2. Studies of Cancer in Humans

2.1 Breast cancer

2.1.1 *Background*

In the previous evaluation (IARC, 1999), most of the epidemiological evidence derived from studies that assessed the use of estrogen alone in relation to subsequent risk for breast cancer. The evidence related to combined therapy with estrogen plus a progestogen was considered to be insufficient to reach any firm conclusion. However, in relation to hormonal menopausal therapy with estrogen alone, the evidence was summarized as follows.

A pooled analysis from 51 studies and a review that included 15 cohort studies and 23 case–control studies showed a small increase in risk for ever use, which increased with longer duration of use (5 years or more), and an increased risk in current and recent users. Some information was available on women who used and then stopped using menopausal estrogen therapy; based on this evidence, the increased risk appeared to disappear several years after cessation of use. There was also evidence to suggest that the increase in risk was predominantly for small, localized tumours of the breast. The data were, however, insufficient to determine whether the risk varied with type of compound or the dose of various compounds used.

This evaluation relied heavily on the pooled analysis from the collaborative group in Oxford (Collaborative Group on Hormonal Factors in Breast Cancer, 1997), which had compiled and re-analysed the original data of 51 studies, 22 of which provided information on the hormonal constituents of the preparations. In the re-analysis, data on hormonal constituents were available for 4640 women; 12% (557) of these women had received combined estrogens and progestogens, and 249 women with breast cancer had used combined treatment. The results showed that, among women who were currently using combined therapy, the relative risk was 1.2 (95% confidence interval [CI], 0.8–1.5; based on 136 exposed cases) for less than 5 years of use and 1.5 (95% CI, 0.9–2.2; based on 58 exposed cases) for more than 5 years of use.

These limited data did not provide a firm basis for any conclusion regarding the effects of the use of combined estrogen–progestogen therapy on the risk for breast cancer. Subsequently, many studies, including clinical trials, have assessed the risk for breast cancer in relation to the use of combined hormonal therapy by menopausal women.

2.1.2 *Randomized clinical trials* (Table 3)

The WHI investigators conducted two large, randomized, double-blind, placebo-controlled trials that evaluated the effects of estrogen alone and estrogen plus progestogen on the prevention of chronic disease in 27 347 postmenopausal women aged 50–79 years (Women's Health Initiative Study Group, 1998; Anderson *et al.*, 2003; Stefanick *et al.*, 2003). The incidence of coronary heart disease was the primary outcome and the incidence of invasive breast cancer was the primary safety outcome. Both trials were interrupted prematurely because of adverse effects.

In these two trials, postmenopausal women were recruited between 1993 and 1998 from 40 US clinical centres mainly by mass mailing (Hays *et al.*, 2003b). All women had baseline mammograms and clinical breast examinations. A total of 16 608 eligible women with a uterus at baseline were randomized in equal proportions to treatment with continuous combined conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5mg per day) in a single tablet or to a matching placebo. A total of 10 739 women who had had a hysterectomy were randomized with equal probability to conjugated equine estrogens (0.625 mg per day) or placebo. The intervention period was planned to end in 2005, giving a projected mean follow-up of 8.5 years. Participants were followed every 6 months; annual visits to the clinic and mammography were required. Designated outcomes were ascertained by self-reporting at every 6-month contact and documented by medical records that were locally and centrally adjudicated. These outcome procedures were performed by study staff who were blinded to treatment assignment. Vital status was known for 96.7 and 94.7% of the participants in the estrogen plus progestogen (mean follow-up, 5.6 years) and estrogen alone trials (mean follow-up, 6.8 years), respectively (Chlebowski *et al.*, 2003; Anderson *et al.*, 2004).

In May 2002, the Independent Data and Safety Monitoring Board recommended that the estrogen plus progestogen trial be stopped on the basis of an adverse effect on the incidence of breast cancer and an overall assessment that risks exceeded benefits. The protocol-specified weighted log-rank statistic for breast cancer (p-value = 0.001) had crossed the pre-defined monitoring boundary for adverse effects (p-value = 0.02) (Rossouw *et al.*, 2002). The weights in this log-rank statistic were defined by time since randomization, and rose linearly from 0 at time of randomization to 1 at year 10 and thereafter; this effectively down-weighted early differences that were thought to be less probably related to treatment. For simplicity, the initial publication presented unweighted hazard ratios for comparisons of all outcomes, based on the locally adjudicated data available on outcomes at the time that the trial was stopped. These analyses did not acknowledge the anticipated time-dependent effect for breast cancer.

The final unweighted hazard ratio of estrogen plus progestogen for invasive breast cancer was 1.24 (95% CI, 1.04–1.50; weighted $p = 0.003$; 349 cases) (Chlebowski *et al.*, 2003). There was a statistically significant interaction with time since randomization that suggested an effect of duration of exposure. In women who took estrogen plus progestogen, tumours were slightly larger, and more likely to be node-positive and to be at regional

Table 3. Randomized clinical trials of combined hormone therapy and the risk for breast cancer[a]

Reference, name of trial	Country	Age at recruitment	Size of trial	Period of trial	Mean duration of follow-up (years)	No. of exposed women	No. (%) of women using placebo	Total no. of breast cancer cases	Histological type of breast cancer	Cases in exposed women	Cases in placebo women	Hazard ratio (95% CI), treated versus placebo
Hulley *et al.* (2002), HERS	USA	44–79	2 763	1993–2000	4.1	1 380	1 383	88	Invasive	34	25	1.38 (0.82–2.31)
Chlebowski *et al.* (2003), WHI	USA	50–79	16 608	1993–98	5.6	8 506	8 102	822	Invasive + *in situ*	245	185	1.24 (1.02–1.50)
									Invasive	199	150	1.24 (1.01–1.54)
									In situ	46	37	1.18 (0.77–1.82)

CI, confidence interval; HERS, Heart and Estrogen/Progestin Replacement Study; WHI, Women's Health Initiative

[a] In both studies, the treated group received 0.625 mg conjugated equine estrogens and 2.5 mg of medroxyprogesterone acetate.

or advanced stages than those diagnosed in women who took placebo. The incidence of in-situ cancers was not significantly elevated (hazard ratio, 1.18; 95% CI, 0.77–1.82; weighted $p = 0.09$; 84 cases). Mammography rates were high (≥ 88.6% in each year) and did not differ between groups (Chlebowski *et al.*, 2003). Limitations of the study included the proportion of women who discontinued study medications (42% for estrogen plus progestogen and 38% for placebo), the proportion who initiated hormonal therapy outside of the trial (6% versus 11%, respectively) and the proportion of women for whom unblinding of clinical gynaecologists was required (40% versus 7%), primarily to manage vaginal bleeding (Rossouw *et al.*, 2002).

The HERS was a randomized, double-blind, placebo-controlled trial designed to test the effects of continuous combined hormonal therapy (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate daily) for the prevention of recurrent coronary heart disease among 2763 women aged 44–79 years with a uterus and with documented coronary disease at enrolment. The trial ended after a mean duration of follow-up of 4.1 years and reported no overall effect on coronary heart disease. No significant effect was found on the incidence of breast cancer (relative risk, 1.38; 95% CI, 0.82–2.31; 88 cases) (Hulley *et al.*, 2002).

2.1.3 *Cohort studies* (Table 4)

Persson *et al.* (1999) assessed the use of combined hormonal menopausal therapy and subsequent risk for breast cancer in a prospective study of 10 472 women in Sweden. Information on use of hormonal therapy was obtained at recruitment to the study through prescription records in pharmacies. The cohort was followed for over 6 years by linkage to the Swedish Cancer Registry, and 198 women were registered with incident breast cancer during that time. The relative risk associated with ever use of combined hormonal menopausal therapy was not specified. However, the relative risk for 1–6 years of use at entry to the study was 1.4 (95% CI, 0.9–2.3) compared with never use or use for less than 1 year, and that associated with use for more than 6 years was 1.7 (95% CI, 1.1–2.6). These results were adjusted for age, length of follow-up, age at first full-term pregnancy, body mass index, education and age at menopause. The results also showed that the estimated relative risks were higher for recent or current use than for past use. Recent or current use was associated with a relative risk of 2.8 (95% CI, 0.8–10.0) and use in the past with a relative risk of 1.9 (95% CI, 0.6–6.1).

In a cohort study in the USA, Schairer *et al.* (2000) investigated whether the use of combined hormonal menopausal therapy increased the risk for breast cancer. The cohort of 46 355 postmenopausal women was recruited from a mammography screening programme and followed for 10 years. During follow-up, 2082 women were diagnosed with breast cancer. Ever use of combined hormonal menopausal therapy was associated with a relative risk of 1.3 (95% CI, 1.0–1.6), but the increase in risk was largely restricted to current users or use within the last 4 years (relative risk, 1.4; 95% CI, 1.1–1.8). These results were adjusted for age, mammography screening, age at menopause, body mass index and level of

Table 4. Cohort studies of the use of combined hormone therapy and the risk for breast cancer

Reference	Country	Age at recruitment (years)	Size of cohort	Period of cohort	Average of follow-up (years)	Total no. of cases	Histological diagnosis	Sub-sites	Hormone therapy (type/regimen)	No. of cases	Relative risk (95% CI)	Comments
Person *et al.* (1999)	Sweden	65 (mean)	10 472	1987–93	5.7	198	Invasive		Never	48	1.0	Adjusted for age, follow-up time, age at first full-term pregnancy, body mass index, education, menopausal age/status
									1–6 years	28	1.4 (0.9–2.3)	
									≥ 6 years	44	1.7 (1.1–2.6)	
Schairer *et al.* (2000)	USA	Not specified	46 355	1980–95	10.2	2802	All	All	Never	761	1.0	Adjusted for age, education, body mass index, age at menopause, mammographic screening
									Ever	101	1.3 (1.0–1.6)	
							Invasive	Ductal/lobular	Never	145	1.0	
									Ever	33	[1.73[a]]	
							Invasive	Ductal only	Never	128	1.0	
									Ever	26	[1.55[a]]	
Beral *et al.* (2003)	UK	50–64	1 084 110	1996–2001	2.6	9364	Invasive		Never	2894	1.0	Adjusted for age, region, socio-economic status, body mass index, alcoholic beverage consumption, ever use of oral contraceptives, time since menopause, parity
									Current	1934	2.00 (1.91–2.09)	
									Duration[b]			
									< 1 year	97	1.45 (1.19–1.78)	
									1–4 years	582	1.74 (1.60–1.89)	
									5–9 years	850	2.17 (2.03–2.33)	
									≥ 10 years	362	2.31 (2.08–2.56)	
									All continuous combined			
									< 5 years	243	1.57 (1.37–1.79)	
									≥ 5 years	388	2.40 (2.15–2.67)	
									All sequential combined			
									< 5 years	403	1.77 (1.59–1.97)	
									≥ 5 years	778	2.12 (1.95–2.30)	

Table 4 (contd)

Reference	Country	Age at recruitment (years)	Size of cohort	Period of cohort	Average of follow-up (years)	Total no. of cases	Histological diagnosis	Sub-sites	Hormone therapy (type/ regimen)	No. of cases	Relative risk (95% CI)	Comments
Jernström *et al.* (2003a)	Sweden	50–64	6 586	1995–2000	4.1	101	NR		Never	2422	1.0	Adjusted for age at entry and time of follow-up; continuous combined formula only
									Ever	NR	3.3 (1.9–5.6)	
									Duration			
									≤ 2 years	NR	3.7 (1.8–7.4)	
									3–4 years	NR	2.2 (0.84–5.9)	
									> 4 years	NR	3.7 (1.8–7.7)	
Olsson *et al.* (2003)	Sweden	25–65	29 508	1990–92	Not specified	556	NR		Never		1.0	Adjusted for age, age at menarche, age at first full-term pregnancy, parity, age at menopause, family history of breast cancer
									Ever combined continuous therapy	622	2.45 (1.61–3.71)	
									Never		1.0	
									Ever combined sequential therapy	655	1.22 (0.74–2.00)	
Bakken *et al.* (2004)	Norway	45–64	31 451	1996–98	Not specified	331	NR	All	Never	130	1.0	Adjusted for age, body mass index, age at menarche, ever use of oral contraceptives, time since menopause, family history of breast cancer, mammography, parity, age at first delivery
									Current	116	2.5 (1.9–3.2)	
									Ever use			
									< 5 years	63	2.3 (1.7–3.2)	
									≥ 5 years	51	2.8 (2.0–4.0)	
									Sequential regimen			
									< 5 years	19	1.7 (1.0–2.8)	
									≥ 5 years	14	2.2 (1.3–3.8)	
									Continuous regimen			
									< 5 years	44	2.6 (1.9–3.7)	
									≥ 5 years	37	3.2 (2.2–4.6)	

Table 4 (contd)

Reference	Country	Age at recruitment (years)	Size of cohort	Period of cohort	Average of follow-up (years)	Total no. of cases	Histological diagnosis	Sub-sites	Hormone therapy (type/ regimen)	No. of cases	Relative risk (95% CI)	Comments
Stahlberg *et al.* (2004)	Denmark	≥ 45	10 874	1993–99	Not specified	244	In situ/ invasive		Never	110	1.0	Adjusted for age at menopause, age at menarche, parity, age at first birth, use of oral contraceptives, history of benign breast disease, smoking, night work, body mass index, height, physical activity, alcoholic beverage intake
									Current	75	2.70 (1.96–3.73)	
									Continuous	23	4.16 (2.56–6.75)	
									< 5 years	4	1.96 (0.72–5.36)	
									5–9 years	6	4.96 (2.16–11.39)	
									≥ 10 years	10	6.78 (3.41–13.48)	
									Current cyclical	52	1.94 (1.26–3.00)	
									< 5 years	10	1.58 (0.79–3.17)	
									5–9 years	9	2.47 (1.23–4.95)	
									≥ 10 years	10	2.18 (1.09–4.33)	
Tjønneland *et al.* (2004)	Denmark	50–60	23 618	1993–97	4.8	423	Invasive	Lobular only	Never	15	1.0	Adjusted for parity, age at first birth, history of benign breast tumour surgery, education, alcoholic beverage consumption, body mass index
									Current	41	3.53 (1.94–6.41)	
								Ductal only	Never	109	1.0	
									Current	158	2.10 (1.64–2.7)	
Ewertz *et al.* (2005)	Denmark	50–67	48 812	1989–2002	10	869	NR		Never	561	1.0	Adjusted for age, age at first birth, parity
									Sequential progestogen-derived progestogen	6	0.57 (0.26–1.28)	
									Sequential testosterone-derived progestogen	80	1.52 (1.21–1.93)	
									Continuous testosterone-derived progestogen	13	0.99 (0.57–1.72)	

Table 4 (contd)

Reference	Country	Age at recruit-ment (years)	Size of cohort	Period of cohort	Average of follow-up (years)	Total no. of cases	Histo-logical diagnosis	Sub-sites	Hormone therapy (type/ regimen)	No. of cases	Relative risk (95% CI)	Comments
Fournier *et al.* (2005)	France	52.8 (mean)	54 548	Non-specified	5.8	NR	Invasive		Never Current use	NR 323	1.0 1.3 (1.1–1.5)	Adjusted for time since menopause, body mass index, age at menopause, parity, age at first full-term pregnancy, family history of breast cancer, personal history of benign breast disease, use of oral contraceptives, mammography screening

NR, not reported
[a] No confidence intervals were provided.
[b] Data on duration missing for 43 women

education. When the data were stratified by body mass index, no increased risk related to the use of hormonal therapy was observed in women with an index > 24.4. However, in women with an index of 24.4 or less, the relative risk associated with 5 years of use or more was 2.0 (95% CI, 1.3–3.0). Thus, hormonal therapy that comprised estrogen plus a progestogen exerted its effects primarily, if not solely, among lean women. The investigators also studied the effect of duration of combined therapy and histological subtypes of breast cancer. The results suggested a similar increase in risk with increasing duration of use for ductal and lobular carcinoma, but the number of cases within the subtypes of breast cancer was small and the results should be interpreted with caution.

Risk for breast cancer and the use of hormonal menopausal therapy was also evaluated in the Million Women Study (Beral *et al.*, 2003). More than a million women in the United Kingdom between 50 and 64 years of age were recruited into the study between 1996 and 2001 and provided detailed information on their use of hormonal menopausal therapy. They were followed up for cancer incidence and death. Half of the women had used some type of hormonal menopausal therapy and nearly 150 000 women were current users of combined hormonal therapy. During 2.6 years of follow-up, 9364 women were diagnosed with invasive breast cancer, and current users were more likely than never users to develop the disease. The relative risk for current compared with never use of combined hormonal therapy at the time of recruitment was 2.00 (95% CI, 1.91–2.09), but the association varied according to duration of use. Among current users, use for 1–4 years was associated with a relative risk of 1.74 (95% CI, 1.60–1.89; 582 exposed cases) compared with never users, and use for 10 years or more was associated with a relative risk of 2.31 (95% CI, 2.08–2.56; 362 exposed cases). In relation to past use, the relative risk was 1.04 (95% CI, 0.94–1.16). The relative risks were adjusted for age, region of residence, socioeconomic status, body mass index, alcoholic beverage consumption, ever use of oral contraceptives, time since menopause and parity. Little variation in the associations was observed among women who used different preparations of combined regimens. Thus, among women who had used a treatment containing medroxyprogesterone acetate for less than 5 years, the relative risk was 1.60 (95% CI, 1.33–1.93), and that for women who had taken it for 5 years or more was 2.42 (95% CI, 2.10–2.80). Similarly, treatment for less than 5 years with a therapy containing norethisterone was associated with a relative risk of 1.53 (95% CI, 1.35–1.75); when use of norethisterone lasted for 5 years or more, the relative risk was 2.10 (95% CI, 1.89–2.34). Different modes of administration were also compared and broadly similar relative risks related to daily (relative risk, 1.57; 95% CI, 1.37–1.79) and cyclical (relative risk, 1.77; 95% CI, 1.59–1.97) use of combined hormonal therapy were found. Among women with a body mass index < 25, the relative risk for breast cancer associated with the use of combined hormonal therapy was 2.31 (95% CI, 2.12–2.53) and that in women with a body mass index of ≥ 25 was 1.78 (95% CI, 1.64–1.94). An attempt was made to assess the association between use of hormonal menopausal therapy and mortality from breast cancer, but, at the time of publication, the data did not allow reliable estimates of this. However, in a letter (Banks *et al.*, 2004), it was reported that, for all types com-

bined, current users had a 30% higher risk for mortality from breast cancer than never users (relative risk, 1.30; 95% CI, 1.11–1.53).

The association of the use of combined hormonal menopausal therapy with an increased risk for breast cancer was assessed in a prospective study in southern Sweden (Jernström *et al.*, 2003a) in a cohort of 6586 women aged 50–64 years at baseline. During 4 years of follow-up by linkage to the Swedish Cancer Registry, 101 women were registered with incident breast cancer. Ever use of combined hormonal menopausal therapy was associated with a relative risk of 3.3 (95% CI, 1.9–5.6) compared with never use. In relation to duration of use, the relative risk associated with use for 2 years or less (relative risk, 3.7; 95% CI, 1.8–7.4) was not substantially different from that associated with use for 5 years or more (relative risk, 3.7; 95% CI, 1.8–7.7).

Another prospective study, conducted in the same region in Sweden as the above study, was based on more than 29 000 women (Olsson *et al.*, 2003). The women were followed up by linkage to the Swedish Cancer Registry, and 556 cases of breast cancer were registered. The analyses focused on the duration of use of combined hormonal menopausal therapy and whether the mode of administration had different effects on the risk for breast cancer. The relative risk associated with daily ever use of combined hormonal menopausal therapy was 2.45 (95% CI, 1.61–3.71), and sequential administration was associated with a relative risk of 1.22 (95% CI, 0.74–2.00) compared with never users. The relative risk increased with recency and duration of use. Compared with never users, those who reported daily use of combined preparations for 4 years or more had a relative risk of 4.60 (95% CI, 2.39–8.84) and those who had taken combined sequential therapy for 4 years or more had a relative risk of 2.23 (95% CI, 0.90–5.56). These results were adjusted for age, age at menarche, age at first full-term pregnancy, parity, age at menopause and family history of breast cancer.

In the NOWAC Study, the association between use of combined hormonal menopausal therapy and the risk for breast cancer was assessed in a prospective follow-up of 31 451 postmenopausal women who were aged 45–64 years at entry (Bakken *et al.*, 2004). Information on the use of hormonal menopausal therapy was collected at recruitment by self-administered questionnaires; during follow-up by linkage to the Norwegian Cancer Registry, 331 women were registered with incident breast cancer. The association for ever use versus never use of combined preparations was not reported, but current users of combined hormonal therapy at study entry had a relative risk of 2.5 (95% CI, 1.9–3.2; 116 exposed cases) compared with never users. For current users of combined therapy for less than 5 years, the relative risk was 2.3 (95% CI, 1.7–3.2; 63 exposed cases); for longer duration of use, the relative risk was 2.8 (95% CI, 2.0–4.0; 51 exposed cases). These results were adjusted for age, body mass index, age at menarche, ever use of oral contraceptives, time since menopause, family history of breast cancer, history of mammography screening and age at first birth. The investigators also studied the effect of daily versus sequential use of progestogens in the combined treatment. Daily treatment for less than 5 years was associated with a relative risk of 2.6 (95% CI, 1.9–3.7; 44 exposed cases); for longer duration of daily treatment, the relative risk was 3.2 (95% CI, 2.2–4.6; 37 exposed cases) compared with

the risk of never users. In comparison, the relative risk associated with a cyclical regimen was 1.7 (95% CI, 1.0–2.8; 19 exposed cases) for less than 5 years of use and 2.2 (95% CI, 1.3–3.8; 14 exposed cases) for 5 years or more.

A cohort study from Denmark investigated whether different progestogens in combined hormonal menopausal therapy exert different effects on the risk for breast cancer (Stahlberg *et al.*, 2004). Brands of combined hormonal menopausal therapy were coded as containing either 'progesterone-like' (typically medroxyprogesterone acetate) or 'testosterone-like' (typically norethisterone or levonorgestrel) progestogens. More than 23 000 nurses received a questionnaire in 1993, of whom nearly 20 000 responded and returned information on their use of combined hormonal menopausal therapy. After exclusions, 10 874 women were eligible for breast cancer follow-up through the Danish Cancer Registry and, among these, 244 women were registered with incident breast cancer during 6 years of follow-up. The association with ever use or with past use of combined hormonal therapy was not specified in the report. However, the relative risk associated with current use at entry to the study was 2.70 (95% CI, 1.96–3.73) compared with the risk of never users. Among current users of combined treatment with 'testosterone-like' progestogens, the relative risk was also increased. When these progestogens were administered daily, the relative risk was 4.16 (95% CI, 2.56–6.75) and when they were given less than daily (termed cyclically or sequentially), the relative risk was 1.94 (95% CI, 1.26–3.00) compared with never users. The report did not provide details on the number of days during a cycle that sequential treatment was given.

Another Danish cohort study (The Diet, Cancer and Health Study) assessed type of hormonal menopausal therapy used in relation to the risk for breast cancer, and specified the association according to histological subtypes (Tjønneland *et al.*, 2004). Among 23 618 women with information on hormonal therapy who were assumed to be postmenopausal, 423 incident cases of breast cancer were identified through the Danish Cancer Registry over a median follow-up of 4.8 years. The results for ever use or past use were not reported. However, the effects of daily and cyclical regimens of combined preparations were compared, and whether these modes of administration exterted different effects on the risk for lobular and ductal breast carcinoma was examined. In relation to lobular carcinoma, rates of breast cancer associated with the use of daily and cyclical regimens were essentially identical, whereas the risk for ductal carcinoma was slightly higher when the progestogens were administered daily compared with sequentially.

In a cohort of 48 812 Danish women who were aged 50–67 years at baseline, Ewertz *et al.* (2005) linked information from the Danish Prescription Database to information on incident cases of breast cancer registered by the Danish Cancer Registry during 10 years of follow-up. Altogether, 869 women were registered with breast cancer during the study period. The effects of different progestogens were studied: combined therapy that contained either levonorgestrel, norethisterone, norgestimate, desogestrel or gestodene was classified as combined treatment with 'testosterone-derived' progestogens, and treatment containing medroxyprogesterone [acetate] as combined treatment with 'progesterone-derived' progestogens. Results related to ever use versus never use of combined preparations were not

reported, but the association with current use was specified for various types of combined regimens. Current cyclical use of estrogen plus a progesterone-derived progestogen was associated with a relative risk of 0.57 (95% CI, 0.26–1.28; six exposed cases). Current daily use of estrogen plus a testosterone-derived progestogen was associated with a relative risk of 0.99 (95% CI, 0.57–1.72; 13 exposed cases); among current users of cyclical regimens of estrogen plus a testosterone-derived progestogen, the relative risk was 1.52 (95% CI, 1.21–1.93; 80 exposed cases). These results were adjusted for age, age at first birth and parity.

Fournier *et al.* (2005) assessed the use of different types of hormonal menopausal therapy in relation to risk for breast cancer among 54 548 French women; 948 primary invasive breast cancers were diagnosed during 5.8 years of follow-up. Average use of combined hormonal menopausal therapy was 2.8 years. The association for ever use versus never use with breast cancer was not specified in the report, but women who were current users of combined hormonal therapy had a relative risk of 1.3 (95% CI, 1.1–1.5) compared with never users. The main aim of this study was to examine the effects of different types of progestogens that were used in the combined treatment. Current use of treatment that contained micronized progesterone (only given transdermally) was associated with a relative risk of 0.9 (95% CI, 0.7–1.2; 55 exposed cases). In contrast, current use of synthetic progestogens was associated with a relative risk of 1.4 (95% CI, 1.2–1.7; 268 exposed cases). These results were adjusted for a range of factors, including age, age at menopause, body mass index, parity, age at first birth, family history of breast cancer and previous use of oral contraceptives.

2.1.4 *Case-control studies* (Table 5)

A large population-based case–control study in Sweden (Magnusson *et al.*, 1999) included 3345 women aged 50–74 years who had been diagnosed with invasive breast cancer and 3454 controls of similar age. The main objective was to assess whether the use of combined hormonal therapy is associated with risk for breast cancer, with particular reference to long duration of use. For ever use of combined therapy, the relative risk for breast cancer was 1.63 (95% CI, 1.37–1.94) compared with never use. Risk increased with duration of use: the relative risk for 2–5 years of use was 1.40 (95% CI, 1.01–1.94), that for 5–10 years of use was 2.43 (95% CI, 1.72–3.44) and that for 10 or more years of use was 2.95 (95% CI, 1.84–4.72). These results were adjusted for age, parity, age at first birth, age at menopause, body mass index and height. The results from two sub-analyses were also presented; however, these analyses did not include only women who had exclusively used combined treatment, but also women who had used estrogen-only treatment at some time. The results suggested that combined preparations that contain testosterone-derived progestogens may confer higher risk (relative risk, 1.68; 95% CI, 1.39–2.03; 324 exposed cases) than combined therapy that contains progesterone-derived progestogens (relative risk, 1.14; 95% CI, 0.69–1.88; 32 exposed cases). The results also showed that

Table 5. Case–control studies of the use of combined hormone therapy and the risk for breast cancer

Reference, location	Study period	Age (years)	Histology	Sub-site	Therapy (type/regimen)	Cases	Controls	Odds ratio	95% CI	Duration			Time since last use		
										Years	Odds ratio	95% CI	Years	Odds ratio	95% CI
Magnusson *et al.* (1999), Sweden	1993–95	50–74	Invasive	All	Never	1738	2201	1.0							
					Ever	409	295	1.63	1.37–1.94	> 2–5	1.40	1.01–1.94			
										> 5–10	2.43	1.72–3.44			
										> 10	2.95	1.84–4.72			
					E + T[a]	324	229	1.68	1.39–2.03	≤ 5	1.33	1.05–1.68			
										> 5	2.74	1.99–3.78			
					Cyclic	102	76	1.48	1.08–2.04	> 2–5	1.34	0.71–2.54			
										> 5–10	1.89	0.88–4.09			
					Continuous	139	124	1.41	1.09–1.83	> 2–5	1.26	0.76–2.09			
										> 5–10	2.89	1.66–5.00			
					E + P[b]	32	34	1.14	0.69–1.88	≤ 5	1.41	0.80–2.51			
										> 5	0.79	0.26–2.39			
Li, C.I. *et al.* (2000), USA (King County, WA)	1988–90	50–64	Invasive and *in situ*	All	Never	180	187	1.0							
				Ductal	Ever	35	55	0.70	0.50–1.20	NR			Current	0.70	0.50–1.10
				Lobular	Ever	12	55	2.50	1.10–4.60	NR			Current	2.60	1.10–5.80
			Invasive	All	Never	159	187	1.0							
				Ductal	Ever	30	55	0.70	0.40–1.20	NR			Current	0.70	0.40–1.10
				Lobular	Ever	9	55	2.60	1.00–6.70	NR			Current	2.60	0.80–5.80
Ross *et al.* (2000), USA (Los Angeles, CA)	1987–96	55–72	Invasive and *in situ*	All	Never	873	784			1.0					
					Ever	425	324	NR		NR					
					Cyclical	218	166			1–5	1.19	NR			
						75	48			> 5–10	1.58	NR			
						27	14			> 10	1.79	NR			
					Daily	59	58								
						23	18			1–5	0.88	NR			
						23	20			> 5–10	1.28	NR			
										> 10	1.23	NR			

Table 5 (contd)

Reference, location	Study period	Age (years)	Histology	Sub-site	Therapy (type/regimen)	Cases	Controls	Odds ratio	95% CI	Duration			Time since last use		
										Years	Odds ratio	95% CI	Years	Odds ratio	95% CI
Kirsh & Kreiger (2002), Canada	1995–96	20–74	Invasive	All	Never	272	283	1.0							
					Ever	48	33	1.22	0.72–2.06	< 1	0.86	0.26–2.82			
										1–4	0.96	0.39–2.39			
										5–9	0.84	0.31–2.24			
										≥ 10	3.48	1.00–12.1			
Newcomb *et al*. (2002), USA (New Hampshire, Wisconsin, Massachusetts)	1992–94	50–79	Invasive	All	Never	3827	4132	1.0							
					Ever	315	286	1.43	1.18–1.74	< 5	1.36	1.07–1.73	Current	1.39	1.12–1.71
										≥ 5	1.57	1.15–2.14	< 5	1.71	0.92–3.18
													≥ 5	2.38	0.82–6.87
				Ductal	Ever	208	286	1.43	1.14–1.79						
				Lobular	Ever	32	286	2.01	1.25–3.22						

Table 5 (contd)

Reference, location	Study period	Age (years)	Histology	Sub-site	Therapy (type/regimen)	Cases	Controls	Odds ratio	95% CI	Duration			Time since last use		
										Years	Odds ratio	95% CI	Years	Odds ratio	95% CI
Weiss *et al.* (2002); Daling *et al.* (2002), USA (Atlanta, GA; Detroit, MI; Philadelphia, PA; Los Angeles, CA; Seattle, WA)	1994–98	35–64	Invasive	All	Never	672	655	1.0							
					Ever	689	630	[1.13]		2–< 5	1.3	0.96–1.63	Current	1.22	0.99–1.50
										≥ 5	1.2	0.92–1.48	≥ 0.5	0.76	0.60–0.97
					Sequential	287	267	[1.05]		2–< 5	1.1	0.73–1.58	Current	0.91	0.67–1.24
										≥ 5	1	0.69–1.32	≥ 0.5	1.07	0.80–1.41
					Continuous	419	352	[1.20]		2–< 5	1.20	0.88–1.65	Current	1.29	1.02–1.64
										≥ 5	1.4	0.98–1.85	≥ 0.5	0.78	0.57–1.06
				Ductal	Never	515	655	1.0							
					Ever	448	534	1.00	0.80–1.30	2–< 5	1.00	0.80–1.30	≥ 5	0.70	0.50–1.10
										≥ 5	1.00	0.80–1.30	> 0–0.5	1.20	0.90–1.50
					Sequential	230	284	1.00	0.80–1.30	0.5–< 5	1.00	0.80–1.40	≥ 5	0.90	0.60–1.40
										≥ 5	1.00	0.70–1.30	> 0–0.5	0.90	0.70–1.30
					Continuous	268	280	1.20	0.90–1.50	0.5–< 5	1.20	0.90–1.50	≥ 5	0.70	0.40–1.30
										≥ 5	1.20	0.90–1.50	> 0–0.5	1.30	1.00–1.70
				Lobular	Never	75	655	1.0							
					Ever	112	534	1.80	1.20–2.60	0.5–< 5	1.60	1.00–2.40	≥ 5	0.90	0.40–2.10
										≥ 5	2.00	1.30–3.20	> 0–0.5	2.20	1.40–3.30
					Sequential	53	284	1.40	0.90–2.20	0.5–< 5	1.30	0.80–2.30	≥ 5	1.30	0.60–2.70
										≥ 5	1.50	0.80–2.60	> 0–0.5	1.40	0.80–2.50
					Continuous	75	280	2.20	1.40–3.50	0.5–< 5	2.10	1.30–3.30	≥ 5	1.60	0.60–4.10
										≥ 5	2.50	1.40–4.30	> 0–0.5	2.40	1.50–3.80

Table 5 (contd)

Reference, location	Study period	Age (years)	Histology	Sub-site	Therapy (type/regimen)	Cases	Controls	Odds ratio	95% CI	Duration			Time since last use		
										Years	Odds ratio	95% CI	Years	Odds ratio	95% CI
Li *et al.* (2003), USA (3-county Puget Sound, WA)	1997–99	65–79	Invasive	All	Never	284	339	1.0							
					Ever	136	964	1.80	1.30–2.50	0.5–< 5	1.30	0.80–2.20	Current	1.9	1.6–2.6
					Sequential	80	55	1.80	1.20–2.70	5–< 15	2.00	1.30–3.20			
					Continuous	159	116	1.60	1.20–2.20						
				Ductal	Never	199	339	1.0							
					Ever	89	96	1.60	1.10–2.30	< 5	1.40	0.8–2.5	Former	2.00	1.1–3.7
										5–< 15	1.60	1.0–2.7	Current	1.70	1.2–2.4
										≥ 15	1.90	1.1–3.2	0.5–< 5	1.30	0.8–2.3
													5–< 15	1.70	1.1–2.7
					Sequential	52	55	1.70	1.10–2.60						
					Continous	102	116	1.50	1.10–2.00						
				Lobular	Never	47	339	1.0							
					Ever	29	96	2.50	1.40–4.30	< 5	1.40	0.8–2.5	Former	2.00	0.7–5.7
										5–< 15	3.40	1.7–7.0	Current	3.10	1.9–5.2
										≥ 15	2.40	1.1–5.5	0.5–< 5	1.30	0.5–3.6
													5–< 15	4.60	2.5–8.5
					Sequential	19	55	2.80	1.50–5.40						
					Continous	40	116	2.70	1.60–4.40						

CI, confidence interval; NR, not reported

[a] Estrogen + testosterone-like progestogen

[b] Estrogen + progesterone-like progestogen

the positive association between the use of hormonal menopausal therapy and risk for breast cancer may be confined to women with a body mass index lower than 27 kg/m^2.

Li, C.I. *et al.* (2000) conducted a case–control study in the USA that involved 537 women who had breast cancer and were 50–64 years of age and 492 controls selected at random from the population. The aim of the study was to investigate whether the use of combined hormonal menopausal therapy has different effects on different histological subtypes of breast cancer. For women who had used combined hormonal therapy for at least 6 months, the relative risk for ductal breast carcinoma was 0.7 (95% CI, 0.5–1.2; 35 exposed cases) and that for lobular breast carcinoma was 2.5 (95% CI, 1.1–4.6; 12 exposed cases). Using a likelihood ratio test, the difference between these two estimates of relative risk was statistically significant ($p = 0.007$). The relative risk associated with current use of combined hormonal therapy for at least 6 months was 2.6 (95% CI, 1.1–5.8) for lobular breast carcinoma compared with the risk in never users. These results were adjusted for age and type of menopause (natural or surgical). In comparison, there was no increase in the risk for ductal breast carcinoma (relative risk, 0.7; 95% CI, 0.5–1.1) related to current use of combined hormonal menopausal therapy. A similar comparison between the estimates suggested that the difference was statistically significant ($p < 0.03$).

The specific aim of a case–control study in the USA (Ross *et al.*, 2000) was to investigate whether daily administration of combined hormonal therapy exerts a different effect on risk for breast cancer than sequential administration. The study included 1897 postmenopausal women with breast cancer and 1637 postmenopausal population controls. The age range of the participants was 55–72 years. The relative risk for ever use versus never use of combined preparations was not reported, but the risk for breast cancer increased with duration of use. For every 5 years of use of combined therapy, the relative risk was 1.24 (95% CI, 1.07–1.45). The risk related to combined regimens with cyclical progestogens was slightly higher than that found for regimens in which progestogens were given daily, but the difference was not statistically significant: for 5 years of use, the odds ratio for the cyclical regimen was 1.38 (95% CI, 1.13–1.68; 320 exposed cases) versus 1.09 (95% CI, 0.88–1.35; 105 exposed cases) for the daily regimen. These results were adjusted for age, age at menarche, family history of breast cancer, age at first full-term pregnancy, parity, age at menopause, previous use of oral contraceptives, body weight and consumption of alcoholic beverages.

A population-based case–control study in Canada on data from the Enhanced Cancer Surveillance Project (Kirsh & Kreiger, 2002) included 320 incident cases of breast cancer and 316 controls (with information or hormonal therapy use) who were frequency-matched by age. A self-administered questionnaire was used to collect information on the use of combined hormonal menopausal therapy between 1995 and 1997. Long duration of use (10 years or longer) of combined estrogen–progestogen therapy was associated with an increased risk (odds ratio, 3.48; 95% CI, 1.00–12.11) compared with never use.

Another large case–control study in the USA (Newcomb *et al.*, 2002) investigated the type and duration of use of combined hormonal menopausal therapy in relation to the risk for breast cancer. The study included 5298 postmenopausal cases of breast cancer aged

50–79 years of age and 5571 control women who were randomly selected from population lists. The relative risk for ever use versus never use of combined regimens was 1.43 (95% CI, 1.18–1.74; 315 exposed cases). Women who used regimens with daily progestogens had a relative risk of 1.45 (95% CI, 1.06–1.99; 115 exposed cases), but the association was similar for women who used the different types of sequential therapy. The relative risk for breast cancer increased with duration of use: the increase per year of combined treatment was approximately 4% (relative risk, 1.04; 95% CI, 1.01–1.08) and that for recent use for more than 5 years was 1.57 (95% CI, 1.15–2.14).

The association between the use of combined hormonal menopausal therapy and the risk for breast cancer was also studied in the CARE [Contraceptive and Reproductive Experience] multicentre case–control study in the USA. Weiss *et al.* (2002) included 1870 postmenopausal women with breast cancer aged 35–64 years and 1953 controls identified by random-digit dialling. Current users for 5 or more years of daily combined hormonal menopausal therapy were at increased risk for breast cancer (odds ratio, 1.54; 95% CI, 1.10–2.17) compared with never users. Among current users, increasing duration of use was associated with increasing risk (p for trend = 0.01). Whether different regimens of combined hormonal menopausal therapy may have different effects on different histological subtypes of breast cancer was also studied within the same study (Daling *et al.*, 2002). Cases were 1749 postmenopausal women under 65 years of age with a diagnosis of breast cancer; the 1953 controls were those included in the study of Weiss *et al.* (2002). The aim was to assess whether combined hormonal therapy increases the risk for lobular breast carcinoma. The tumours were grouped into three histological categories: 1386 patients had ductal carcinoma, 148 had lobular carcinoma and 115 women were diagnosed with a mixture of these histological subtypes. Another 100 patients were divided among less prevalent histological types of breast cancer. The association with ever use (≥ 6 months) versus never use of combined menopausal therapy was not reported, but current daily use of combined treatment was associated with an increased risk for invasive lobular disease (odds ratio, 2.2; 95% CI, 1.4–3.5; 75 exposed cases). The relative risks were adjusted for age, race, study site and age at menopause.

A case–control study in the USA (Li *et al.*, 2003) assessed duration and patterns of use of combined hormonal therapy in relation to histological subtypes and hormonal receptor status of breast cancer. The study included 975 women aged 65–79 years who had invasive breast cancer classified according to histology and hormone receptor status and 1007 population controls. For women who had ever used combined hormonal therapy only, the relative risk for breast cancer was 1.8 (95% CI, 1.3–2.5) compared with the risk in never users. When examined by histological subtype, ever users of combined hormonal menopausal therapy had an increased risk for both invasive ductal carcinoma (relative risk, 1.6; 95% CI, 1.1–2.3; 89 exposed cases) and invasive lobular carcinoma (relative risk, 2.5; 95% CI, 1.4–4.3; 29 exposed cases). The increased risk for lobular carcinoma was greater in women who had used combined therapy for a relatively long time. For lobular carcinoma, the relative risk for use for between 5 and 15 years was 3.4 (95% CI, 1.7–7.0) and that for use for longer than 15 years was 2.4 (95% CI, 1.1–5.5). Both current and former

use for at least 6 months were associated with an increased risk for all histological subtypes. With regard to different hormone receptor properties, the results showed that, among ever users, the relative risk for estrogen and progesterone receptor-positive tumours was 2.0 (95% CI, 1.5–2.7). The risk increased with duration of use, but did not differ according to whether progestogens were given sequentially (relative risk, 1.8; 95% CI, 1.2–2.7) or daily (relative risk, 1.6; 95% CI, 1.2–2.2). In relation to estrogen or progesterone receptor-negative breast cancer, no increase in risk was found, but low statistical power related to hormone receptor-negative disease limited the ability of the study to evaluate this subtype of breast cancer reliably.

2.2 Endometrial cancer

Postmenopausal women who use estrogen-only therapy are at an increased risk for endometrial cancer, and the risk increases with increasing duration of use (IARC, 1999). To counteract this risk, many women use combined estrogen–progestogen regimens. At the time when the previous evaluation on this topic was made, only four published studies provided information on the effects of the combined regimens on the risk for endometrial cancer, and the limited available evidence suggested that the addition of progestogens reduced the elevated risk associated with estrogen.

2.2.1 *Descriptive studies*

Using data from the Southern California Kaiser Foundation Health Plan, Ziel *et al.* (1998) reported patterns of prescription of hormonal menopausal therapy among women aged over 45 years in 1971–93 and related them to trends in the incidence of endometrial cancer. Use of combined estrogen–progestogen regimens began to increase during the mid-1980s. A log-linear model fitted to the data indicated that, since about 1984, the prescription of progestogens together with estrogens was negatively associated with the incidence rates of endometrial cancer. The authors concluded that their observation was consistent with the hypothesis that progestogens administered in conjunction with estrogens can protect against much of the increased risk for endometrial cancer associated with the use of estrogens alone.

2.2.2 *Randomized trials*

In a trial in which 168 institutionalized women were randomized to receive estrogen–progestogen menopausal therapy or placebo, no case of endometrial cancer occurred in the treated group and one case occurred in those who received placebo (Nachtigall *et al*., 1979).

The HERS randomized 2763 women with previous coronary heart disease to either placebo or a daily regimen of 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate. The women were then followed up for 4.1 years on average (Hulley

et al., 1998). During the follow-up period, two endometrial cancers were diagnosed in the treated group and four were diagnosed in the placebo group to give a relative risk of 0.49 (95% CI, 0.09–2.68) for use of continuous combined therapy compared with placebo.

In the WHI Trial, 16 608 women who had not had a hysterectomy were randomized to receive placebo or a daily regimen of 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate. After an average follow-up of 5.6 years, Anderson *et al.* (2003) reported that 27 incident cases of endometrial cancer had occurred among those randomized to continuous combined hormonal therapy and 31 cases among those randomized to placebo. The relative risk was 0.81 (95% CI, 0.48–1.36) for the use of continuous combined therapy compared with placebo.

2.2.3 *Cohort studies*

Cohort studies that presented relative risk estimates for endometrial cancer associated with the use of estrogen–progestogen menopausal therapy published from 1999 onwards are summarized in Table 6.

Hammond *et al.* (1979) followed up approximately 600 women, approximately half of whom had used either estrogen-only or estrogen–progestogen preparations and half of whom had not used hormones. No cases of endometrial cancer were observed among the 72 women who received estrogen–progestogen therapy, whereas three cases were observed among women who did not. No person–years or age-adjusted relative risks were reported.

Gambrell (1986) reported that the incidence of endometrial cancer among women who had used combined hormonal therapy (eight cases in 16 327 woman–years) was lower than that among women who did not use any hormonal therapy (nine cases in 4480 woman–years). No age-adjusted relative risks were reported.

Persson *et al.* (1999) updated their earlier report on the follow-up of a cohort of Swedish women who had used hormonal menopausal therapy (Persson *et al*., 1989). The cohort had initially been identified through pharmacy records; in 1987–88, the women were mailed a follow-up questionnaire requesting further details on their use of hormonal therapy and other personal characteristics. The 8438 women who replied were linked to the National Swedish Cancer Registry; 66 endometrial cancers were identified in the cohort up to December 1993. In comparison with the population rates in the Uppsala health care region, the relative risk for endometrial cancer associated with use of estrogen–progestogen therapy was 1.4 (95% CI, 0.9–2.3; six exposed cases) for 1–6 years of use and 1.7 (95% CI, 1.1–2.6; 11 exposed cases) for more than 6 years of use. There was no significant difference according to duration of use. Estimates of relative risk were not given according to the number of days per month that progestogens were added to estrogen therapy or by time since last use of the therapy.

Pukkala *et al.* (2001) linked prescription records for hormonal menopausal therapy to cancer registry data in Finland and compared incidence rates of endometrial cancer in users of combined therapy with those in the general population in Finland. Among 78 549 women who were taking progestogens added to estrogen therapy for 10–12 days every month, the

Table 6. Cohort studies of the use of estrogen–progestogen menopausal therapy use and risk for endometrial cancer by number of days that progestogens were added to estrogen therapy per month, duration of use and type of progestogen

Reference, location	Study period	Age range (years)	Source population	Type/measure of combined therapy	No. of cases	Relative risk (95% CI)	Comments
Persson *et al.* (1999), Sweden	1987–93	65 (median)	8438 women	None	12	1.0	Adjusted for age, length of follow-up, age at first full-term pregnancy, body mass index, education, menopausal age/status
				Any progestogen added to estrogen			
				Duration			
				≤ 6 years	6	1.4 (0.9–2.3)	
				> 6 years	11	1.7 (1.1–2.6)	
Pukkala *et al.* (2001), Finland	1994–97	Any age	94 505 women	Progestogens 14 days every 3 months	61	2.0 (1.6–2.6)	Standardized incidence ratios, using the female Finnish population
				Progestogens 10–12 days per month	141	1.3 (1.1–1.6)	
Bakken *et al.* (2004), Norway	1991–NR	45–64	67 336 women	None	45	1.0	Adjusted for age, body mass index, smoking, ever use of oral contraceptives, time since menopause, parity, age at last birth
				Any	11	0.7 (0.4–1.4)	

Table 6 (contd)

Reference, location	Study period	Age range (years)	Source population	Type/measure of combined therapy	No. of cases	Relative risk (95% CI)	Comments
Beral *et al.* (2005), United Kingdom	1996–2002	50–65	716 738 women	None	773	1.0	Adjusted for age, region of residence, socioeconomic status, body mass index, alcoholic beverage consumption, ever use of oral contraceptives, time since menopause, parity
				Progestogens, every day/month			
				Any	73	0.71 (0.59–0.90)	
				Duration			
				< 5 years	28	0.55 (0.37–0.80)	
				≥ 5 years	44	0.90 (0.66–1.22)	
				Type of progestogen			
				Norethisterone	46	0.76 (0.57–1.03)	
				Medroxyprogesterone acetate	27	0.63 (0.43–0.93)	
				Progestogens, 10–14 days/ month			
				Any	242	1.05 (0.90–1.22)	
				Duration			
				< 5 years	95	0.90 (0.72–1.12)	
				≥ 5 years	140	1.17 (0.97–1.41)	
				Type of progestogen			
				Norgestrel	183	1.09 (0.93–1.29)	
				Norethisterone	53	0.93 (0.70–1.23)	

CI, confidence interval; NR, not reported

standardized incidence ratio (SIR) for endometrial cancer was 1.3 (95% CI, 1.1–1.6; 141 cases); among 15 956 women who used progestogens added to estrogen for 14 days every 3 months, the standardized incidence ratio was 2.0 (95% CI, 1.6–2.6; 61 cases).

Bakken *et al*. (2004) followed 67 336 Norwegian women aged 45–64 years who were recruited in 1991–97. Information on use of hormonal therapy was obtained from self-completed questionnaires and incident cancers were determined by linkage to data from the Cancer Registry of Norway. Among 7268 women who were using estrogen–progestogen menopausal therapy at the time of recruitment, 11 incident endometrial cancers were diagnosed. The associated relative risk was 0.7 (95% CI, 0.4–1.4), adjusted for age, body mass index, tobacco smoking, use of oral contraceptives, time since menopause, parity and age at first birth. Estimates of relative risk were not given according to the number of days per month that progestogens were added to estrogen therapy or by time since last use of the therapy.

In 1996–2001, the Million Women Study Collaborators (Beral *et al.*, 2005) recruited over a million women in the United Kingdom aged 50–65 years through the National Health Service Breast Screening Programme. Information was collected on the last formulation of hormonal therapy used and the total duration of use of such therapy or any type of hormonal therapy. This self-reported information showed 97% agreement with prescription records on whether combined or estrogen-only menopausal therapy was currently used (Banks *et al*., 2001). At recruitment, 716 738 members of the cohort were postmenopausal and had not had a hysterectomy or previous diagnosis of cancer. Follow-up of these women via national cancer registries over an average of 3.4 years identified 1320 women with incident endometrial cancer. Compared with never users of hormonal therapy (773 cases), the relative risks for endometrial cancer were 0.71 (95% CI, 0.56–0.90; 73 exposed cases) for any use of continuous estrogen–progestogen therapy and 1.05 (95% CI, 0.91–1.22; 242 exposed cases) for any use of cyclical estrogen–progestogen therapy (usually including progestogens for 10–14 days per month). The relative risks were adjusted for age, region of residence, socioeconomic status, body mass index, alcoholic beverage consumption, ever use of oral contraceptives, time since menopause and parity. The difference between the effects of continuous and cyclical estrogen–progestogen therapy was highly significant ($p = 0.006$). Most women were current or recent users of these therapies at the time of recruitment into the study and, although there was no significant difference in the findings between current and past users, there was limited power to detect any difference, since the average time since last use was only 1–3 years among former users. Among women who had last used a combined therapy (both continuous and cyclical), there were no significant differences according to duration of use or the constituent progestogen. Nine factors that could potentially modify the effects of hormonal therapy on endometrial cancer were examined, and only body mass index consistently showed a significant interaction. Among women with body mass indices of < 25, 25–29 and ≥ 30 kg/m^2, respectively, the relative risks for endometrial cancer were 1.07 (95% CI, 0.73–1.56), 0.88 (95% CI, 0.60–1.30) and 0.28 (95% CI, 0.14–0.55) for use of continuous combined therapy and 1.54 (95% CI, 1.20–1.99), 1.07 (95% CI, 0.82–1.40) and 0.67 (95% CI, 0.49–0.91) for use of cyclical combined therapy.

2.2.4 *Case–control studies*

The case–control studies that presented relative risk estimates for endometrial cancer associated with the use of estrogen–progestogen menopausal therapy are summarized in Table 7.

A multicentre study was conducted with 300 menopausal women who had been diagnosed with endometrial cancer at seven US hospitals located in five different areas of the country and 207 age-, race- and residence-matched control women from the general population (Brinton & Hoover, 1993). Use of any estrogen–progestogen therapy for 3 months or longer was reported by 11 (4%) of the case women and nine (5%) of the control women (odds ratio, 1.8; 95% CI, 0.6–4.9 adjusted for age, parity, weight and years of oral contraceptive use).

Jick *et al.* (1993) studied women who were members of a large health maintenance organization in western Washington State, USA. Women with endometrial cancer were identified from the tumour registry of the organization and control women were other members; both groups included only women who used the pharmacies of the organization and who had previously completed a questionnaire sent to all female members for a study of mammography. Use of hormonal menopausal therapy was ascertained from the pharmacy database. Relative to women who had never or briefly (≤ 6 months) used menopausal hormones, those who had used any estrogen–progestogen therapy within the previous year had a non-significant increased risk (odds ratio, 1.9; 95% CI, 0.9–3.8; 18 cases), after adjustment for age, calendar year, age at menopause, body mass and history of oral contraceptive use. Former users (last use ≥ 1 year earlier) had no significant increase in risk (odds ratio, 0.9; 95% CI, 0.3–3.4; six incident cases), but the statistical power to compare current and past users was limited.

Beresford *et al.* (1997) expanded the study population originally investigated by Voigt *et al.* (1991) and evaluated the risk for endometrial cancer among women who had used estrogen–progestogen therapy exclusively. Women who had been diagnosed with endometrial cancer in 1985–91 were identified from a population-based cancer registry and their characteristics were compared with control women from the general population in western Washington State, USA. The analysis included 394 cases and 788 controls. Relative to women who had never or briefly (≤ 6 months) used menopausal hormones, women who had used only estrogen–progestogen therapy had a borderline increased risk for endometrial cancer (odds ratio, 1.4; 95% CI, 1.0–1.9), after adjustment for age, body mass and county of residence. For women who had used estrogen–progestogen therapy for ≤ 10 days per cycle for at least 5 years, the odds ratio was 3.7 (95% CI, 1.7–8.2; five exposed cases); among women who had used combined therapy with progestogens added cyclically for more than 10 days each month for at least 5 years, the relative risk was 2.5 (95% CI, 1.1–5.5). Statistical power to compare current and past users was limited. Using data from the same study population, McKnight *et al.* (1998) reported that the relative risk associated with the use of cyclical progestogens added for 10–24 days per month was 2.6 (95% CI, 1.3–5.5; 14 exposed cases) among women who had never used estrogen-only previously,

Table 7. Case–control studies of estrogen–progestogen therapy and endometrial cancer risk, by number of days progestogen was added per cycle, duration, and type of progestogen

Reference, location	Study period	Age range (years)	Source of controls	Type/measure of combined therapy	No. of subjects		Adjusted odds ratio (95% CI)	Comments
					Cases	Controls		
Brinton & Hoover (1993), USA (seven hospitals in five areas)	1987–90	20–74	General population	No use	222	176	1.0	Adjusted for age, parity, weight, years of oral contraceptive use
				Any use for ≥ 3 months[a]	11	9	1.8 (0.6–4.9)	
Jick *et al.* (1993), USA (Washington State)	1989–89	50–64	Members of health maintenance organization	No use or use ≤ 6 months	97	606	1.0	Adjusted for age, calendar year, age at menopause, body mass index, oral contraceptive use
				Current/recent	18	83	1.9 (0.9–3.8)	
				Duration (years)				
				< 3	NR	NR	2.2 (0.7–7.3)	
				≥ 3	NR	NR	1.3 (0.5–3.4)	
Beresford *et al*. (1997), USA (Washington State)	1985–91	45–74	General population	No use or use ≤ 6 months	337	685	1.0	Adjusted for age, body mass index, country of residence
				Any use	67	134	1.4 (1.0–1.9)	
				Progestogen ≤ 10 days/month				
				Duration (months)				
				6–35	12	14	2.1 (0.9–4.7)	
				36–59	3	7	1.4 (0.3–5.4)	
				≥ 60	15	12	3.7 (1.7–8.2)	
				Progestogen > 10 days/month				
				Duration (months)				
				6–35	10	31	0.8 (0.4–1.8)	
				36–59	5	23	0.6 (0.2–1.6)	
				≥ 60	12	16	2.5 (1.1–5.5)	
				Progestogen every day/month	9	33	0.6 (0.3–1.3)	

Table 7 (contd)

Reference, location	Study period	Age range (years)	Source of controls	Type/measure of combined therapy	No. of subjects		Adjusted odds ratio (95% CI)	Comments
					Cases	Controls		
Pike *et al.* (1997), USA (California)	1987–93	50–74	General population (neighbours)	*Any use, progestogen < 10 days/month*[b]				Adjusted for age at menarche, time to regular cycle, parity, weight, duration of breast feeding, amenorrhoea, tobacco smoking, oral contraceptive use, age at menopause
				Duration (months)				
				0	759	744	1.0	
				1–24	35	22	1.4 (NR)	
				25–60	12	12	1.5 (NR)	
				≥ 60	27	13	3.5 (NR)	
				Any use, progestogen ≥ 10 days/month				
				Duration (months)				
				0	754	703	1.0	
				1–24	37	30	1.0 (NR)	
				25–60	19	25	0.7 (NR)	
				≥ 60	23	33	1.1 (NR)	
				Any use, progestogen every day/month				
				Duration (months)				
				0	739	710	1.0	
				1–24	45	41	1.1 (NR)	
				25–60	25	15	1.4 (NR)	
				≥ 60	24	25	1.3 (NR)	
Weiderpass *et al.* (1999), Sweden	1994–95	50–74	General population	No use	573	2798	1.0	Adjusted for age, age at menopause, parity, age at last birth, body mass index and duration of previous menopausal hormone use
				Any use[a]	119	477	1.3 (1.0–1.7)	
				Progestogen ~10 days/month, ever	90	300	2.0 (1.4–2.7)	
				Duration (years)				
				< 5	38	191	1.5 (1.0–2.2)	
				≥ 5	40	78	2.9 (1.8–4.6)	
				Progestogen, every day/month, ever	41	237	0.7 (0.4–1.0)	
				Duration (years)				
				< 5	32	162	0.8 (0.5–1.3)	
				≥ 5	2	53	0.2 (0.1–0.8)	

Table 7 (contd)

Reference, location	Study period	Age range (years)	Source of controls	Type/measure of combined therapy	No. of subjects		Adjusted odds ratio (95% CI)	Comments
					Cases	Controls		
Jain *et al*. (2000), Canada (Ontario)	1994–98	> 48	Property assessment list of the Ontario Ministry of Finance	No use	292	316	1.0	Adjusted for age, weight, menarche age, age at menopause, period disorders, education, parity, smoking and physical activity
				Ever use of combined therapy	128	136	1.37 (0.99–1.89)	
				Progestogen for ~10 days/month, ever	65	87	1.05 (0.71–1.56)	
				Duration (years)				
				< 3	18	40	0.57 (0.31–1.06)	
				≥ 3	47	47	1.49 (0.93–2.40)	
				Progestogen every day/month only	15	14	1.51 (0.67–3.42)	
Mizunuma *et al*. (2001), Japan	1995–97	62.0 (mean)	63 hospitals	Never use of therapy	934	1188	1.0	Adjusted for age, parity, body mass index, height
				Ever use of combined therapy				
				Duration (months)				
				< 12	6	6	0.9 (0.3–3.0)	
				≥ 12	2	6	0.6 (0.1–3.1)	
Newcomb & Trentham-Dietz (2003), USA (Wisconsin)	1991–94	40–79	Medicare beneficiaries	No use	402	1667	1.0	Adjusted for age, parity, body mass index, tobacco smoking, oral contraceptive use
				Ever use of any combined therapy	48	166	1.69 (1.15–2.47)	
				Progestogen added for				
				< 10 days/month	8	21	2.43 (1.00–5.92)	
				10–21 days/month	14	71	1.10 (0.59–2.07)	
				> 21 days/month	20	62	2.26 (1.27–4.00)	
				Progestogen for ≤ 21 days/month				
				Medroxyprogesterone acetate				
				< 10 mg	6	24	1.29 (0.49–3.36)	
				> 10 mg	10	54	1.11 (0.53–2.32)	
				Progestogen for > 21 days/month				
				Medroxyprogesterone acetate				
				< 10 mg	12	45	1.68 (0.82–3.43)	
				> 10 mg	2	8	5.75 (1.75–18.9)	

CI, confidence interval; NR, not reported

[a] Women taking estrogen only included

[b] Use of estrogen only and other combined therapy adjusted for in the analysis

but only 0.21 (95% CI, 0.07–0.66; four exposed cases and controls) among women who had used estrogen-only therapy previously. In a study that included the same study subjects, Hills *et al.* (2000) reported that the relative risk associated with the use of progestogens added to estrogen on a daily basis was 0.6 (95% CI, 0.3–1.3; nine exposed cases, 33 exposed controls).

Pike *et al.* (1997) identified 833 women with endometrial cancer from a population-based cancer registry in Los Angeles County, CA, USA, and matched them to control women of similar age and race (white) who lived in the same neighbourhood as the matched case or to 791 women randomly identifed from the US Health Care Financing Administration computer tapes. The risk for endometrial cancer was investigated among women who had used estrogen–progestogen with progestogen added for fewer than 10 days per cycle, for ≥ 10 days per cycle and continuously. The relative risks were [1.9 (95% CI, 1.3–2.6)] for fewer than 10 days per cycle and [0.96 (95% CI, 0.69–1.34)] for ≥ 10 days per month [the referent group for each analysis was women who had never used that type of therapy]. The odds ratios for every additional 5 years of use were 1.9 (95% CI, 1.3–2.7) and 1.1 (95% CI, 0.8–1.4), respectively, after adjustment for age at menarche, time to regular cycles, parity, weight, duration of breast-feeding, amenorrhoea, tobacco smoking, duration of oral contraceptive use and age at menopause. No significant increase in the odds ratio was found for daily use of progestogens together with estrogens (relative risk, 1.23; 95% CI, 0.88–1.71; 94 exposed cases, 81 exposed controls); for every additional 5 years of use, the odds ratio increased by 1.1 (95% CI, 0.8–1.4). No comparisons were made between current and past users of these therapies.

Weiderpass *et al.* (1999) conducted a population-based case–control study in Sweden of 709 women aged 50–74 years who were diagnosed with endometrial cancer in 1994–95 and 3368 matched controls. When users of estrogen–progestogen menopausal therapy were compared with never users of any type of therapy, the overall relative risk for endometrial cancer was 1.3 (95% CI, 1.0–1.7; 119 exposed cases, 477 exposed controls). All analyses were adjusted by age, age at menopause, parity, age at last birth, body mass index and duration of previous use of various types of menopausal hormones. The odds ratio was 2.0 (95% CI, 1.4–2.7) for use of progestogens added cyclically for an average of 10 days each month and 0.7 (95% CI, 0.4–1.0) for use of continuous combined therapy. Among the users of therapy with progestogens added cyclically, the relative risk was significantly higher in women who had used hormonal therapy for more than 5 years (odds ratio, 2.9; 95% CI, 1.8–4.6) than in those who had used them for shorter durations (odds ratio, 1.5; 95% CI, 1.0–2.2). Among users of continuous combined therapy, the risk was lower in women who had used the therapy for more than 5 years (odds ratio, 0.2; 95% CI, 0.1–0.8) than in those who had used them for shorter durations (odds ratio, 0.8; 95% CI, 0.5–1.3). There were no significant differences in risk according to the specific progestogenic constituent of the therapy.

Jain *et al.* (2000) conducted a population-based case–control study in Ontario, Canada, on 512 women with endometrial cancer and 513 controls. Cases identified through the Ontario Cancer Registry were diagnosed between 1994 and 1998. Controls were identified

from property assessment lists maintained by the Ontario Ministry of Finances. Subjects were interviewed at home. For women who reported that they had used estrogen–progestogen menopausal therapy compared with those who had never used any type of therapy, the relative risk for endometrial cancer was 1.37 (95% CI, 0.99–1.89). All analyses were adjusted by age, education, parity, weight, age at menarche, tobacco smoking, past oral contraceptive use, education, and calorie intake and expenditure. Among the users of combined therapy, there were no significant differences according to duration of use, recency of use or the number of days each month that progestogens were added to estrogen therapy but statistical power to compare such patterns of use was limited.

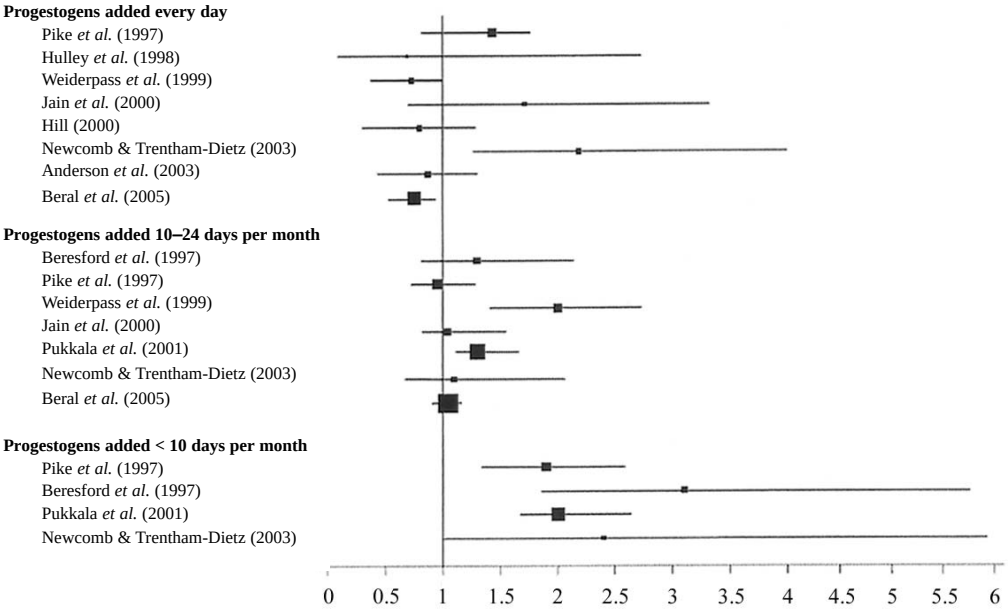
Mizunuma *et al*. (2001) conducted a hospital-based case–control study in Japan of 1025 women who were diagnosed with endometrial cancer in 1995–97 and 1267 matched controls from 63 hospitals. Women who used estrogens with progestin for ≥ 12 months had an odds ratio of 0.6 (95% CI, 0.11–3.11), and those who used estrogens without progestin for ≥ 12 months had an odds ratio of 2.6 (95% CI, 0.23–28.2). Among the users of combined therapy, there were no significant differences according to duration of use; data on risk were not given according to the number of days per month that progestogens were added to estrogen therapy.

Newcomb and Trentham-Dietz (2003) conducted a population-based case–control study in Wisconsin, USA, of 591 women aged 40–79 years who were diagnosed with endometrial cancer in 1991–94 and 2045 matched controls. For ever use of any type of estrogen–progestogen menopausal therapy compared with never use, the odds ratio for endometrial cancer was 1.69 (95% CI, 1.15–2.47). All analyses were adjusted for age, parity, body mass index, tobacco smoking and past oral contraceptive use. For progestogens added cyclically for fewer than 10 days each month, the odds ratio for endometrial cancer was 2.43 (95% CI, 1.00–5.92); for progestogens added cyclically for 10–21 days each month, the relative risk was 1.10 (95% CI, 0.59–2.07); and for daily use of progestogens, the relative risk was 2.26 (95% CI, 1.27–4.00). There were no significant differences in risk according to recency of use, duration of use or the dose of progestogen used, but the power to detect such differences was low.

2.2.5 *Overview*

Two randomized trials, four cohort studies and eight case–control studies have reported relative risks for endometrial cancer associated with the use of combined estrogen–progestogen therapy. Most investigators found that the fewer days each month that progestogens were added to estrogen therapy, the higher was the relative risk for endometrial cancer. Figure 2 summarizes the overall findings. Five of eight studies, including the Million Women Study, reported risks below unity for the addition of progestogen every day. Five of six studies on progestogens added for 10–24 days per month and all four studies on progestogens added for < 10 days per month reported an increased risk for endometrial cancer (Million Women Study Collaborators, 2005).

Figure 2. Summary of published studies on the relation between use of combined estrogen–progestogen hormonal therapy and endometrial cancer, according to the number of days per month that progestogens are added to estrogen therapy



Adapted from Million Women Study Collaborators (2005)

Among the eight studies that reported on the effect of progestogens added to estrogen therapy on a daily basis, only one (Newcomb & Trentham-Dietz, 2003) found that the risk for endometrial cancer was significantly higher in never users of any type of hormonal therapy.

Overall, no consistent trend was found with increasing duration of use of continuous combined therapy (Table 8), and no significant differences were found according to the specific type of progestogen used (Beral *et al.*, 2005) or according to progestogen dose (Newcomb & Trentham-Deitz, 2003).

In the seven studies that reported on the effect of progestogens added to estrogens for 10–21 days per month, all found that the risk for endometrial cancer was similar to or slightly higher than that seen in never users of any type of hormonal therapy (Table 9). Five of the seven studies presented results separately according to duration of use of the therapy and, in every study, the relative risk tended to be higher with longer use. Among users of hormonal therapy with progestogens added for 10–21 days per month, no significant differences were found according to the specific type of progestogen used (Beral *et al.*, 2005).

Table 8. Summary of results on the association of endometrial cancer with the daily addition of progestogens to estrogen therapy

Reference, location	Exposure category	No. of cases	No. of controls/ population at risk	Relative risk/ odds ratio (95% CI)
Observational studies				
Pike *et al.* (1997), USA	No use	739	710	1.0
	Any use	94	81	1.07 (0.80–1.43)
	Duration ≥ 5 years	24	33	1.34 (NR)
Weiderpass *et al.* (1999), Sweden	Never	641	3 014	1.0
	Ever	41	237	0.7 (0.4–1.0)
	Duration ≥ 5 years	2	32	0.2 (0.1–0.8)
Hill *et al.* (2000), USA	No use of any hormonal therapy	392	793	1.0
	Ever continuous hormonal therapy	9	33	0.6 (0.3–1.3)
Jain *et al.* (2000), Canada	No use	292	316	1.0
	Exclusive use of continuous hormonal therapy	15	14	1.51 (0.67–3.42)
Newcomb & Threntham-Dietz (2003), USA	No use	402	1 667	1.0
	Any use	20	62	2.26 (1.27–4.00)
Beral *et al.* (2005), United Kingdom	Never users	763	395 786	1.0
	Any use	73	69 577	0.71 (0.56–0.90)
	Duration ≥ 5 years	44	33 600	0.90 (0.66–1.22)
Randomized trials				
Hulley *et al.* (1998), USA	Placebo[a]	2		1.0
	Estrogen-progestin[a]	4		0.49 (0.09–2.68)
Anderson *et al.* (2003), USA	Placebo[b]	27		1.0
	Estrogen-progestin[b]	31		0.81 (0.48–1.36)

CI, confidence interval; NR, not reported
[a] 2763 women were randomized.
[b] 16 608 women were randomized.

All four studies that reported on the risk for endometrial cancer associated with use of combined hormonal therapy with progestogens added for less than 10 days per month found an increased risk for endometrial cancer associated with such use, although the risk was lower than that associated with the use of estrogen-only therapy (Beresford *et al*., 1997; Pike *et al*., 1997; Pukkala *et al.*, 2001; Newcomb & Trentham-Dietz, 2003). The two studies that reported results according to duration of use found that the risk tended to be higher with longer use (Table 10).

Table 9. Summary of results from studies of endometrial cancer and the addition of progestogens cyclically to estrogen therapy for 10–21 days each month

Reference, location	Exposure category	No. of cases	No. of controls/ population at risk	SIR/odds ratio (95% CI)
Beresford *et al.* (1997), USA	Never	270	593	1.0
	Any use	25	64	1.3 (0.8–2.2)
	Duration ≥ 5 years	12	16	2.5 (1.1–5.5)
Pike *et al.* (1997), USA	No use	754	703	1.0
	Any use	79	88	1.07 (0.82–1.41)
	Duration > 5 years	23	33	1.09 [NR]
Weiderpass *et al.* (1999)[a], Sweden	Never	597	2 963	1.0
	Ever	90	300	2.0 (1.4–2.7)
	Duration ≥ 5 years	40	78	2.9 (1.8–4.6)
Jain *et al.* (2000)[b], Canada	No use	292	316	1.0
	Any use	65	87	1.05 (0.71–1.56)
	Duration ≥ 3 years	47	47	1.49 (0.93–2.40)
Pukkala *et al.* (2001), Finland	Any use	141	105[c]	1.3 (1.1–1.6)
Newcomb & Threntham-Dietz (2003), USA	No use	402	1 667	1.0
	Any use	14	71	1.10 (0.59–2.07)
Beral *et al.* (2005), United Kingdom	No use	763	395 785	1.0
	Any use	242	145 486	1.05 (0.91–1.22)
	Duration ≥ 5 years	140	75 000	1.17 (0.97–1.41)

CI, confidence interval; NR, not reported; SIR, standardized incidence ratio
[a] The average duration of use of progestogens was about 10 days each month.
[b] All but six cases used progestogens for 10 or more days each month.
[c] Expected number of cases, based on incidence rates of endometrial cancer in Finland

Taken together, the results are consistent with the view that the addition of progestogens to estrogen therapy lessens the risk associated with the use of estrogens alone, and that the greater the number of days per month that progestogens are added, the greater is the reduction in risk. The addition of progestogens for less than 10 days per month is associated with a clear increase in the risk for endometrial cancer. To reduce the rates of endometrial cancer in menopausal women to levels that are found in never users of hormonal therapy, progestogens may need to be added to estrogens most of the time and possibly on a daily basis. Since the use of combined estrogen–progestogen therapy began relatively recently, there is as yet little information on the effects of combined estrogen–progestogen therapy on the risk for endometrial cancer many years after cessation of use.

Table 10. Summary of results of studies of endometrial cancer and the addition of progestogens to estrogen therapy cyclically for < 10 days each month

Reference, location	Exposure category	No. of cases	No. of controls/ population at risk	Relative risk/ odds ratio (95% CI)
Beresford *et al*. (1997), USA	Never	270	593	1.0
	Any use	25	26	3.1 (1.7–5.7)
	Duration ≥ 5 years	15	12	3.7 (1.7–8.2)
Pike *et al*. (1997), USA	No use	759	744	1.0
	Any use	74	49	1.9 (1.3–2.6)
	Duration > 5 years	27	13	3.49 (NR)
Pukkala *et al.* (2001), Finland	Any use	61	30	2.0 (1.6–2.6)
Newcomb & Threntham-Dietz (2003), USA	No use	402	1667	1.0
	Any use	8	21	2.4 (1.0–5.9)

CI, confidence interval; NR, not reported

2.3 Cervical cancer

Persistent infection by certain types of human papillomavirus (HPV) is generally considered to be a necessary cause of cervical cancer (IARC, 2007). However, only a small proportion of women who are infected by these viruses develop a cervical neoplasm, which clearly indicates that co-factors probably play an etiological role. Since the uterine cervix is responsive to estrogens and progestogens, these hormones could act to modify the carcinogenic potential of an HPV infection. Combined estrogen–progestogen hormonal therapy at menopause is one exogenous source of these hormones. Their possible role in cervical carcinogenesis has not been studied adequately in humans. Combined estrogen–progestogen hormonal therapy has not been widely used for a sufficiently long period of time for adequate epidemiological study of the risk for cervical cancer in relation to long-term use or to use a long time after initial or most recent exposure.

2.3.1 *HPV infection*

Two randomized trials have provided some initial information of relevance (Smith *et al.*, 1997; Anderson *et al.*, 2003). In a study from Iowa, USA, among women who were enrolled in the Postmenopausal Estrogen/Progestin Intervention trial (Smith *et al*., 1997), 105 women aged 45–64 years were initially tested for nine high-risk types of HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52) in cervical scrapings on enrolment and two years later using polymerase chain reaction (PCR)-based technology. Table 11 shows the results at

Table 11. Summary of results from a randomized trial of estrogen and estrogen–progestogen combinations that show percentages of women who were HPV-positive or HPV-negative at baseline and who were HPV-positive after 2 years of treatment

Treatment	HPV-negative at baseline			HPV-positive at baseline		
	Total no. of women	HPV-positive at 2 years		Total no. of women	HPV-positive at 2 years	
		No.	%		No.	%
Placebo	17	3	17.6	5	1	20.0
CEE[a]	12	3	25.0	8	3	37.5
CEE + progestogen (all combinations)	36	7	19.4	27	7	25.9
CEE/2.5 MPA[b]	11	2	18.2	8	3	37.5
CEE/10 MPA[c]	12	2	16.7	10	2	20.0
CEE/200 MP[d]	13	3	23.1	9	2	22.2
Any hormone treatment	48	10	20.8	35	10	28.6

From Smith *et al.* (1997)
CEE, conjugated equine estrogens; HPV, human papillomavirus; MP, micronized progesterone; MPA, medroxyprogesterone acetate
[a] CEE, 0.625 mg daily
[b] 0.625 mg CEE plus 2.5 mg MPA daily
[c] 0.625 mg CEE daily plus 10 mg MPA daily on days 1–12 of cycle
[d] 0.625 mg CEE daily plus 200 mg MP daily on days 1–12 of cycle

2 years in women who initially tested HPV-positive or HPV-negative. Among women who initially tested negative for HPV DNA, the percentage that became positive was not significantly higher in any of the treatment groups than in the placebo group. The treatment groups included one estrogen-only group and three estrogen–progestogen groups. When these three groups were combined, the percentage that were HPV DNA-positive after 2 years of follow-up was also not statistically significantly different in the combined group than in the placebo group. Thus, the incidence of HPV (or recrudescence of existing infection missed on enrolment) was apparently not influenced by estrogen–progestogen treatment. Among women who were initially positive for HPV DNA, the percentage that remained positive at 2 years did not vary significantly by treatment, and the percentage in the three estrogen–progestogen groups combined was not significantly different from that in the placebo group. In any individual woman, the type of HPV at 2 years was not always the same as the type at baseline. The infections at 2 years thus represented a mixture of new and persistent infections. The results did not provide evidence to suggest that estrogen–progestogen therapy alters the risk for either new or persistent infection. Five women were found 2 years after enrolment to have an abnormal Papanicolaou (Pap) smear; four had

atypical cells of undetermined significance and one had atypical squamous cells. No such cells occurred in women with a positive HPV DNA test at baseline or concurrently with a suspicious Pap smear; their relevance to cervical carcinoma and the sensitivity of the HPV DNA assays used were therefore questioned. Abnormal Pap smears were not associated with treatment group. At baseline, the prevalence of HPV DNA was 22.7% in the placebo group and varied from 40.0 to 45.5% in the four treatment groups, suggesting that women in the placebo group may have been at lower risk for HPV infection than those in the treatment groups. If this were the case, it would bias the results towards higher rates of HPV being observed in the treatment groups than in the placebo group at follow-up, and this, in addition to chance, could explain the slightly higher rates of HPV in some of the treatment groups than in the placebo group as shown in Table 11. [However, this study was of low statistical power, so that true differences in rates of HPV infection among study groups could have been missed. Larger studies of longer duration will be needed to determine more definitively whether estrogen–progestogen therapy alters the risk for acquisition or persistence of HPV.]

2.3.2 *Cervical neoplasia*

Table 12 summarizes results relevant to cervical cancer from the WHI (Anderson *et al*., 2003). Between October 1993 and October 1998, women who had not had a hysterectomy aged 50–79 years in 40 participating clinics in the USA were randomized to either treatment

Table 12. Summary of results from a randomized trial of estrogen–progestogen combination showing percentages of women at follow-up with LGSIL, HGSIL and cervical cancer

Treatment	Total no. of women[a]	Results of Pap smears						Reported cervical cancer[b,c]	
		LGSIL		HGSIL		Cancer[b]			
		No.	%	No.	%	No.	%	No.	%[d]
Placebo	7599	420	5.5	29	0.4	3	0.04	8	0.02
CEE/MPA[e]	7950	619	7.8	25	0.3	2	0.03	5	0.01

From Anderson *et al.* (2003)
CEE, conjugated equine estrogen; HGSIL, high-grade squamous intrepithelial lesion; LGSIL, low-grade squamous intraepithelial lesion; MPA, medroxyprogesterone acetate
[a] 503 women in the placebo group and 556 women in the estrogen–progestogen group with no follow-up smears excluded
[b] Whether *in situ* or invasive not stated in published report
[c] Not stated whether reported cervical cancer cases include those detected at Papanicolaou smear screening.
[d] Annualized %
[e] 0.625 mg CEE plus 0.25 mg MPA daily

with 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate daily (n = 8506) or placebo (n = 8102). Most women had Pap smears every 3 years. After a mean follow-up period of 5.6 years, the incidence of cervical cancer as reported from the 40 participating clinics did not differ significantly between the treatment and placebo groups (hazard ratio, 1.4; 95% CI, 0.5–4.4). It was not indicated whether the cancers were invasive or *in situ*. There were significantly ($p < 0.001$) more low-grade squamous intraepithelial lesions in the treatment group (7.8%) than in the placebo group (5.5%), but the relationship of these lesions to cervical neoplasia is uncertain. Furthermore, this may result from more women in the treatment group having had Pap smears as part of a clinical evaluation for vaginal bleeding than those in the placebo group. There was no significant difference in rates of high-grade squamous intraepithelial lesions (HSIL) or of cervical cancer (presumably carcinoma *in situ*) detected by Pap smears in the two groups of women. Although this study provides little cause for concern that combined continuous estrogen–progestogen therapy for over 5 years alters the risk for cervical cancer, the statistical power to detect an alteration in risk of any type of cervical carcinoma was low, and the duration of follow-up was too short to determine whether risk is increased a long time after initial or last use. The increased risk for HSIL in the treated group warrants further investigation.

2.3.3 *Overview*

There is little evidence from these two randomized trials to suggest that combined estrogen–progestogen therapy alters the risk for persistent HPV infection, HSIL or cervical cancer, but both studies were of limited statistical power to detect true increases in risks in women who are exposed to these treatments.

2.4 Ovarian cancer

2.4.1 *Background*

Major findings of cohort and case–control studies published before the last evaluation (IARC, 1999), including two meta-analyses (Garg *et al*., 1998; Coughlin *et al.*, 2000), and a re-analysis of individual data on hormonal therapy and risk for ovarian cancer indicate that long-term use of hormonal therapy is associated with a moderate, but consistent excess risk for ovarian cancer (IARC, 1999; Negri *et al*., 1999; Bosetti *et al.*, 2001). In a meta-analysis of 10 published studies (nine case–control, one cohort), the overall risk for invasive ovarian cancer for ever users of hormonal therapy was 1.15 (95% CI, 1.05–1.27), with no difference in risk for hospital-based and population-based case–control studies (Garg *et al*., 1998). Another meta-analysis of 15 studies (Coughlin *et al*., 2000), however, found no significant overall association (relative risk, 1.1; 95%, CI, 0.9–1.7). The studies that have been published since the last evaluation (IARC, 1999) are summarized below.

2.4.2 *Controlled clinical trials*

The WHI, a randomized, controlled primary prevention trial, included 8506 women aged 50–79 years who were treated with combined hormonal therapy and 8102 untreated women (Writing Group for the Women's Health Initiative Investigators, 2002). In the group that received combined hormonal therapy, 20 cases of ovarian cancer occurred versus 12 in the placebo group, which corresponded to a multivariate relative risk of 1.58 (95% CI, 0.77–3.24). Nine deaths from ovarian cancer occurred in the combined hormonal therapy group versus three in the placebo group (relative risk, 2.70; 95% CI, 0.73–10.00) (Anderson *et al.*, 2003).

2.4.3 *Cohort studies*

One cohort study (Pukkala *et al*., 2001) provided data on combined hormonal therapy and ovarian cancer. In this Finnish record linkage study, 15 956 women who received long-cycle hormonal therapy (with added progestogen every 2nd or 3rd month) and 78 549 who used monthly cycle therapy were identified from the medical reimbursement register of the national Social Insurance Institution (between 1994 and 1997). Cancer incidence was ascertained through the files of the population-based country-wide Finnish Cancer Registry. By the end of follow-up, 23 cases of ovarian cancer in the long-cycle cohort and 104 in the monthly cycle cohort were observed, to yield SIRs of 1.0 (95% CI, 0.63–1.5) and 1.1 (95% CI, 0.93–1.4), respectively.

A cohort study based on the Breast Cancer Detection Demonstration Project included 329 incident cases of ovarian cancer (Lacey *et al.*, 2002). Compared with never use of any type of hormonal therapy, the relative risk for exclusive use of combined hormonal therapy was 1.1 (95% CI, 0.64–1.7; 18 cases), in the absence of any duration–risk relation (relative risk for ≥ 2 years of use, 0.80; 95% CI, 0.35–1.8). The relative risk for use of combined hormonal therapy after that of estrogen-only therapy was 1.5 (95% CI, 0.91–2.4; based on 21 cases).

2.4.4 *Case–control studies* (Table 13)

In a population-based study of 793 incident cases of epithelial ovarian cancer diagnosed between 1990 and 1999 in Queensland, New South Wales and Victoria, Australia, and 855 controls (Purdie *et al*., 1999), the relative risk adjusted for age, education, area of residence, body mass index, hysterectomy, tubal sterilization, use of talc, tobacco smoking, oral contraceptive use, parity and family history of breast or ovarian cancer was 1.34 (95% CI, 0.83–2.17) for the use of estrogens and progestogens in combination. There was no consistent relation with duration of use, time since last use or any other time factor.

In a case–control study from Sweden of 193 epithelial borderline cases, Riman *et al*. (2001) reported an odds ratio of 0.98 (95% CI, 0.57–1.68) for estrogens with cyclic progestogens and 0.87 (95% CI, 0.46–1.64) for estrogens and continuous progestogens compared with never users. None of the trends in risk with duration of use were significant.

Table 13. Case–control studies of the use of combined hormonal therapy and the risk for ovarian cancer

Reference, location	No. of cases	No. of controls	Odds ratio[a] (95% CI)		
			Ever use	Longest use (duration)	Current/recent use
Purdie *et al.* (1999), Australia	793	855	1.34 (0.83–2.17)	1.33 (0.88–2.00) (> 3 years)	1.24 (0.73–2.09)
Riman *et al.* (2001), Sweden (borderline neoplasms)	193	3899	0.98 (0.57–1.68) sequential	0.91 (0.44–2.03) (≥ 2 years)	–
			0.87 (0.46–1.64) continuous	0.89 (0.35–2.28) (≥ 2 years)	–
Riman *et al.* (2002), Sweden (invasive neoplasms)	655	3899	1.41 (1.15–1.72)	2.03 (1.30–3.17) (≥ 10 years)	–
Sit *et al.* (2002), USA	484	926	1.06 (0.74–1.52) conjugated estrogens 1.08 (0.59–2.00) non-conjugated estrogens	–	–
Glud *et al.* (2004), Denmark	376	1111	1.14 (1.01–1.28)[b] 1.00 (0.95–1.06)[c]	–	–
Pike *et al.* (2004), USA	477	660	–	0.90 (0.55–1.48)[d] (≥ 5 years)	–
			–	1.13 (0.15–8.3)[e]	–

CI, confidence interval

[a] Reference category was never use of combined hormonal therapy.

[b] Per additional gram of estrogen intake

[c] Per additional gram of progestogen intake

[d] Natural menopause

[e] Hysterectomy

In the same study that included 655 cases of ovarian cancer and 3899 controls aged 50–74 years, the odds ratio was 1.41 (95% CI, 1.15–1.72) for ever use of combined hormone therapy (Riman *et al*., 2002). For longest use (≥ 10 years), the odds ratio was 2.03 (95% CI, 1.30–3.17). There was no consistent pattern for time since last use. Adjustment was made for age, parity, body mass index, age at menopause, hysterectomy and duration of oral contraceptive use. The results were similar for serous, mucinous and endometrioid ovarian cancers. No information was presented on sequential or combined hormonal therapy.

A study conducted between 1994 and 1998 in Delaware Valley, USA, included 484 cases of ovarian cancer aged 45 years or over and 926 community controls frequency-matched by age and area of residence (Sit *et al*., 2002). Adjustment was made for age, parity, oral contraceptive use, family history of ovarian cancer and history of tubal ligation. The hormonal therapy formulation was classified as estrogen plus progestogen or estrogen alone. The relative risk was 1.06 (95% CI, 0.74–1.52) for progestogen with conjugated estrogens and 1.08 (95% CI, 0.59–2.00) for progestogen with non-conjugated estrogens.

A nationwide case–control study was conducted in Denmark between 1995 and 1999 and included 376 cases of ovarian cancer and 1111 population controls (Glud *et al*., 2004). The results were presented in terms of groups of estrogen or progestogen intake, with adjustment for parity, use of oral contraceptives, family history of ovarian cancer and infertility. The odds ratio per additional gram of intake was 1.14 (95% CI, 1.01–1.28) for estrogens and 1.00 (95% CI, 0.95–1.06) for progestogens and was similar for estrogen only (odds ratio, 1.05; 95% CI, 0.97–1.14) and combined estrogen–progestogen therapies (odds ratio, 1.08; 95% CI, 1.01–1.16). There was no relationship with duration of use independent from cumulative dose.

A case–control study was conducted between 1992 and 1998 in Los Angeles County, CA, USA, on 477 cases of invasive epithelial ovarian cancer and 660 populations controls aged 18–74 years (Pike *et al*., 2004). Participation rates were approximately 80% of cases and 70% of controls approached. Multivariate relative risks were adjusted for age, ethnicity, socioeconomic status, education, family history of ovarian cancer, tubal ligation, use of talc, nulliparity, age at last birth, menopausal status, age at menopause and use of oral contraceptives. Among women with natural menopause, the odds ratios per 5 years of use were 1.16 (95% CI, 0.92–1.48) for estrogen-only therapy and 0.97 (95% CI, 0.77–1.23) for combined hormonal therapy. Corresponding values for women with surgical menopause were 1.11 (95% CI, 0.92–1.35) and 1.30 (95% CI, 0.63–2.67).

2.5 Liver cancer

Persson *et al.* (1996) studied cancer risks after hormonal menopausal therapy in a population-based cohort of 22 579 women aged 35 years or more who lived in the Uppsala health care region in Sweden. Women who had ever received a prescription for hormonal menopausal therapy between 1977 and 1980 were identified and followed until 1991; information on use of hormones was obtained from pharmacy records. The expected numbers of cases

were calculated from national incidence rates. There was no information on tobacco smoking or alcoholic beverage consumption. There were 43 cancers of the hepatobiliary tract that comprised 14 hepatocellular carcinomas, five cholangiocarcinomas, 23 gallbladder cancers and one unclassified. The expected number was 73.2, to give an SIR of 0.6 (95% CI, 0.4–0.8) for any type of hormonal menopausal therapy. The SIRs for treatment with estradiol combined with levonorgestrel were 0.6 (95% CI, 0.1–2.3) for hepatocellular carcinoma, 0.7 (95% CI, 0.0–3.8) for cholangiocarcinoma and zero (six cases expected) for gallbladder cancer. There was no information on infection with hepatitis viruses.

2.6 Colorectal cancer

2.6.1 *Background*

The previous monograph (IARC, 1999) reported details from three cohort studies and one case–control study on the use of combinations of estrogens and progestogens. Since then, new data have been published on the risks and benefits of estrogen plus progestogen treatment in menopausal women, including two randomized trials (the WHI Trial and the HERS Follow-up Study) (Hulley *et al.*, 2002; Writing Group for the Women's Health Initiative Investigators, 2002), one cohort study (Pukkala *et al.*, 2001) and two case–control studies (Jacobs *et al.*, 1999; Prihartono *et al.*, 2000). Other studies have focused on estrogen only or did not provide separate information for estrogen only and combined hormonal therapy (Paganini-Hill, 1999; Csizmadi *et al.*, 2004; Hannaford & Elliot, 2005; Nichols *et al.*, 2005).

2.6.2 *Randomized trials*

Two large randomized clinical trials have been published that provided information on combined hormonal therapy and colorectal cancer (Table 14).

The HERS was a randomized trial of the use of estrogen plus progestogen in which 2763 menopausal women under 80 years of age at baseline who had coronary artery disease and no prior hysterectomy were recruited at 20 outpatient and community settings between 1993 and 2000 in the USA (Hulley *et al.*, 2002). Of these, 1380 women were allocated to the treatment group (0.625 mg per day conjugated estrogens plus 2.5 mg per day medroxyprogesterone acetate) and 1383 to the placebo group. After a mean of 4.1 years of follow-up, 11 cases of colon cancer were observed in the combined hormonal therapy group versus 16 in the placebo group, which corresponded to a relative risk of 0.69 (95% CI, 0.32–1.49) (Hulley *et al.*, 2002).

The WHI Study was a randomized, controlled, primary prevention trial (that was planned to continue for 8.5 years) in which 16 608 menopausal women aged 50–79 years who had a uterus at baseline were recruited at 40 clinical centres between 1993 and 1998 in the USA. Of these, 8506 women were allocated to the treatment group (0.625 mg per day conjugated estrogens plus 2.5 mg per day medroxyprogesterone acetate) and 8102 to the placebo group (Writing Group of the Women's Health Initiative, 2002). At the end of

Table 14. Randomized clinical trials on the association between the use of combined hormonal therapy and the risk for colorectal cancer

Reference, location	Participants Outcome No. cases/group size	Relative risk (95% CI)	Comments
Chlebowski *et al.* (2004), USA	Healthy postmenopausal women with intact uterus Colorectal cancer Treatment group: 43/8506 Placebo group: 72/8102	0.56 (0.38–0.81)	WHI study; treatment: 0.625 mg/day conjugated estrogens plus 2.5 mg/day medroxy-progesterone acetate; multi-centre study; terminated early
Hulley *et al.* (2002), USA	Postmenopausal women with previous heart disease Colon cancer Treatment group: 11/1380 Placebo group: 16/1383	0.69 (0.32–1.49)	HERS; treatment: 0.625 mg/day conjugated estrogens plus 2.5 mg/day medroxy-progesterone acetate; multi-centre study; terminated early

CI, confidence interval; HERS, Heart and Estrogen/Progestin Replacement Study; WHI, Women's Health Initiative

active intervention (mean follow-up, 5.6 years), 43 cases of invasive colorectal cancer were observed in the combined hormonal therapy group versus 72 in the placebo group (relative risk, 0.56; 95% CI, 0.38–0.81) (Chlebowski *et al.*, 2004). The reduction in the risk for colorectal cancer in the hormonal therapy group was largely confined to local disease (relative risk, 0.26; 95% CI, 0.13–0.53), rather than regional or metastatic disease (relative risk, 0.87; 95% CI, 0.54–1.41). Within the category of regional or metastatic disease, the cancers in the hormonal therapy group were associated with a greater number of positive nodes than the corresponding types of cancer in the placebo group (Chlebowski *et al.*, 2004).

2.6.3 *Cohort studies* (Table 15)

In addition to the three cohort studies reviewed previously (IARC, 1999), one cohort study (Pukkala *et al.*, 2001) provided new data on the potential association between the use of combined hormonal therapy and the risk for colorectal cancer. In this Finnish record linkage study, 15 956 women who took long-cycle hormonal therapy (administered orally on a 3-month basis: 70 days 2 mg estradiol valerate, 14 days 2 mg estradiol valerate plus 20 mg medroxyprogesterone acetate and 7-day tablet-free period) and 78 549 who took monthly or short-cycle (11 days 2 mg estradiol valerate, 10 days 2 mg estradiol valerate and 0.25 mg levonorgestrel and 7-day tablet-free period) hormonal therapy were identified from the medical reimbursement register of the national Social Insurance Institution (between 1994 and 1997); cancer incidence was ascertained through the files of the population-based country-wide Finnish Cancer Registry. SIRs were computed by

Table 15. Cohort studies on the association between the use of combined hormonal therapy and the risk for colorectal cancer

Reference, location	No. cases (or deaths)/cohort size	Follow-up (years)	Relative risk (95% CI) (ever versus never use)	Comments
Risch & Howe (1995), Canada	230/32 973	14	Colon, 1.07 (0.58–1.99) Rectum, 1.16 (0.53–2.52)	Linkage study (cancer registry–drug database); age-adjusted
Persson *et al.* (1996), Sweden	295/22 597	13	Colon, 0.6 (0.4–1.0) Rectum, 0.8 (0.4–1.3)	Relative risk for incident cancer (age-adjusted); no effect among 5573 hormone users (fixed combined brand); relative risk for mortality from colon cancer adjusted for age, 0.6 (95% CI, 0.2–1.1)
Troisi *et al.* (1997), USA	313/33 779	7.7	Colon, 1.4 (0.7–2.5)	Relative risk adjusted for age (unaltered when adjusted for education, body mass index, parity or use of oral contraceptives); no differences right/left colon; no trend with duration of use
Pukkala *et al.* (2001), Finland	11/15 956[a] 50/78 549[b]	5	Colon, 0.67 (0.34–1.20) Colon, 0.85 (0.63–1.10)	Linkage study (Social Insurance Institution drug database and Cancer Registry); relative risk adjusted for age; recency and duration of use not assessed

CI, confidence interval

[a] Long cycle (2 or 3-month) administration of combined hormonal therapy

[b] Short cycle (1-month) administration of combined hormonal therapy

comparing the observed number of cases in the assembled cohort with those expected using national incidence rates. By the end of follow-up, 11 cases of colon cancer were observed in the long-cycle cohort and 50 cases in the monthly cycle cohort, to yield an age-adjusted SIR for colon cancer of 0.67 (95% CI, 0.34–1.20) and 0.85 (95% CI, 0.63–1.10), respectively (Pukkala *et al.*, 2001).

2.6.4 *Case–control studies* (Table 16)

Since the previous evaluation (IARC, 1999), a nested case–control study of more than 1400 women aged 55–79 years who were enrolled from the Group Health Cooperative, a health maintenance organization in Washington State, USA, has been published (Jacobs *et al.*, 1999). Between 1984 and 1993, 341 incident cases of colon cancer and 1679 controls matched by age and length of enrolment in the cooperative were identified. From the records of prescriptions for progestogen tablets, the authors identified 268 cases and 1294 controls who had used combined hormonal therapy during a 5-year period (progestogen-only users and estrogen-only users excluded). The age-adjusted odds ratio for colon

Table 16. Case–control studies on the association between the use of combined hormonal therapy and the risk for colorectal cancer

Reference, location	No. cases/ controls	Odds ratio (95% CI)[a]	Comments
Newcomb & Storer (1995), USA	694/1622	Colon, 0.54 (0.28–1.0)[a] Rectum, 1.1 (0.51–2.5)[a]	Adjustment for age, alcoholic beverage consumption, body mass index, family history of cancer, sigmoidoscopy
Jacobs *et al.* (1999), USA	268/1294	Colon < 180 tablets[b], 0.59 (0.28–1.24) ≥ 180 tablets[b], 1.04 (0.59–1.82)	Nested case–control study in a health maintenance organization; adjustment for age; further adjustment for smoking, height, weight, body mass index, oral contraceptive use, parity, age at first birth, age at menopause and hysterectomy status did not alter the odds ratios.
Prihartono *et al.* (2000), USA	404/404	Colon Last use < 1 year, 0.9 (0.4–2.2) Duration ≥ 5 years, 0.7 (0.2–2.5)	Adjusted for fat, fruit and vegetable intake, physical activity, body mass index, history of screening for colorectal cancer

CI, confidence interval

[a] Ever use versus never use

[b] Progestogen tablet counts: assuming 100% compliance and 10 progestogen tablets per month, consumption of < 180 tablets is equivalent to 1.5 years of use and consumption of ≥ 180 tablets is equivalent to ≥ 1.5 years of consumption.

cancer was 0.59 (95% CI, 0.28–1.24) for those who consumed less than 180 progestogen tablets [assuming 100% compliance and 10 progestogen tablets per month, consumption of 180 tablets is equivalent to 1.5 years of use] and 1.04 (95% CI, 0.59–1.82) for those who consumed > 180 tablets [or used combined hormonal therapy for more than 1.5 years] compared with never users. Adjustment for other covariates did not substantially change these estimates. Duration of use and analysis of colon subsite was not presented for users of combined hormonal therapy.

Prihartono *et al.* (2000) conducted a matched population-based case–control study among women aged 20–69 years in Massachusetts, USA, between 1992 and 1994, and included 515 incident cases of colon cancer (out of 1847 potential eligible cases) and 515 matched controls. The final analysis was restricted to pairs of women with natural menopause or who had had a hysterectomy (404 cases, 404 matched controls). Recent use (interval since last use, < 1 year) of combined hormonal therapy showed an odds ratio of 0.9 (95% CI, 0.4–2.2; 13 exposed cases, 15 exposed controls). Longer duration of use (> 5 years) of combined hormonal therapy showed an odds ratio of 0.7 (95% CI, 0.2–2.5; seven exposed cases, nine exposed controls). The odds ratio was adjusted for fat, fruit and vegetable intake, physical activity, body mass index and history of screening for colorectal cancer.

2.7 Lung cancer

The large population-based mortality study in Sweden (Persson *et al.*, 1996) found no association with lung cancer in users of combined hormonal therapy, and a similar study in Finland found non-significant associations for long (SIR, 1.2; 95% CI, 0.69–1.9) or monthly (SIR, 0.75; 95% CI, 0.53–1.0) cycles of hormonal therapy (Pukkala *et al.*, 2001).

A case–control study in Texas, USA, in which 60 cases of lung cancer and 78 controls reported use of combined hormonal therapy reported a multivariate odds ratio of 0.61 (95% CI, 0.40–0.92) (Schabath *et al.*, 2004).

The HERS (Hulley *et al.*, 2002) and WHI (Writing Group for the Women's Health Initiative Investigators, 2002) trials showed a hazard ratio of 1.39 (95% CI, 0.84–2.28) and 1.04 (95% CI, 0.71–1.53) for lung cancer, respectively.

2.8 Other cancers

Data on other cancers were inadequate for an evaluation as nearly all studies failed to report the type of hormonal therapy used.