.*, 1992b).

Earlier studies (La Vecchia *et al.*, 1982b; Weiss *et al.*, 1982) had suggested that endometrioid neoplasms are related to post-menopausal oestrogen therapy, but this suggestion was not confirmed in several subsequent studies (Kaufman *et al.*, 1989; Whittemore *et al.*, 1992). It was thus unclear whether post-menopausal oestrogen therapy is consistently related to any specific histotype of ovarian cancer; however, a recent Canadian study (Risch, 1996) gave relative risks of 1.4 for serous, 1.9 for endometrioid and 0.7 for mucinous tumours, and significant trends in risk with duration of use for serous and endometrioid tumours. The issue of a potential histotype-specific relationship is therefore still open to discussion, although it remains possible that ovarian cancer cases in women who had used post-menopausal oestrogen therapy are more often classified as endometrioid. The available data therefore suggest that there is little or no association between use of post-menopausal oestrogen therapy and invasive epithelial ovarian neoplasms or those of borderline malignancy. No adequate data were available on post-menopausal oestrogen therapy and non-epithelial (germ-cell or sex-cord-stromal) ovarian neoplasms.

2.5 Liver cancer

2.5.1 *Cohort studies*

Goodman *et al.* (1995) reported the results of a study of risk factors for liver cancer in Hiroshima and Nagasaki, Japan. Information was collected by questionnaire from 36 133 men and women between 1978 and 1981, who were followed through population-based cancer registries until 1989. There were 242 cases of hepatocellular carcinoma in the two cities, of which 86 were in women; information on use of female hormone preparations was available for 76 of these cases. Details of the type of female hormones used were not collected, but oral contraceptive use is very rare in Japan and it is likely that the hormones were largely given as post-menopausal hormonal therapy. Sixty-nine of the case women had never used hormones, and seven had used these preparations. The risk for any use relative to no use of hormones, adjusted for city, age at the time of the atomic bombing, attained age and radiation dose to the liver, was 1.3 (95% CI, 0.6–2.8). There was no information on infection with hepatitis viruses, but infection with hepatitis B virus is common in western Japan.

Persson *et al.* (1996) studied the cancer risk after post-menopausal hormonal therapy in a population-based cohort of 22 579 women aged 35 or more and living in the Uppsala health care region, Sweden. Women who had ever received a prescription for post-menopausal hormonal therapy between 1977 and 1980 were identified and followed-up until 1991. Information on hormone use was obtained from pharmacy records. The expected numbers of cases were calculated from national incidence rates. There was no information on smoking or alcohol consumption. The standardized incidence ratio for all cancers was

1.0 (95% CI, 0.9–1.0). There were 43 cancers of the hepatobiliary tract, comprising 14 hepatocellular carcinomas, five cholangiocarcinomas, 23 gall-bladder cancers and one unclassified; the expected number was 73.2, giving a standardized incidence ratio of 0.6 (95% CI, 0.4–0.8) for any type of post-menopausal hormonal therapy. The ratios for hepatocellular carcinoma were 0.8 (95% CI, 0.4–1.6) for treatment with oestradiol or conjugated oestrogens and 0.5 (95% CI, 0.2–1.4) for treatment with oestriol and other oestrogens. The relative risks for cholangiocarcinoma were 0.7 (95% CI, 0.1–2.0) for treatment with oestradiol or conjugated oestrogens and 0.3 (95% CI, 0.0–1.7) for treatment with oestriol and other oestrogens. There was no information on infection with hepatitis viruses.

2.5.2 *Case–control studies*

Yu *et al.* (1991) used a population-based cancer registry to identify histologically confirmed hepatocellular carcinomas diagnosed in women aged 18–74 between 1984 and 1990 who were black or white residents of Los Angeles County, United States. Two neighbourhood controls were sought for each case and matched on sex, year of birth and race. Eighty-four of 412 (20.4%) eligible patients were interviewed (70.6% died before attempted contact), of which 10 were excluded from the analysis because the diagnosis of hepatocellular carcinoma was not confirmed. The response rate among the initially selected controls was 71%. Adjustment for smoking and alcohol did not alter the results. Ten of the 25 case women (40.0%) had used Premarin® or other oestrogens, in comparison with 19 of the 58 female controls (32.8%). The relative risks, adjusted for duration of use of oral contraceptives, were 1.1 (95% CI, 0.3–3.6) for any use and 0.8 (95% CI, 0.2–4.5) for use for up to 12 months, 1.0 (95% CI, 0.2–5.1) for 13–60 months and 1.0 (95% CI, 0.2–6.0) for 61 months or more. Seven case women had one or more markers of hepatitis B and C viral infections; when these cases were excluded, use of Premarin® was still not related to hepatocellular carcinoma after adjustment for duration of use of oral contraceptives.

Tavani *et al.* (1996) studied the relationship between the risk for biliary cancer and factors related to female hormones in Milan, northern Italy, between 1984 and 1993. The cases were in 31 women aged 27–76 with histologically confirmed cancers of the biliary tract (of whom 17 had gall-bladder cancers); the controls were 377 women, age frequency-matched with cases, who were in hospital for acute, non-neoplastic, non-digestive conditions. Post-menopausal oestrogen therapy was used by 4 of 31 cases and 21 of 377 controls, yielding a relative risk, adjusted for age and history of cholelithiasis, of 2.2 (95% CI, 0.7–7.2).

2.6 Colorectal cancer

2.6.1 *Descriptive studies*

The incidence of colon cancer is similar for men and women, while a male predominance is found for rectal cancer. The female:male ratio of colon cancer incidence is relatively higher at pre-menopausal ages, suggesting an influence of some biological correlate

of sex. Over the last two decades, mortality rates from these cancers in many developed countries have declined in women but not in men (La Vecchia *et al.*, 1998).

2.6.2 *Cohort studies*

(*a*) *Colorectal adenomas*

Grodstein *et al*. (1998) reported that 838 of 59 002 post-menopausal women had developed colorectal adenomas. There was no association between hormonal therapy and the incidence of adenomas overall, but current users had a lower risk for large (≥ 1 cm) adenomas than women who had never used hormones (relative risk, 0.74; 95% CI, 0.55–0.99).

(*b*) *Colorectal cancer*

Cohort studies on post-menopausal oestrogen therapy and cancers of the colon and rectum are summarized in Table 10.

Wu *et al*. (1987) followed a cohort of 7345 women in a large retirement community in California, United States, representing 62% of those to whom a questionnaire had been mailed; 4060 women reported ever having used post-menopausal oestrogen therapy of any type. After a four-year follow-up, 68 incident cases of colorectal cancer were identified. No association with risk for colorectal cancer was found (age-adjusted relative risk, 0.98; 95% CI, 0.5–1.8, for < 8 years of use and 1.0, 95% CI, 0.6–1.8 for ≥ 8 years' use).

A cohort of 22 597 Swedish women (mean age, 55 years) who received a prescription for post-menopausal oestrogen therapy were followed-up for cancer incidence and deaths through national cancer registries for an average of 6.7 years (Adami *et al*., 1989) and, subsequently, for 13 years from 1977 through 1991 (Persson *et al*., 1996). Overall, 153 incident cases and 62 deaths due to cancer of the colon and 80 incident cases of rectal cancer were observed. Information on exposure to post-menopausal oestrogen therapy was available only from accumulated pharmacy records; women were categorized into three exclusive compound groups according to the formulation prescribed: any oestradiol compounds or conjugated oestrogens, 11% of whom also received a progestogen; other oestrogens, chiefly a weak oestriol compound; and a fixed oestrogen–progestogen combination. For those for whom oestradiol compounds or conjugated oestrogens had ever been prescribed, the relative risk was 0.9 (95% CI, 0.7–1.1) for incident colorectal cancer and 0.9 (95% CI, 0.7–1.2) for incident rectal cancer (Persson *et al.*, 1996); a significant decrease in risk for mortality from colon cancer was observed (0.6; 95% CI, 0.4–0.9). The corresponding relative risks for women who had received only other oestrogens were 1.0 (95% CI, 0.8–1.3) for new cases of colon cancer, 0.8 (95% CI, 0.5–1.2) for new cases of rectal cancer and 0.8 (95% CI, 0.5–1.2) for death from colon cancer. The relative risk for exposure to any type of oestrogen was 0.9 for the incidence of either colon or rectal cancer and 0.7 (95% CI, 0.5–0.9) for mortality from colon cancer.

In an initial report from the Nurses' Health Study (Chute *et al*., 1991), there was no significant association between hormonal therapy and colon or rectal cancer after an

Table 10. Cohort studies of use of post-menopausal oestrogen therapy and colorectal cancer

Reference, country	Size of cohort	Follow-up (years)	No. of cases of colorectal cancer	Type of use	Relative risk (RR; 95% confidence interval) (any versus no use)					Duration of use	Recency of use	Adjustment, comments
					Colon–rectum	Colon	Right colon	Left colon	Rectum			
Wu *et al.* (1987), California, USA	7 345	4	68	–	1.00 (NS)	–	–	–	–	No effect (RR ≥ 8 years' use, 1.0; 0.6–1.8)	NR	Age
Adami *et al.* (1989); Persson *et al.* (1996), Sweden	23 244	13	233, 62 deaths	OT	0.9 (0.7–1.1)	–	–	–	0.9 (0.7–1.2)	No effect	NR	Age; RR for colon mortality, 0.6 (0.4–0.9)
				Oestriol	1.0 (0.8–1.3)	–	–	–	0.8 (0.5–1.2)			
				Any type	0.9 (0.7–1.2)	–	–	–	0.9 (0.7–1.1)			
Chute *et al.* (1991); Grodstein *et al.* (1998), USA	59 002	14	262			0.64 (0.48–0.85)	0.56 (0.35–0.91)	0.79 (0.50–1.2)	0.67 (0.40–1.1)	No effect (RR ≥ 5 years' use, 0.72; 0.53–0.96)	No risk reduction after 5 years' duration (RR, 0.92; 0.70–1.2)	Age, body mass index, COC use, family history of cancer, diet, alcohol, smoking and age at menopause
				Current users		0.65 (0.50–0.83)						
				Past users		0.86 (0.67–1.1)						
Bostick *et al.* (1994); Folsom *et al.* (1995), Iowa, USA	41 837	6	293	Current users		0.73 (0.47–1.1)	–	–	–	Inverse trend (RR, 0.31 for ≤ 5 years' use)	No effect	Age, body mass index, weight:height ratio, alcohol, exercise and medical history
				Past users		0.80 (0.61–1.1)	–	–	–			

Table 10 (contd)

Reference, country	Size of cohort	Follow-up (years)	No. of cases of colorectal cancer	Type of use	Relative risk (RR; 95% confidence interval) (any versus no use)					Duration of use	Recency of use	Adjustment, comments
					Colon–rectum	Colon	Right colon	Left colon	Rectum			
Calle *et al*. (1995), USA	422 373	7	897 deaths	–	–	0.71 (0.61–0.83)	–	–	–	Significant trend (RR for > 11 years' use, 0.54; 0.39–0.76)	Stronger effect among current users (RR, 0.55; 0.40–0.76)	Age, body mass index, parity, menopause, COC, diet, exercise, race and smoking
Risch & Howe (1995), Canada	33 003	14	230	–	1.0 (0.74–1.5)	1.3 (0.86–1.9)	–	–	0.64 (0.33–1.2)	RR, 0.65 (0.21–2.6) for ≥ 5 years)	Not shown	Age Linkage study
Troisi *et al*. (1997), USA	33 779	7.7	313	Un-opposed OT	–	1.1 (0.7–1.5)	1.6 (1.0–2.7)	0.8 (0.5–1.5)	1.2 (0.7–2.3)	No effect	RR for recent use, 0.78 (0.55–1.1)	Age (but unaltered by education, body mass index, parity and COC use)
				Any OT	0.99 (0.79–1.2)	1.1 (0.81–1.6)	1.7 (1.0–2.7)	0.98 (0.58–1.7)	1.1 (0.59–1.9)			

NS, not significant; OT, oestrogen therapy; NR, not reported; COC, combined oral contraceptives

eight-year follow-up. After 14 years, however, Grodstein *et al*. (1998) reported that 262 of 59 002 post-menopausal women had developed colorectal cancer. In this analysis, current use was associated with a decreased risk, the relative risk adjusted for several potential confounding variables being 0.65 (95% CI, 0.50–0.83). The results were not changed (relative risk, 0.64; 95% CI, 0.49–0.82) after exclusion of women who had undergone a screening sigmoidoscopy, suggesting that the lower risk was not due to more intensive screening of women who had used hormones. This association disappeared five years after hormone use was discontinued (relative risk, 0.92; 95% CI, 0.70–1.2).

In a prospective cohort study of 35 215 women aged 55–69 years with a driver's licence and without a history of cancer in Iowa, United States, from 1986 through 1990 (Bostick *et al*., 1994), 212 new cases of colon cancer were documented. The relative risk for colon cancer associated with post-menopausal oestrogen therapy use, adjusted for age, parity, height, energy and vitamin intake, was 0.93 (95% CI, 0.68–1.3) for former users and 0.82 (95% CI, 0.50–1.3) for current users. The study cohort was updated by Folsom *et al*. (1995), who followed-up 41 837 women aged 55–69 years for two additional years. The relative risk for colon cancer (293 observed cases), adjusted for age, body mass index, waist-to-hip ratio, exercise, alcohol and medical history, was 0.80 (95% CI, 0.61–1.1) in former users and 0.73 (95% CI, 0.47–1.1) in current users. The lowest relative risk was seen for short-term (≤ 5 years) current post-menopausal oestrogen therapy use (relative risk, 0.3; 95% CI, 0.10–0.98).

A cohort of 676 526 female participants (median age, 56) in the Cancer Prevention Study II was recruited in 1982 from all over the United States (Calle *et al*., 1995). By the end of 1989, 43 862 (6.5%) of the women had died. A total of 897 deaths from colon cancer occurred among 422 373 post-menopausal women who had not had cancer at entry to the study. The relative risk associated with any use of post-menopausal oestrogen therapy, adjusted for age, race, body mass index, parity, menopause, combined oral contraceptive use, dietary habits, exercise, smoking and aspirin use, was 0.71 (95% CI, 0.61–0.83). The risk reduction was strongest for women who were current users at the time of entry to the cohort (0.55; 95% CI, 0.40–0.76), and there was a significant trend of decreasing risk with increasing years of use (at entry) among all users (relative risk for users of > 11 years, 0.54; 95% CI, 0.39–0.76). No data on incidence were available.

A record linkage cohort study was carried out in Saskatchewan, Canada, between the Prescription Drug Plan Database (1976–87) and the Provincial Cancer Registry Database (1960–90) on all 33 003 resident women aged 43–49 (Risch & Howe, 1995). Of 32 973 women who did not have colorectal cancer at the beginning of the study, 230 developed this cancer. For users of post-menopausal oestrogen therapy, the age-adjusted relative risk was 1.3 (95% CI, 0.86–1.9) for colon cancer, 0.64 (95% CI, 0.33–1.2) for rectal cancer and 1.0 (95% CI, 0.74–1.5) for both together.

A cohort of 64 182 women was selected for follow-up within the Breast Cancer Detection Demonstration project between 1973 and 1980 in 27 cities of the United States (Troisi *et al*., 1997). Telephone interviews were conducted between 1979 and 1986 with 61 434 women. The analyses were restricted to 33 779 post-menopausal women (41–80 years of

age; mean age, 59) who completed the follow-up questionnaire between 1987 and 1989. After an average follow-up of 7.7 years, 313 cases of colorectal cancer were identified (84 from death certificates). Any use of post-menopausal oestrogen therapy was not related to the risk for colorectal cancer (age-adjusted relative risk, 0.99; 95% CI, 0.79–1.2). The relative risk for recent use of five or more years' duration was 0.75 (95% CI, 0.50–1.1). The risks were similar for colon cancer and rectal cancer. Eighty-four per cent of the person–years of post-menopausal oestrogen therapy use were accounted for by oestrogen use alone: the relative risks for any use of oestrogen alone were similar to those for any use of post-menopausal oestrogen therapy (relative risk, 1.1; 95% CI, 0.7–1.5 for colon; and 1.2; 95% CI, 0.7–2.3 for rectum).

2.6.3 *Case–control studies*

(*a*) *Colorectal polyps*

Potter *et al*. (1996) undertook a case–control study in Minnesota, United States, between 1991 and 1994 of cases in 219 women, aged 30–74, with colonoscopy-proven, pathology-confirmed, adenomatous polyps of the colon and rectum. Two control groups were selected: 438 women without polyps at colonoscopy and 247 community controls matched on age and postal code; the response rates of all three groups were around 65%. The multivariate relative risks for use of post-menopausal oestrogen therapy for fewer than five years, compared with no use, among post-menopausal women were 0.52 (0.32–0.85) in comparison with colonoscopy-negative controls and 0.74 (0.44–1.3) in comparison with community controls. For five or more years of use, the corresponding figures were 0.39 (0.23–0.67) and 0.61 (0.34–1.1).

Jacobson *et al*. (1995) studied patients with colorectal adenomatous polyps between 1986 and 1988 in New York, United States. The cases (128) were in cancer-free women aged 35–84 years in whom an adenoma was detected at the index colonoscopy. The 283 controls were cancer-free women with a normal index colonoscopy at the same institution as the cases. The adjusted relative risk associated with post-menopausal oestrogen therapy was 0.7 (95% CI, 0.3–1.2).

Chen *et al.* (1998) studied 187 women with colorectal polyps and 188 controls, aged 50–75 years, who were members of a prepaid health plan and underwent sigmoidoscopy in 1991–93. For women who used post-menopausal oestrogen therapy in the year before sigmoidoscopy relative to women who did not (37 cases and 38 controls), the relative risk adjusted for age, sigmoidoscopy date, physical activity, bone mass index, smoking and ethnicity was 0.57 (95% CI, 0.35–0.94). The risk for > 5 years of use (16 cases and 30 controls) was 0.49 (95% CI, 0.25–0.97).

(*b*) *Colorectal cancer*

Case–control studies of use of post-menopausal oestrogen therapy and the risks for cancers of the colon and rectum are summarized in Table 11.

A case–control study was conducted in 1976–77 in Washington State, United States, on 143 white women with colorectal cancer, aged 45–74 years, and 707 white women of

Table 11. Case–control studies of use of post-menopausal oestrogen therapy and colorectal cancer

Reference, country	No. of cases/ no. of controls	Type of controls	Type of use	Relative risk (RR; 95% confidence interval) (any versus no use)					Duration of use	Recency of use	Adjustment, coments
				Colon-rectum	Colon	Right colon	Left colon	Rectum			
Weiss *et al*. (1981), Washington, USA	143/707	Popu-lation	≤ 5 years ≥ 6 years	1.1 (0.7–1.9) 1.0 (0.6–1.6)	–	–	–	–	No trend	NR	Age
Potter & McMichael (1983), Adelaide, Australia	155/311	Popu-lation		–	0.8 (0.4–1.5)	–	–	1.5 (0.8–3.0)			Reproductive variables (diet had no effect); use of hormones other than COC
Davis *et al*. (1989), Canada	720/349	Cancer patients	Current users Past users	1.5 (0.8–2.7) 1.1 (0.7–1.9)	–	–	–	–	NR	NR	Age and parity No distinction possible between OT and COC use
Furner *et al*. (1989), Chicago, USA	90/208	Spouses		0.5 (0.27–0.90)	–	0.8 (0.27–2.6)	0.6 (0.27–1.3)	0.2 (0.03–0.77)	No trend	NR	Age, parity, hysterectomy
Fernandez *et al*. (1998), including data from Negri *et al*. (1989); Fernandez *et al*. (1996), Italy	1 536/3 110	Hospital		0.58 (0.44–0.76)	0.59 (0.43–0.82)	0.35 (0.15–0.80)	0.67 (0.44–1.0)	0.48 (0.31–0.75)	Significant (RR for ≥ 2 years' use, 0.46; 0.26–0.81)	RR for ≥ 10 years since last use, 0.52 (0.27–0.99)	Age, education, family history of cancer, body mass index, parity, menopause, COC and energy intake

Table 11 (contd)

Reference, country	No. of cases/ no. of controls	Type of controls	Type of use	Relative risk (RR; 95% confidence interval) (any versus no use)					Duration of use	Recency of use	Adjustment, coments
				Colon-rectum	Colon	Right colon	Left colon	Rectum			
Peters *et al*. (1990), Los Angeles, USA	327/327	Neigh-bours	< 5 years 5–14 years ≥ 15 years		1.3 (0.88–2.0) 1.1 (0.64–1.8) 1.1 (0.58–1.9)	1.4 (0.80–2.6) 1.1 (0.47–2.6) 1.2 (0.51–2.8)	1.2 (0.69–2.3) 1.1 (0.55–2.2) 0.75 (0.30–1.8)	–	No effect	NR	Family history of cancer, parity, menopause, exercise, fat, alcohol and calcium intake
Wu-Williams *et al*. (1991), North America and China	189/494 (North America) 206/618 (China)	Neigh-bours			2.1 $p = 0.14$ 2.9 $p = 0.01$	– –	– –	0.5 $p = 0.23$ 1.3 $p = 0.56$	NR; mostly short duration of use	NR	Use of 'other hormones' Unadjusted but unaltered by exercise, saturated fat intake and years in the USA Artificial menopause was a risk factor in China
Gerhardsson de Verdier & London (1992), Sweden	299/276	Popu-lation		–	0.6 (0.4–1.0)	0.4 (0.2–0.8)	1.0 (0.5–1.9)	0.7 (0.4–1.3)	No trend	NR	Age Hormone use included both OT and COC, but mostly OT
Jacobs *et al*. (1994), Seattle, USA	148/138	Popu-lation		–	0.60 (0.35–1.0)	0.46 (0.23–0.91)	0.74 (0.39–1.4)	–	Significant trend (RR ≥ 5 years' use, 0.47; 0.24–0.91)	RR of current users, 0.53 (0.29–0.96)	Age, vitamin intake and hysterectomy Greater protection for multiparous women

Table 11 (contd)

Reference, country	No. of cases/ no. of controls	Type of controls	Type of use	Relative risk (RR; 95% confidence interval) (any versus no use)					Duration of use	Recency of use	Adjustment, coments
				Colon-rectum	Colon	Right colon	Left colon	Rectum			
Newcomb & Storer (1995), Wisconsin, USA	694/1 622	Popu-lation	Unopposed oestrogen (recent use) Any OT		0.54 (0.34–0.88) 0.73 (0.56–0.94)	– 0.43 (0.22–0.84) (recent use)	– 0.64 (0.39–1.0) (recent use)	0.90 (0.46–1.76) 1.2 (0.83–1.6)	Significant trend (p = 0.002)	Lower RR for < 10 years since last use, 0.54 (0.36–0.80) for colon	Age, alcohol, body mass index, family history of cancer and sigmoidoscopy
Kampman *et al*. (1997), USA	815/1 019	Members of medical care organi-zation		–	0.82 (0.67–0.99)	NR	NR	–	No trend (RR ≥ 10 years' use, 0.86)	RR for recent use, 0.71 (0.56–0.89)	Age, family history of cancer, aspirin, energy intake, COC and exercise
Yood *et al*. (1998), Detroit, USA	60/143	Members of health mainte-nance organi-zation	Current use Past use	0.34 (0.11–0.99) 0.40 (0.12–1.4)	–	0.55 (0.14–2.2)	0.32 (0.30–1.7)	–	NR	NR	Age, race, reproductive variables, dietary habits and colonoscopy

NR, not reported; COC, combined oral contraceptives; OT, oestrogen therapy

the same ages drawn from a population survey in the area (Weiss *et al*., 1981). Use of post-menopausal oestrogen therapy of any type was not related to cancer risk (age-adjusted relative risk, 1.1; 95% CI, 0.7–1.9 for ≤ 5 years' use; and 1.0; 95% CI, 0.6–1.6 for ≥ 6 years' use).

Potter and McMichael (1983) conducted a case–control study in Adelaide, Australia, between 1979 and 1980 on 155 cases of colorectal cancer (out of 212 eligible cases) and 311 control women selected from the local electoral roll. The relative risk, adjusted for reproductive variables, for use of oestrogen therapy of any type, apart from oral contraceptives, was 0.8 (95% CI, 0.4–1.5) for colon cancer and 1.5 (95% CI, 0.8–3.0) for rectal cancer.

A case–control study conducted in Alberta, Canada, between 1969 and 1973 included data on 528 cases of colon cancer, 192 of rectal cancer (i.e. 69% of identified colorectal cancers in the study area) and 349 control women aged 35 and more (Davis *et al*., 1989). The controls were women with cancers at sites not associated with endocrine factors (chiefly cancers of the mouth and stomach). The estimated relative risk for use of exogenous hormones (including post-menopausal oestrogen therapy and combined oral contraceptives) among women over 50, as a surrogate for post-menopausal oestrogen therapy, adjusted for age and parity, was 1.5 (95% CI, 0.8–2.7) for current use and 1.1 (95% CI, 0.7–1.9) for past use.

Ninety women with colorectal cancer and 208 controls who were the wives of colorectal cancer patients were interviewed between 1980 and 1983 in Chicago, United States, representing 63% of the subjects initially contacted (Furner *et al*., 1989). The relative risk associated with post-menopausal oestrogen therapy [not otherwise specified] adjusted for age, parity and hysterectomy was 0.5 (95% CI, 0.27–0.90). The inverse association was stronger for cancer of the rectum (relative risk, 0.2; 95% CI, 0.03–0.77; two cases) than for cancers of the right colon (0.8; 0.27–2.63; six cases) or left colon (0.6; 0.03–0.77; 12 cases). No trend in risk emerged with duration of post-menopausal oestrogen therapy.

A hospital-based case–control study conducted in Milan, Italy, between 1985 and 1992 (Negri *et al*., 1989; Fernandez *et al*., 1996) included 709 women with colon cancer (median age, 61 years) and 992 women in hospital for acute, non-digestive, non-hormone-related disorders. The relative risk for women who had ever used post-menopausal oestrogen therapy, adjusted for age, social class, family history of cancer, menarche and parity was 0.40 (95% CI, 0.25–0.66). The risk decreased with increasing duration of use (0.46 for ≤ 2 years; 0.25 for > 2 years of use). No consistent trend was observed with time since first or last use. Another case–control study conducted with a similar protocol in six Italian areas between 1992 and 1996 (Talamini *et al*., 1998) included 537 women with colon cancer, 291 women with rectal cancer and 2081 control women in hospital for acute conditions unrelated to hormonal or gynaecological diseases. The relative risk for any use of post-menopausal oestrogen therapy, adjusted for age, centre, education, exercise and energy intake, was 0.6 (95% CI, 0.3–1.0) for rectal cancer and 1.0 (95% CI, 0.69–1.5) for colon cancer; however, only about 10% of post-menopausal women had had post-menopausal oestrogen

therapy. A pooled analysis of the two Italian studies described by Fernandez *et al*. (1996) and Talamini *et al*. (1998) included 994 women with cancer of the colon and 542 with cancer of the rectum, in addition to 3110 hospital controls (Fernandez *et al*., 1998). The relative risks for any use, adjusted for age, education, family history of cancer, body mass index, parity, menopause, combined oral contraceptive use and energy intake, were 0.59 (95% CI, 0.43–0.82) for colon cancer and 0.48 (95% CI, 0.31–0.75) for rectal cancer. The inverse association was stronger for cancer of the right colon (0.35; 0.15–0.80) than for that of the left colon (0.67; 0.44–1.03). Significant trends in risk by duration of use emerged for all subsites. The decrease in the relative risk associated with post-menopausal oestrogen therapy was greater 10 or more years after cessation of use (relative risk, 0.50 for colon and 0.54 for rectum) than earlier.

Peters *et al*. (1990) conducted a population-based case–control study in Los Angeles, United States, between 1983 and 1986. A total of 327 white women with colon cancer (out of 472 eligible cases) and 327 individually matched neighbourhood controls were interviewed. The relative risks, adjusted for age, family history of cancer, parity, menopause, exercise, fat, calcium and alcohol intake, for < 5, 5–14 and ≥ 15 years' duration of use, were 1.3 (95% CI, 0.88–2.0), 1.1 (95% CI, 0.64–1.8) and 1.0 (95% CI, 0.58–1.9), respectively. The risk estimates were similar for cancers of the right and left colon.

A population-based case–control study was conducted among Chinese women in western North America and China between 1981 and 1986 with a common protocol (Wu-Williams *et al*., 1991). It included 395 women with colorectal cancer, 189 from North America and 206 from China, and 1112 age-matched controls, 494 and 618, respectively. The unadjusted relative risk for rectal cancer associated with the use of hormones other than combined oral contraceptives was 0.5 in North America and 1.3 in China (neither significant). The relative risk for colon cancer was 2.1 ($p = 0.14$) in North America and 2.9 ($p = 0.01$) in China. About 90% of the post-menopausal oestrogen therapy users had used hormones for one year or less.

A population-based case–control study was performed in Stockholm, Sweden, in 1986–88, which included 299 cases and 276 controls (i.e. about 80% of eligible subjects) (Gerhardsson de Verdier & London, 1992). The questionnaire used did not allow distinction between post-menopausal oestrogen therapy and combined oral contraceptives. The age-adjusted relative risk for hormone use was 0.6 (95% CI, 0.4–1.0) for colon cancer, 0.7 (95% CI, 0.4–1.3) for rectal cancer, 0.4 (95% CI, 0.4–1.0) for cancer of the right colon and 1.0 (95% CI, 0.5–1.9) for cancer of the left colon.

Jacobs *et al*. (1994) conducted a case–control study among women aged 30–62 years in Seattle, United States, between 1985 and 1989. It included 193 new cases of colon cancer (out of 295 eligible cases) and 194 controls (out of 227 eligible controls) selected by random-digit dialling. Among post-menopausal women aged ≥ 45 years (i.e. 148 cases and 138 controls), the relative risk associated with use of post-menopausal oestrogen therapy, adjusted for age, vitamin intake and hysterectomy, was 0.60 (95% CI, 0.35–1.0) for colon cancer, with estimates of 0.47 (95% CI, 0.24–0.91) for ≥ 5 years' use and 0.53 (95% CI, 0.29–0.96) for current use.

A case–control study was conducted between 1990 and 1991 in Wisconsin, United States (Newcomb & Storer, 1995). After exclusion of pre-menopausal women, 694 women with colorectal cancer (480 colon and 214 rectum) and 1622 control women (randomly selected from lists of licensed drivers and Medicare beneficiaries) were included. The relative risk for any use of post-menopausal oestrogen therapy, adjusted for age, alcohol, body mass index, family history of cancer and history of sigmoidoscopy, was 0.73 (95% CI, 0.56–0.94) for colon cancer and 1.2 (95% CI, 0.83–1.6) for rectal cancer. Among recent users, the relative risk for colon cancer was 0.54 for both use of post-menopausal oestrogen therapy of any type and use of oestrogens only. The inverse association was stronger for recent use ($p < 0.001$).

Kampman *et al*. (1997) conducted a case–control study between 1992 and 1995 in the United States among women aged 30–79 who were members of a medical care programme, covering 894 cases of colon cancer (out of 1521 eligible cases) and 1120 control women (63% of those who were contacted). The relative risk for colon cancer (adjusted for age, family history of cancer, aspirin and energy intake) of post-menopausal women (i.e. 815 cases and 1019 controls) for use of oestrogen therapy for longer than three months was 0.82 (95% CI, 0.67–0.99). The inverse assocation was confined to recent users (i.e. < 1 year before diagnosis) (relative risk, 0.71; 95% CI, 0.56–0.89). No trend with duration of post-menopausal oestrogen therapy was observed (relative risk for ≥ 10 years of use, 0.86). The reduced relative risk associated with post-menopausal oestrogen therapy use did not appear to be explained by confounding factors such as dietary habits, body mass index or physical activity. Although the number of routine sigmoidoscopies did not differ significantly between women who had ever and never had post-menopausal oestrogen therapy, those who had used it had undergone more sigmoidoscopies because of symptoms.

A case–control study was conducted among members of a large health maintenance organization in Detroit, United States. The preliminary results (Yood *et al*., 1998) on 60 women with colorectal cancer and 143 population controls showed an adjusted relative risk associated with post-menopausal oestrogen therapy of 0.34 (95% CI, 0.11–0.99) for current users and 0.40 (95% CI, 0.12–1.40) for past users.

2.7 Cutaneous malignant melanoma

2.7.1 *Descriptive studies*

The incidence of melanoma has increased at a rate of 3–7% per year in most Caucasian populations in the last decades (Armstrong & Kricker, 1994). Changes in recreational patterns of exposure to the sun and, to some extent, increasing detection account for the observed rises. The incidence rates are similar in men and women, although a female excess is found in some countries, e.g. the United Kingdom and the Nordic countries.

Cohort and case–control studies of cutaneous and ocular malignant melanoma and post-menopausal oestrogen therapy are summarized in Table 12.

Table 12. Studies on use of post-menopausal oestrogen therapy (OT) or combined hormonal therapy (HT) and cutaneous malignant melanoma

Reference, country	No. of cases/ no. of controls	Type of controls	Type of use	RR (95% CI) for any versus no use	Duration of use	Recency of use	Adjustment, comments
Cohort							
Persson *et al*. (1996), Sweden	22 597 (60 cases)		Any OT HT	0.9 (0.7–1.1) 0.6 (0.3–1.1)	NR	NR	Age 13 years' follow-up. Standardized mortality ratio, 0.5 (95% CI, 0.2–1.0) No association with non-melanomatous skin cancer
Case–control							
Holly *et al*. (1983) Seattle, USA	87/863	Population	1–3 years 4–7 years ≥ 8 years	1.1 0.85 1.0	No effect	NR	Age RR very similar for 61 cases of SSM
Lew *et al*. (1983), Massachusetts, USA	111/107	Friends of cases	–	–	–	–	No difference in OT use
Beral *et al*. (1984), Sydney, Australia	287/574	Hospital and population		1.4 (0.78–2.6)	NR	NR	Age
Holman *et al*. (1984), Western Australia	276/276	Population		1.5 (0.87–2.7)	No trend	NR	Age and residence RR very similar for SSM (1.9; 0.88–4.2)
Gallagher *et al*. (1985), Canada	361/361	Members of health plans	< 1 year 1–4 years ≥ 5 years	1.0 1.0 0.9	No trend	No effect	Age, education, phenotype and freckling RR similar for SSM
Green & Bain (1985), Queensland, Australia	91/91	Population		–	–	–	Age 11 cases and 11 controls reported use of hormonal therapy other than COC

Table 12 (contd)

Reference, country	No. of cases/ no. of controls	Type of controls	Type of use	RR (95% CI) for any versus no use	Duration of use	Recency of use	Adjustment, comments
Østerlind *et al*. (1988), Denmark	151/297	Population	Oestrogen, unopposed	1.3 (0.8–2.1)	No trend (RR for > 7 years' use, 1.2; 0.7–2.2)	NR	Age, naevi and sunbathing No difference in risk between histological subtypes
			Oestrogen, opposed	1.5 (0.8–2.8)			
Holly *et al*. (1994), San Francisco, USA	452/935	Population	Conjugated oestrogens, after oophorectomy	2.4 (1.1–5.2)	No trend	NR	Age and education but unaltered by phenotype and sun Similar risks for SSM
			Any OT, after natural menopause	0.88 (0.50–1.6)			
			Hysterectomy with no or one ovary removed	2.0 (0.8–5.0)			
			Any OT after bilateral oophorectomy	2.2 (1.0–4.7)			
Westerdahl *et al*. (1996), Sweden	403/707	Population	HT, any	1.0 (0.5–1.8)	No trend	No effect of age at first or last use	Phenotype, naevi and sunburns Risks were similar at different anatomical sites
Ocular melanoma							
Hartge *et al*. (1989), Philadelphia, USA	214/209	Detached retina		2.0 (1.2–3.0)	No effect (RR for ≥ 6 years' use, 2.2; 0.9–5.8)	NR	Age and oophorectomy Similar risks for users of conjugated oestrogens and users of other formulations

RR, relative risk; CI, confidence interval; NR, not reported; SSM, superficial spreading melanoma; COC, combined oral contraceptives

2.7.2 *Cohort studies*

One cohort investigation (see section 2.6.2) provided information on post-menopausal oestrogen therapy and the risk for cutaneous malignant melanoma (Persson *et al*., 1996), expressed as incidence and mortality rates, among 22 597 Swedish women. After 13 years of follow-up, 60 new cases and eight deaths from cutaneous malignant melanoma were recorded. The age-adjusted standardized incidence ratios for any use of post-menopausal oestrogen therapy were 0.9 (95% CI, 0.7–1.1) for a diagnosis of cutaneous malignant melanoma and 0.5 (95% CI, 0.2–1.0) for death from this condition.

2.7.3 *Case–control studies*

Holly *et al*. (1983) conducted a case–control study in Seattle, United States, between 1976 and 1979 of 87 women aged 37–74 years (out of 124 eligible) with histologically confirmed cutaneous malignant melanoma, 61 of whom had superficial spreading melanomas. The controls were 863 age-matched women (response rate, 93%), who represented a random sample of the population from which the cases were derived. The age-adjusted relative risks for any use of post-menopausal oestrogen therapy among women ≥ 45 were close to unity: 1.1, 0.85 and 1.0 for 1–3, 4–7 and ≥ 8 years of use, respectively, for all histological types combined. Very similar risks were found when the analysis was restricted to women with superficial spreading melanomas (1.1, 1.1 and 0.98, respectively).

Lew *et al*. (1983) studied 111 women with cutaneous malignant melanoma in Massachusetts, United States, during 1978–79 and 107 controls chosen among friends of the cases. No difference in the frequency of post-menopausal oestrogen therapy use was reported between cases and controls, but detailed data were not shown.

Beral *et al*. (1984) investigated 287 women aged 15–54 years in Sydney, Australia, between 1978 and 1980, who had received a diagnosis of cutaneous malignant melanoma (new and prevalent cases) between 1974 and 1980, and 574 age-matched controls, who were hospital patients for the new cases and from the population for prevalent cases. Post-menopausal oestrogen therapy use was slightly more frequent among cases (6.6%) than controls (4.7%; unadjusted relative risk, 1.4; 95% CI, 0.78–2.6).

In another case–control study carried out in Western Australia between 1980 and 1981 (Holman *et al*., 1984), the cases were those of 276 women under the age of 80 (mean age, 45) with histologically proven pre-invasive or invasive cutaneous malignant melanoma (out of 373 eligible women). The controls were 276 age-matched women extracted from the electoral roll (out of 458 sampled women). Fourteen percent of subjects had ever taken hormone tablets or injections containing an oestrogen but no progestogen; of these, 59% had taken them for menopausal symptoms. The relative risk associated with any post-menopausal oestrogen therapy, adjusted for age and area of residence, were 1.5 (95% CI, 0.87–2.7) for all cutaneous malignant melanoma and 1.9 (95% CI, 0.88–4.2) for superficial spreading melanoma. No trend in risk with duration of use was seen.

Gallagher *et al*. (1985) conducted a case–control study in western Canada between 1979 and 1981 that included 361 women aged 20–79 years (out of 412 eligible cases) with cutaneous malignant melanoma, of whom 269 had superficial spreading melanoma, and

361 age-matched control women selected from medical plan listings (59% response rate). No association was found with any post-menopausal oestrogen therapy; the relative risks, adjusted for age, education, skin colour, hair colour and freckling, were 1.0 for < 1 or 1–4 years of use and 0.9 for ≥ 5 years of use. The risks for superficial spreading melanoma were identical.

Green and Bain (1985) studied the effect of female hormones on the incidence of cutaneous malignant melanoma in Queensland, Australia, between 1979 and 1980 in 91 women aged 15–81 years (92% of eligible women) with a first cutaneous malignant melanoma; lentigo maligna melanomas were not included. The control women consisted of a random sample of 91 women drawn from the electoral rolls, who were matched with cases by age and residence. The frequency of use of hormones other than oral contraceptives was low, and it was the same in cases and controls.

A case–control study on cutaneous malignant melanoma was carried out in Denmark between 1982 and 1985 (Østerlind *et al*., 1988). The case series consisted of 280 women aged 20–79 with newly diagnosed cutaneous malignant melanoma, of whom 207 had superficial spreading melanoma (out of 304 eligible women); lentigo maligna melanomas were not included. The controls consisted of 536 women selected from the National Population Register (out of 677 originally identified). Among post-menopausal women (i.e. 151 cases and 297 controls), the relative risk for cutaneous malignant melanoma among users of unopposed post-menopausal oestrogen therapy (adjusted for age, naevi and sunbathing) was 1.3 (95% CI, 0.8–2.1). For users of post-menopausal oestrogen therapy of any type, the relative risk was 1.1 (95% CI, 0.7–1.7). No trend in risk with increasing duration of use was found (relative risk for ≥ 7 years of use, 1.2; 95% CI, 0.7–2.2). There was no difference in risk for subtypes of melanoma, including superficial spreading melanoma.

Holly *et al*. (1994) carried out a case–control study of cutaneous malignant melanoma between 1981 and 1987 in San Francisco, United States, among 452 white women aged 25–59, 355 of whom had superficial spreading melanoma; 79% of those eligible were interviewed. Random-digit dialling was used to identify 935 control women of the same age (77% of those contacted). The relative risks associated with post-menopausal oestrogen therapy in pre-menopausal or naturally menopaused women were close to 1.0: for women with a natural menopause, the relative risk was 0.88 (95% CI, 0.50–1.6). The relative risk of women who had undergone a hysterectomy without removal of both ovaries was 2.0 (95% CI, 0.85–4.5), and that for women who had had bilateral oophorectomy was 2.2 (95% CI, 1.0–4.7). No difference was found according to the dose of conjugated oestrogens.

Westerdahl *et al*. (1996) carried out a case–control study on exposure to hormones in southern Sweden between 1988 and 1990. The cases were those of 403 women with a first histopathological diagnosis of cutaneous malignant melanoma, and the 707 age-matched control women were randomly selected from the National Population Registry. Post-menopausal oestrogen therapy had been used by 13% of the cases and 14% of the controls, giving a relative risk, adjusted for phenotype, naevi and sunburns, of 1.0 (95% CI, 0.5–1.8). No associations were found between cutaneous malignant melanoma and duration of post-

menopausal oestrogen therapy, age at first use or age at latest use. Consistent results were found for cutaneous malignant melanoma at different anatomical sites.

2.8 Intraocular malignant melanoma

A case–control study carried out between 1979 and 1980 in Philadelphia, United States, of ocular melanoma included 239 women (mean age, 58) with intraocular malignant melanoma (out of 444 eligible cases) and 223 control matched by age and race (Hartge *et al*., 1989). The controls were patients with detached retinas. The relative risk for post-menopausal women who reported using oestrogen therapy, adjusted for age and history of oophorectomy, was 2.0 (95% CI, 1.2–3.0) and that for ≥ 6 years of use was 2.2 (95% CI, 0.9–5.8) (Table 12).

2.9 Thyroid cancer

2.9.1 *Descriptive studies*

Cancer of the thyroid is a rare, very heterogeneous disease. The rate of mortality from this cancer has been falling slowly, whereas the incidence has been increasing in most developed countries over the last three decades (Franceschi & La Vecchia, 1994). The incidence rates are two- to threefold higher for women than for men, and the difference is greatest for well-differentiated papillary carcinomas for women aged 25–44 (Franceschi & Dal Maso, 1998). A positive correlation between parity and the incidence of thyroid cancer was reported from individual data on all (1.1 million) Norwegian women born 1935–69 (Kravdal *et al*., 1991).

2.9.2 *Case–control studies*

These studies are summarized in Table 13.

The case–control study of McTiernan *et al*. (1984) was carried out in Seattle, United States, between 1980 and 1981. The cases were those of 183 women aged 18–80 with papillary, follicular and mixed thyroid carcinomas, diagnosed between 1974 and 1979, who represented 65% of those identified through the cancer surveillance system of western Washington, United States. The controls were women aged 18–80 identified through random-digit dialling; of 478 eligible controls, 394 were interviewed. The majority of the patients and controls (87%) were white. Among women over 30 years of age (153 cases and 281 controls), the age-adjusted relative risk for any use of post-menopausal oestrogen therapy (34% of cases and 27% controls) was 1.4 (95% CI, 0.89–2.3) for thyroid cancer overall and 1.9 (95% CI, 1.1–3.4) for tumours of the papillary type. The relative risk for ≥ 3 years' duration of use was 1.2 for all thyroid cancers and 1.6 for papillary thyroid cancer. The association was slightly stronger when only women whose tumours were found by a physician (rather than by the woman herself) were included.

A case–control study carried out in Connecticut, United States, between 1978 and 1980 by Ron *et al.* (1987) included 159 women aged 20–76 with thyroid cancer, i.e. 80% of those identified through the Connecticut Tumor Registry. Tumour slides were reviewed centrally. The controls were 285 women frequency-matched to the cases on age. Random-digit

Table 13. Case–control studies on use of oestrogen therapy and thyroid cancer

Reference, country	No. of cases/ no. of controls	Type of controls	RR (95% CI) for any versus no use	Duration of use	Adjustment, comments
McTiernan *et al*. (1984), Seattle, USA	153/281	Population	All 1.4 (0.89–2.3) Papillary 1.9 (1.1–3.4)	No trend (RR for ≥ 3 years' use, 1.2)	Age Risk slightly higher for cases found by physicians
Ron *et al*. (1987), Connecticut, USA	71/123	Population, ≥ 35 years	0.5 (NS)	NR	Age, parity, radiotherapy and benign thyroid disease
Franceschi *et al*. (1990), Italy	71/94	Hospital	0.3 (0.1–1.1)	NR	Age and residence
Kolonel *et al*. (1990), Hawaii, USA	140/328	Population	0.9 (0.5–1.7)	NR	Age and ethnic group
Levi *et al*. (1993b), Switzerland	91/306	Hospital	1.8 (0.6–5.2)	NR	Age and history of benign thyroid disease
Hallquist *et al*. (1994), northern Sweden	123/140		1.1 (0.3–3.7)	NR	Age
Galanti *et al*. (1996), Norway and Sweden	74/134	Population, post-menopausal	0.98 (0.39–2.5)	No effect (RR for > 2 years' duration, 1.2; 0.25–5.3)	Age and parity

RR, relative risk; CI, confidence interval; NS, not significant; NR, not reported

dialling was used to select controls under 65 years of age, while controls over 65 years were chosen from the Medicare roster. Post-menopausal oestrogen therapy had ever been used by 8/71 cases and 23/123 controls over the age of 35. The relative risk, adjusted for age, parity and history of radiotherapy and benign thyroid diseases was 0.5 (not significant).

Franceschi *et al*. (1990) conducted a case–control study in the provinces of Pordenone, Padua and Milan, northern Italy, between 1986 and 1992, which included 165 women under 75 years old with newly diagnosed, histologically confirmed thyroid cancer. The control women, frequency-matched by age to the cases, were 214 in-patients identified in the same network of hospitals with diagnoses of acute, non-neoplastic, non-hormonal diseases. The response rates exceeded 95% among both cases and controls. All of the study subjects were interviewed during their hospital stay. Among post-menopausal women, any use of oestrogen therapy was reported by five of 71 cases and 17 of 94 controls (relative risk adjusted for age and area of residence, 0.3; 95% CI, 0.1–1.1).

A case–control study of thyroid cancer was conducted between 1980 and 1987 in Hawaii, United States (Kolonel *et al*., 1990), and consisted of 140 women from five ethnic groups, 18 years or older, with thyroid cancer identified through the Hawaii Tumour Registry. The histological type of the tumours was reviewed centrally. The controls were 328 women, age-matched to cases, selected from among people participating in a concurrent health surveillance programme. Questionnaires were administered at home, with response rates of 79% for cases and 74% for controls. The relative risk for women who had ever used post-menopausal oestrogen therapy (15% of control women), adjusted for age and ethnic group, was 0.9 (95% CI, 0.5–1.7).

Levi *et al*. (1993b) studied risk factors for thyroid cancer in the Canton of Vaud, Switzerland, between 1988 and 1990. The cases were those of 91 women, aged 12–72, with histologically confirmed thyroid cancer. The controls were 306 women admitted to the same hospital as the cases for acute conditions. Post-menopausal oestrogen therapy had ever been used by seven of 91 cases and 31 of 306 controls. The relative risk, adjusted for age and history of benign thyroid diseases, was 1.8 (95% CI, 0.6–5.2).

Hallquist *et al*. (1994) conducted a case–control study on thyroid cancer in northern Sweden between 1980 and 1989. The cases were those of 123 women, aged 20–70, with histopathologically confirmed thyroid cancer, identified through the Swedish Cancer Registry. The controls were 240 women randomly drawn from the National Population Registry of the same counties as the cases. All of the study subjects returned a mailed questionnaire. Use of post-menopausal oestrogen therapy was uncommon (five cases and nine controls) and unrelated to the risk for thyroid cancer; the age-adjusted relative risk was 1.1 (95% CI, 0.3–3.7).

Galanti *et al*. (1996) carried out a case–control study on thyroid cancer in northern Norway and central Sweden between 1985 and 1993. The cases were those of 191 women aged 17–72 years with histologically confirmed papillary, follicular or mixed carcinoma of the thyroid gland. The controls were 341 age-matched women selected from the national population registries. Information was based on a mailed questionnaire, with a response rate of over 90%. Among post-menopausal women, use of any type of oestrogen

therapy was reported by 13 of 74 cases and 24 of 134 controls; the relative risk, adjusted for age and parity, was 0.98 (95% CI, 0.39–2.5). The relative risk for use for more than two years was 1.2 (95% CI, 0.25–5.3).

2.10 Other cancers

La Vecchia *et al*. (1994) assessed the role of female hormones in gastric cancer in Milan, Italy, between 1985 and 1993. The cases were those of 229 post-menopausal women with newly diagnosed, histologically confirmed gastric cancer. The controls were 614 post-menopausal women in hospital for acute, non-neoplastic, non-digestive tract conditions. The relative risk for users of post-menopausal oestrogen therapy, adjusted for age, education, family history of cancer and dietary habits, was 0.54 (95% CI, 0.3–1.1).

Chow *et al*. (1995) studied 165 cases of renal-cell cancer in women aged 20–79 and 227 age- and frequency-matched population controls in Minnesota, United States, between 1988 and 1990. Among post-menopausal women (134 cases and 173 controls), the relative risk for any use of post-menopausal oestrogen therapy, adjusted for age, smoking and body mass index, was 1.8 (95% CI, 1.1–3.0). There was no trend with duration of use.

Lindblad *et al*. (1995) evaluated the effect of exogenous hormones on the incidence of renal-cell cancer in Australia, Denmark, Germany, Sweden and the United States during 1989–91. The cases were those of 608 women aged 20–79 with histologically confirmed renal-cell cancer identified mainly through local cancer registries. The controls were 766 women sampled from local residential lists and frequency-matched by age to the cancer cases. The relative risk of post-menopausal oestrogen therapy users, adjusted for age, smoking and body mass index, was 1.0 (95% CI, 0.8–1.4). For > 7 years of use, the relative risk was 1.2 (95% CI, 0.7–2.0). The risk did not vary with the age at starting post-menopausal oestrogen therapy.

In the record-linkage study of a cohort of 22 597 Swedish women to whom post-menopausal oestrogen therapy had ever been prescribed (Persson *et al*., 1996), a 13-year follow-up showed the following standardized incidence ratios for cancer: vulva/vagina, 1.2 (95% CI, 0.7–1.8); pancreas, 1.1 (95% CI, 0.9–1.4); brain, 0.8 (95% CI, 0.6–1.0); lung, 1.0 (95% CI, 0.8–1.2); urinary bladder, 0.9 (95% CI, 0.7–1.1); other skin cancers, 0.9 (95% CI, 0.7–1.3); endocrine glands other than thyroid, 1.0 (95% CI, 0.8–1.3) and connective tissue, 1.6 (95% CI, 1.0–2.4).