2. Studies of Cancer in Humans

2.1 Breast cancer

The progesterone present during natural cycles and the progestogens added in hormonal therapy may be important in cancer etiology (Stanford & Thomas, 1993). Some epidemiological data suggest that short menstrual cycles or having many regular cycles during a life-time, reflecting exposure to progesterone, may have an adverse effect on the risk for breast cancer (Kelsey *et al*., 1993). Several studies (Anderson *et al*., 1982; Longacre & Bartow, 1986; Going *et al*., 1988; Potten *et al*., 1988; Anderson *et al*., 1989), but not all (Vogel *et al*., 1981), indicate that progesterone in natural cycles and exogenous progestogens in the cycles of users of combined oral contraceptives augment proliferative activity in breast epithelial cells (Key & Pike, 1988). Furthermore, progesterone probably down-regulates oestrogen receptors but maintains the numbers of progesterone receptors in natural cycles (Söderqvist *et al*., 1993). As increased proliferation may cause neoplastic cell transformation (Preston-Martin *et al*., 1990), progestogens in treatment regimens may further enhance the risk for breast cancer.

The use of added progestogens to control menstrual bleeding and to prevent development of hyper- and neoplasia of the endometrium in women with an intact uterus has increased markedly since the 1970s, when reports of an increased risk for endometrial cancer after unopposed oestrogen therapy were first published. Both use and the number of progestogen compounds (progesterone- or testosterone-derived) and treatment schedules (cyclical, sequential, long cycle and continuous) have surged. For these reasons, the effects of progestogen combinations on the risk for breast cancer is an important topic in epidemiological research; however, epidemiological data on the effects of oestrogen plus progestogen treatment are rather scarce, especially for long-term use. Some data on the risks associated with combined use are available in nine cohort studies and five case–control studies. The Collaborative Group on Hormonal Factors in Breast Cancer (1997) pooled and re-analysed individual data on such use from some of these and other studies (see section 2.1.3).

2.1.1 *Cohort studies*

The cohort studies on use of post-menopausal oestrogen–progestogen therapy and breast cancer are summarized in Table 1.

Hunt *et al.* (1987) reported the results of the surveillance of a cohort of 4544 women recruited at 21 menopause clinics in Great Britain, all of whom had been placed on hormones and 43% with a variety of combined progestogens for an average of 67 months. The incidence of breast cancer was ascertained through several sources, including mailed questionnaires, morbidity registers and hospital notes. On the basis of about 20 000 person–years of observation and 50 observed cases, a standardized incidence ratio (SIR) of 1.6 (95% confidence interval [CI], 1.2–2.1) was calculated for any use. Analyses of use of oestrogens only or oestrogens plus progestogens, by classifying the different regimens, did not produce any interpretable results. A trend of increasing risk with increasing time since first use (SIR, 3.1; 95% CI, 1.5–5.6 after 10 years or longer) was found for all types of treatment.

In the cohort study of Bergkvist *et al.* (1989), over 23 000 women were recruited by analysing registered prescriptions for various types of hormonal treatment dispensed in six counties in central Sweden. These women were followed-up by record-linkage with the National Cancer Registry. Individual data on exposure and risk factors were obtained from the accumulated prescriptions and from questionnaires sent to a sample of the cohort and all 253 women with newly diagnosed cases of breast cancer. In cohort and nested case–control analyses, exposure to oestrogens alone for nine years or longer was associated with a relative risk of 1.8 (95% CI, 1.0–3.1); for exposure to oestradiol combined with levonorgestrel, the relative risk was 4.4 (based on 10 cases only) after use for more than six years. In women with mixed intakes of oestrogens only and oestrogens plus progestogens exceeding six years, the relative risk estimates varied between 1.2 and 7.2 (not significant).

This cohort was also followed-up for death from breast cancer by linkage to a population-based mortality registry (Yuen *et al.*, 1993). On the basis of prescription data collected during 1977–80 and corrected external mortality rates (calculated from newly diagnosed cases of breast cancer only), an overall standardized mortality ratio (SMR) of 0.8 (95% CI, 0.2–1.1) emerged. When only those women to whom an oestradiol–levonorgestrel combination had been prescribed were included, the SMR was similarly close to baseline, 0.8 (95% CI, 0.4–1.3). In the same study, Persson *et al.* (1996) conducted a 13-year record-linkage follow-up, yielding 634 new cases of breast cancer. Any use of an oestradiol–levonorgestrel combination conferred a slightly increased relative risk (1.3; 95% CI, 1.1–1.4), whereas women receiving oestradiol or conjugated oestrogens only had no alteration of their risk (RR, 0.9; 95% CI, 0.8–1.1).

The results of the Nurses' Health Study were reported on at least two occasions by Colditz *et al.* (1992, 1995). Data on exposure and risk factors were obtained from a baseline questionnaire in 1976 which was administered every two years for up-dates and ascertainment of breast cancer outcome. In the latest report (1995), the cohort of over 121 000 women had been followed-up for 16 years, resulting in over 700 000 person–years of observation and 1935 cases of breast cancer. The results were similar to those reported

Table 1. Summary of cohort studies on post-menopausal oestrogen-progestogen therapy and breast cancer

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Hunt *et al*. (1987)	Menopause clinics in the UK, 1978–82, counsel for menopausal symptoms	Cohort of 4 544 women who used hormones ≥ 1 year; 17 830 person–years; follow-up through contact letters and medical record data; exposure data through baseline interview	**Incidence**: 50 cases Any use of hormones: incidence: SIR, 1.6 (95% CI, 1.2–2.1) Time since first intake: trend for incidence ≥ 10 years: SIR, 3.1 (95% CI, 1.5–5.6) 43% of all treatment episodes combined with progestogens, analyses by subcategories not feasible	Possible selection bias in study of mortality Heterogeneous exposure regimens with regard to progestogens
Bergkvist *et al*. (1989)	Six counties in Sweden, 1977–83; women given hormonal therapy; age, ≥ 35 years	Population-based cohort; 23 244 women; 133 375 person–years; follow-up through record linkage with National Cancer Registry; exposure data from prescriptions; questionnaire data in a random sample; cohort, case–cohort and case–control analyses	**Incidence**: 253 cases Regimens, duration ≥ 9 years: oestrogens alone: RR, 1.8 (95% CI, 1.0–3.1) oestrogen and progestogens > 6 years: RR, 4.4 (95% CI, 0.9–22)	Low power to examine long-term progestogen combined regimens
Colditz *et al*. (1992)	Nurses' Health Cohort, USA, 1976–88, 30–55 years at entry	Cohort, 118 300 nurses at post-menopausal ages; 480 665 person–years; individual follow-up through questionnaires, 95% complete for incidence and 98% for deaths; internal comparisons; baseline questionnaire, 1976; up-dated questionnaires every 2 years	**Incidence**: 12 years' follow-up, 1 050 cases Post-menopausal hormones: any use: RR,1.1 (95% CI, 1.0–1.2) current use: RR, 1.3 (1.1–1.5) Oestrogen and progestogen, current intake: RR, 1.5 (95% CI, 1.0–2.4)	Main relationship with current intake
Yuen *et al*. (1993)	Uppsala health care region, Sweden, 1977–80; women given hormonal therapy	See Bergkvist *et al*. above; follow-up through record linkage with Causes of Death Registry; comparison with external, *corrected* mortality rates; exposure data from prescriptions	**Mortality**, 12 years' follow-up, 73 deaths Any use: oestradiol and progestogen: SMR, 0.8 (95% CI, 0.4–1.3)	Exposure only from prescription data (population rates corrected for prevalent cases)

Table 1 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Schairer *et al*. (1994)	Populations in 27 cities, USA, breast cancer screening, 1980–89	Cohort of 49 017 participants; 313 902 person–years; follow-up through interviews and questionnaires; information on exposure and risk factors from questionnaires	**Incidence**, both in-situ and invasive tumours, 1 185 cases Conjugated oestrogens, combinations with progestogens All tumours: any use: oestrogens and progestogens: RR, 1.2 (95% CI, 1.0–1.6) In-situ tumours: oestrogens and progestogens: any use: RR, 2.3 (95% CI, 1.3–3.9) current use: RR, 2.4 (95% CI, 1.2–4.7) past use: RR, 2.3 (95% CI, 1.0–5.4)	Risk relationship limited to in-situ tumours Low power to assess long-term duration of oestrogen and progestogen regimens
Risch & Howe (1994)	Inhabitants of Saskatchewan, Canada, 43–49 years of age, 1976–91	Registry-based cohort; 33 003 women followed-up through linkage to cancer registry; 448 716 person–years; exposure data from prescription roster	Incidence: 15 years' follow-up, 742 cases Conjugated oestrogens, added progestogens Oestrogens and progestogens: no significant risk increase	Limited power to study long-term oestrogen–progestogen combined treatment
Colditz *et al*. (1995)	Nurses' Health Cohort, see Colditz *et al*. (1992) above	Cohort of 121 700 nurses; 725 550 person–years; baseline questionnaire in 1976, questionnaires every two years, up-dates on exposure and outcome (follow-up)	Incidence: 16 years' follow-up, 1 935 cases Conjugated oestrogens and added progestogens Current intake: conjugated oestrogen: RR, 1.3 (95% CI, 1.1–1.5) Any use: oestrogen and progestogen: RR, 1.4 (95% CI, 1.2–1.7)	No relationship with past use Detection bias unlikely First study to show an increased risk for death with hormonal therapy
Persson *et al*. (1996)	See Yuen *et al*. (1993) above, Swedish cohort	22 597 women with registered hormone prescriptions; record linkage follow-up of incidence and mortality; risk factor data in questionnaire survey	Incidence, 13 years' follow-up, 634 cases Prescriptions for various regimens any use: oestradiol/levonorgestrel: RR, 1.3 (95% CI, 1.1–1.4)	No data on duration

Table 1 (contd)

Reference	Study base	Design: cohort, follow-up, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Persson *et al*. (1997)	Participants in mammography screening, Uppsala, Sweden, 1990–92, 40–74 years	Cohort of 30 982 women participating in two screening rounds; follow-up through screening and in diagnostic registry of pathology department; questionnaires at visits; nested case–control approach.	Follow-up through June 1995: 435 cases (87% invasive), 1 740 controls any use: all compounds: odds ratio, 1.1 (95% CI, 0.8–1.4) Duration ≥ 11 years: Oestradiol and progestogen: odds ratio, 2.4 (95% CI, 0.7–8.6) Oestradiol–conjugated oestrogen alone: odds ratio, 1.3 (95% CI, 0.5–3.7)	Low power in regimen subgroups

SIR, standardized incidence ratio; SMR, standardized mortality ratio

earlier, showing increased risks for current intake of conjugated oestrogens alone (relative risk, 1.3; 95% CI, 1.1–1.5) and for combinations with progestogens (chiefly medroxyprogesterone acetate; relative risk, 1.4; 95% CI, 1.2–1.7). Owing to the low statistical power, no data were presented on the risk for use of combinations with progestogens by categories of duration.

Schairer *et al.* (1994) followed a cohort of some 49 000 women participating in a breast cancer screening programme in several cities in the United States. To ascertain data on their exposure, risk factors and occurrence of breast cancer, the women were sent questionnaires or were interviewed. After a mean follow-up of 7.2 years, 1185 cases of in-situ or invasive breast cancer had occurred. For both types of tumour together, any use of oestrogens plus progestogens yielded a relative risk of 1.2 (95% CI, 1.0–1.6); for in-situ tumours only, a significant excess risk was noted (2.3; 95% CI, 1.3–3.9). The risk estimates were 2.4 (95% CI, 1.2–4.7) for current use and 2.3 (95% CI, 1.0–5.4) for past use.

Risch and Howe (1994) used a prescription database to establish a cohort of some 33 000 women in the province of Saskatchewan, Canada, who had received hormonal treatment. Through linkage with the population-based cancer registry, 742 newly diagnosed cases of breast cancer were ascertained during 15 years of follow-up. Use of oestrogens plus progestogens was not associated with a significant change in the risk for breast cancer. In this study, the power to show any effects of combined use was low, with only three exposed cases.

Persson *et al.* (1997) investigated breast cancer incidence in relation to hormonal treatment in a cohort of some 31 000 women who had participated in mammography screening on two regular visits. Data on their exposure to hormones and reproductive factors were collected through interviews at the visits. In all, 435 new cases of breast cancer were ascertained during five years of follow-up, chiefly through mammography screening but also through linkage to a local pathology register; 87% of the cases were invasive. In a nested case–control study, use of oestradiol plus a progestogen (usually norethisterone acetate) for 11 years or longer was associated with a relative risk of 2.4 (95% CI, 0.7–8.6), whereas use of oestradiol alone was associated with a relative risk of 1.3 (95% CI, 0.5–3.7). The risk for combined long-term use seemed to be greater than for other use, but the difference in risk estimates between the two treatment types was not statistically significant.

2.1.2 *Case–control studies*

The results of case–control studies on use of post-menopausal oestrogen–progestogen therapy and breast cancer are shown in Table 2.

In a case–control study in Denmark of 1486 cases and 1336 controls, Ewertz (1988) had the opportunity to examine the effects of various treatment regimens. Data were collected through mailed questionnaires, filled in by 88% of the cases and 78% of the controls, with details on reproductive factors and hormone use. Women who had ever used oestradiol–progestogen combined treatments had a non-significantly increased relative risk of 1.4 (95% CI, 0.9–2.1) compared with a relative risk of 1.0 (95% CI, 0.8–1.3) for use of oestrogen only. Analyses by duration were not possible owing to the small numbers.

Table 2. Summary of case–control studies of post-menopausal oestrogen-progestogen therapy and breast cancer

Reference	Study base	Design: number of cases and controls, data	Risk relationships: relative risk (RR) and 95% confidence intervals (95% CI)	Comments
Ewertz (1988)	Denmark, 1983–84, > 70 years	Population-based, national. 1 486 cases/1 336 controls (random); self-administered, mailed questionnaire	Oestradiol and oestradiol–progestogen combinations: Combination oestradiol–progestogens any use: RR, 1.4 (95% CI, 0.9–2.1)	First study to show similar risk with combined treatments
Kaufman *et al*. (1991)	Metropolitan areas, primarily eastern USA, 1980–86, post-menopausal women, 40–69 years	Hospital-based; 1 686 cases/ 2 077 controls; interviews	Oestrogens and progestogens, any use: RR, 1.7 (95% CI, 0.9–3.6)	Low power for long-term treatment with oestrogen-progestogen combinations
Yang *et al*. (1992)	British Columbia, Canada, 1988–89, post-menopausal women, < 75 years	Population-based; 699 cases/685 controls (random); mailed questionnaire	Mainly conjugated oestrogens: any use: oestrogens and progestogens: RR, 1.2 (95% CI, 0.6–2.2)	Low power in analyses of use of oestrogen plus progestogen
Stanford *et al*. (1995)	13 counties, Washington State, USA, 1998–90, cancer survey system, white women, 50–64 years	Population-based; 537 cases/492 controls (random-digit dialling); personal interviews	Conjugated oestrogens, added progestogens: Combined, any use: odds ratio, 0.9 (95% CI, 0.7–1.3) Duration ≥ 8 years: odds ratio, 0.4 (95% CI, 0.2–1.0)	Low power for long-term use
Newcomb *et al*. (1995)	Four states in northern/eastern USA, tumour registries, 1988–91, age < 75	Population-based; 3 130 cases/ 3 698 controls (from rosters); personal interviews	'Non-contraceptive hormones, oestrogens and progestogen combinations': any use of progestogen in combination: RR, 1.0 (95% CI, 0.8–1.3) Duration ≥ 15 years: RR, 1.1 (95% CI, 0.5–2.3) No trend with timing	Limited power for long-duration categories No effects in sub-groups

In a study by Kaufman *et al.* (1991), 1686 case and 2077 hospital-based control women were interviewed. Only 1% of the controls had used oestrogen–progestogen combinations. Women who had ever used such combined treatments showed an elevated relative risk, but with wide confidence limits (relative risk, 1.7; 95% CI, 0.9–3.6). Use of oestrogen only, at any time or for several years, was not associated with an excess risk.

Yang *et al.* (1992) examined the effects of conjugated oestrogens and combinations with progestogens in a population-based study of 699 cases and 685 controls. Data on exposure and risk factors were acquired from mailed questionnaires. Use of oestrogens plus progestogens, reported by 3% of the controls, was linked to a risk near the baseline (1.2; 95% CI, 0.6–2.2).

Stanford *et al.* (1995) conducted a population-based study on 537 cases of breast cancer and 492 controls in Washington State, United States, using random-digit dialling to recruit controls. Data from personal interviews revealed that 21% of the controls had used combined treatments. The relative risk was 0.9 (95% CI, 0.7–1.3) for any use and 0.4 (95% CI, 0.2–1.0) for use for eight years and more.

Newcomb *et al.* (1995) presented data on combined use from the largest population-based study of breast cancer hitherto reported, 3130 cases and 3628 controls, from four states in northern and eastern United States. Data obtained at interview showed that about 4% of the healthy controls had used combined progestogen treatment, but few of these women had had long-term treatment. Any use of progestogen combinations was associated with a baseline risk (1.0; 95% CI, 0.8–1.3), whereas use for 15 years or longer (based on 15 cases and 15 controls) gave a relative risk of 1.1 (95% CI, 0.5–2.3). There was no indication of a trend with categories of duration of intake.

2.1.3 *Pooled analysis of individual data*

The Collaborative Group on Hormonal Factors in Breast Cancer (1997) compiled and re-analysed the original data from 51 studies, of which 22 provided data on the hormonal constituents of the preparations. Of the eligible women in the re-analysis, such data were available for 4640, 12% of whom had received combinations of oestrogens and progestogens. Current use or last use 1–4 years before diagnosis, with a duration of less than five years, was associated with a relative risk of 1.2 (95% CI, 0.8–1.5), and a duration of five years or longer with a relative risk of 1.5 (95% CI, 0.9–2.2). These estimates were not statistically different from those for the corresponding categories of oestrogen-only use (RR, 1.3).

These limited data do not provide a basis for firm conclusions on the effects of oestrogen–progestogen use on the risk for breast cancer. One major limitation is the small amount of information available on use for many years. Overall, there is little evidence to suggest that added progestogens confer a risk different from that associated with oestrogens alone.

2.2 Endometrial cancer

Women who use oestrogen–progestogen regimens have a lower occurrence of endometrial hyperplasia than those who use oestrogen-only therapy, especially when the progestogen is used for 10 or more days per month or continuously with oestrogen (Sturdee *et al.*, 1978; Thom *et al.*, 1979; Paterson *et al.*, 1980; Postmenopausal Estrogen/Progestin Interventions Trial, 1996; Speroff *et al.*, 1996). Depending on the type, dose and duration of progestogen supplementation, it may be given for 10–14 days once every three months as well, in a so-called 'long cycle' regimen. In two studies in which women were followed-up for one to two years while receiving a 14-day supplementation with 10 or 20 mg medroxyprogesterone acetate, less than 2% developed hyperplasia (Ettinger *et al.*, 1994; Hirvonen *et al.*, 1995). In contrast, in a Scandinavian randomized controlled trial, a higher occurrence of hyperplasia was found in women who received a 10-day supplementation of 1 mg norethisterone (6%) than in women who received monthly progestogen supplementation (< 1%) (Cerin *et al.*, 1996). Although information is available on endometrial hyperplasia, there is much less information on combined oestrogen–progestogen therapy and the risk for endometrial cancer.

2.2.1 *Randomized trial*

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

2.2.2 *Cohort studies*

Only three cohort studies have provided information on the risk for endometrial cancer among women who used combined therapy relative to women who did not use any post-menopausal hormonal therapy.

Hammond *et al.* (1979) (see Table 5 of the monograph on 'Post-menopausal oestrogen therapy') followed-up approximately 600 hyperoestrogenic women, roughly half of whom used either oestrogen-only or oestrogen–progestogen preparations and half of whom did not use hormones. No cases of endometrial cancer were observed among the 72 women who received oestrogen–progestogen therapy, whereas three cases were observed among the non-users.

In the cohort study of Gambrell (1986) (summarized in Table 5 of the monograph on 'Post-menopausal oestrogen therapy'), the incidence of endometrial cancer among women who used combined hormonal therapy (eight cases/16 327 woman–years) was lower than that among women who did not use any hormonal therapy (nine cases/4480 woman–years) [no age-adjusted results were reported].

A Swedish cohort study (Persson *et al.*, 1989) (see Table 5 of the monograph on 'Post-menopausal oestrogen therapy') of endometrial cancer occurrence among women using combination therapy identified through pharmacy records in comparison with the population rates in the Uppsala health care region, showed that women using oestrogen-only

therapy (predominantly oestradiol) had an increased risk (48 cases observed versus 34.3 expected; relative risk, 1.4; 95% CI, 1.1–1.9), whereas no increase in risk was found in women using combination therapy (seven cases observed versus 7.6 expected; relative risk, 0.9; 95% CI, 0.4–2.0).

2.2.3 *Case–control studies*

The case–control studies on post-menopausal oestrogen–progestogen therapy and endometrial cancer risk are summarized in Table 3.

Jick *et al.* (1993) studied women who were members of a large health maintenance organization in western Washington State, United States. Women with endometrial cancer were identified from the tumour registry of the organization, and the control women were other members; both groups included only those 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 post-menopausal hormonal therapy was ascertained from the pharmacy database. Relative to women who had never or briefly (≤ six months) used menopausal hormones, those who had used any oestrogen–progestogen therapy within the previous year had a slightly increased risk (odds ratio, 1.9; 95% CI, 0.9–3.8), after adjustment for age, calendar year, age at menopause, body mass index and history of oral contraceptive use, although those with a longer duration of use (≥ three years) did not. Former users (last use ≥ one year earlier) had no increase in risk (odds ratio, 0.9; 95% CI, 0.3–3.4). Women with recent (within the past year) oestrogen-only use (32 cases and 26 controls) had a strongly elevated risk for endometrial cancer (odds ratio, 6.5; 95% CI, 3.1–13), but no increased risk was seen for past users of oestrogen alone (odds ratio, 1.0; 95% CI, 0.5–2.0).

A multicentre study was conducted with 300 menopausal women with endometrial cancer diagnosed at seven hospitals, in Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina, United States, and 207 age-, race- and residence-matched control women from the general population (Brinton *et al*., 1993). Any oestrogen–progestogen therapy for three months or longer was reported by 4% of the case women and 5% of the control women (odds ratio, 1.8; 95% CI, 0.3–0.7), after adjustment for age, parity, weight and years of oral contraceptive use. Use of oestrogens only was associated with a relative risk of 3.4 (95% CI, 1.8–6.3).

Pike *et al.* (1997) identified 833 women with endometrial cancer from a population-based cancer registry in Los Angeles County, United States, and matched them to control women of similar age and race (white) who lived in the same neighbourhood block as the matched case or to 791 randomly identifed women on the United States Health Care Financing Administration computer tapes. The risk for endometrial cancer was investigated among women who had used unopposed oestrogens, oestrogen–progestogen with progestogen added for fewer than 10 days per cycle, oestrogen–progestogen with progestogen added for 10 or more days per cycle and continuous combined therapy. An elevated risk was noted for women with longer use of oestrogen–progestogen if the progestogen

Table 3. Summary of case–control studies of post-menopausal oestrogen–progestogen therapy and endometrial cancer risk, by number of days progestogen was added per cycle and duration, when available

Reference	Location; period	Age (years)	Source of controls	Participation (%)		Type/measure of combined therapy	No. of subjects		Adjusted odds ratio (95% CI)
				Cases	Controls		Cases	Controls	
Jick *et al.* (1993)	Washington; USA; 1979–89	50–64	Members of health maintenance organization	NR	NR	No use, ≤ 6 months' use	97	606	Referent
						Any use within past year[a]	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)
						Any use ≥ 1 year previously	6	64	0.9 (0.3–3.4)
Brinton *et al*. (1993)	Five US areas; 1987–90	20–74	General population	86	66	No use	222	176	Referent
						Any use for ≥ 3 months[a]	11	9	1.8 (0.6–4.9)
Pike *et al.* (1997)	California, USA; 1987–93	50–74	General population (neighbours)	57	NR	*Any use, progestogen < 10 days/cycle*[b]			
						Duration (months)			
						0	759	744	Referent
						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/cycle			
						Duration (months)			
						0	754	703	Referent
						1–24	37	30	1.0 (NR)
						25–60	19	25	0.7 (NR)
						> 60	23	33	1.1 (NR)
						Any use, progestogen all days/cycle			
						Duration (months)			
						0	739	710	Referent
						1–24	45	41	1.1 (NR)
						25–60	25	15	1.4 (NR)
						> 60	24	25	1.3 (NR)

Table 3 (contd)

Reference	Location; period	Age (years)	Source of controls	Participation (%)		Type/measure of combined therapy	No. of subjects		Adjusted odds ratio (95% CI)
				Cases	Controls		Cases	Controls	
Beresford *et al.* (1997)	Washington, USA; 1985–91	45–74	General population	72	73	No use, ≤ 6 months' use	337	685	Referent
						Any use[c]	67	134	1.4 (1.0–1.9)
						Progestogen ≤ 10 days/cycle			
						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/cycle			
						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)
						Current use only			
						Progestogen ≤ 10 days/cycle			
						Duration (months)			
						6–59	11	13	2.2 (0.9–5.2)
						≥ 60	14	9	4.8 (2.0–11)
						Progestogen > 10 days/cycle			
						Duration (months)			
						6–59	12	48	0.7 (0.4–1.4)
						≥ 60	12	15	2.7 (1.2–6.0)

CI, confidence interval; NR, not reported

[a] Women with unopposed oestrogen use included

[b] Use of unopposed oestrogen and other combined therapy adjusted for in the analysis

[c] Women with unopposed oestrogen use excluded

was added for fewer than 10 days per cycle, but not if it was added for 10 or more days per cycle; the odds ratio was 1.9 (95% CI, 1.3–2.7) for each additional five years of use and 1.1 (95% CI, 0.8–1.4) after adjustment for age at menarche, time to regular cycles, parity, duration of incomplete pregnancies, weight, duration of breast-feeding, amenorrhoea, smoking, duration of oral contraceptive use, age at menopause and the other hormonal treatments. No increase in risk was noted for women who had had continuous combined therapy; the odds ratio for each additional five years of use was 1.1 (95% CI, 0.8–1.4). Each additional five years of unopposed oestrogen use was associated with a roughly twofold elevation in risk, with an odds ratio of 2.1 for each five-year period (95% CI, 1.9–2.5).

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 only oestrogen–progestogen therapy. Women with endometrial cancer were identified from a population-based cancer registry and compared with control women from the general population in western Washington State, United States. After some exclusions, 394 cases and 788 controls were available for the analysis. Relative to women who had never or briefly (≤ six months) used menopausal hormones, women who had used only oestrogen–progestogen therapy had a slightly increased risk (odds ratio, 1.4; 95% CI, 1.0–1.9), after adjustment for age, body mass and county of residence. An elevated risk was noted among women with five or more years of exclusive oestrogen–progestogen use, regardless of the number of days a progestogen had been used. For women using oestrogen–progestogen therapy for ≤ 10 days/cycle, the odds ratio was 3.7 (95% CI, 1.7–8.2); the risk was similar for use on more than 10 days/cycle (odds ratio, 2.5; 95% CI, 1.1–5.5), and similar results were found when the analysis was restricted to current oestrogen–progestogen users. The small numbers of women (eight cases and 11 controls) who had used only oestrogen–progestogen therapy for five or more years, with the highest dose of medroxyprogesterone acetate (10 mg) added for more than 10 days/cycle, still had a significant increase in risk (odds ratio, 2.7; 95% CI, 1.0–6.8). Unopposed oestrogen therapy taken for at least six months was associated with a relative risk for endometrial cancer of 4.0 (95% CI, 3.1–5.1).

In summary, most of the small number of epidemiological studies conducted to date have shown no effect or a modest increase in the risk for endometrial cancer among women using combined hormonal therapy relative to women who had not used menopausal hormones. In all of the studies summarized above, a lower risk for endometrial cancer was associated with use of combined hormonal therapy than with oestrogen-only therapy. The two studies that were large enough to evaluate cyclic use of progestogen reported two- to fourfold increases in risk associated with use of oestrogen–progestogen if the progestogen was added for approximately 10 days or less per cycle (Beresford *et al*., 1997; Pike *et al*., 1997), but only one found an elevated risk if the progestogen was added for 10 days or more per cycle (Beresford *et al*., 1997). It is not clear whether the few cancers appearing in women taking oestrogens and progestogens represent failure of the progestogen to protect the endometrium or failure of the women to take the prescribed progestogen.

2.3 Ovarian cancer

2.3.1 *Cohort study*

In the cohort study of Hunt *et al*. (1987) described in section 2.1.1, six cases of ovarian cancer were observed up to 1986 among users of post-menopausal hormonal therapy versus 6.92 expected, corresponding to a nonsignificant SIR of 0.9 (95% CI, 0.3–1.9). In a follow-up until 1988 on mortality only (Hunt *et al.*, 1990), four more deaths from ovarian cancer were observed versus 6.33 expected (SMR, 0.63; 95% CI, 0.0–1.4).

2.3.2 *Case–control study*

In a multicentre case–control study of 377 cases of ovarian cancer and 2030 controls conducted between 1976 and 1985 in various areas of Canada, Israel and the United States (Kaufman *et al.*, 1989), only 1–2% of cases and controls had ever used combination post-menopausal therapy. The multivariate relative risk was 0.7 (95% CI, 0.2–1.8).

2.4 Liver cancer

Persson *et al.* (1996) studied cancer risks after post-menopausal hormonal therapy in a population-based cohort of 22 579 women aged 35 or more living in the Uppsala health care region in Sweden. Women who had ever received a prescription for post-menopausal hormonal therapy between 1977 and 1980 were identified and followed until 1991; information on hormone use was obtained from pharmacy records. The expected numbers of cases were calculated from national incidence rates. There was no information on smoking or alcohol consumption. The SIR for all cancers was 1.0 (95% CI, 0.9–1.0). There were 43 cancers of the hepatobiliary tract, comprising 14 hepatocellular carcinomas, five cholangiocarcinomas, 23 gall-bladder cancers and one unclassified. The expected number was 73.2, giving an SIR of 0.6 (95% CI, 0.4–0.8) for any type of post-menopausal hormonal therapy. The SIRs for treatment with oestradiol combined with levonorgestrel were 0.6 (95% CI, 0.1–2.3) for hepatocellular carcinoma and 0.7 (95% CI, 0.0–3.8) for cholangiocarcinoma. There was no information on infection with hepatitis viruses.

2.5 Colorectal cancer

In most of the studies on the influence of post-menopausal hormonal therapy on the risk for colorectal cancer, it was not possible to distinguish formulations. Only a few investigations provided separate information on combinations of oestrogens and progestogens, but in all instances the use of opposed hormonal therapy was very limited and was generally restricted to recent use. The available studies are summarized in Table 4.

2.5.1 *Cohort studies*

In a Canadian record linkage study described in detail in the monograph on ‘Post-menopausal oestrogen therapy’ (Risch & Howe, 1995), no case of colon or rectal cancer occurred in women who had used both oestrogens and progestogens and not oestrogens only; however, the number of such women (171) was small. One case of colon cancer

Table 4. Studies on use of post-menopausal oestrogen–progestogen therapy and colorectal cancer

Reference	Country	Population (follow-up) or cases/controls	Relative risk (RR) (95% confidence interval [CI]) (any versus no use)		Adjustment/comments
			Colon	Rectum	
Cohort					
Risch & Howe (1995)	Canada	33 003 (14 years) 230 cancers	–	–	Age No case of colorectal cancer among 171 hormone users
Persson *et al*. (1996)	Sweden	23 244 (13 years) 233 cancers, 62 deaths	0.6 (0.4–1.0)	0.8 (0.4–1.3)	Age No effect among 5 573 hormone users Refers to a fixed combined brand. RR for colon cancer mortality, 0.6 (95% CI, 0.2–1.1)
Troisi *et al*. (1997)	USA	33 779 (7.7 years) 313	1.4 (0.7–2.5)		Age (but unaltered by education, body mass index, parity or use of combined oral contraceptives)
Case–control					
Newcomb & Storer (1995)	Wisconsin, USA	694/1 622	Recent use: 0.54 (0.28–1.0)	1.1 (0.51–2.5)	Age, alcohol, body mass index, family history of cancer and sigmoidoscopy Combined post-menopausal hormonal therapy was used by 18% of users

occurred among 648 women who had used both oestrogen and progestogen and also oestrogens alone. [No estimates for relative risks were provided in the paper.]

In the Swedish cohort followed by Persson *et al*. (1996) (see section 2.4), 5573 women (i.e. about 25% of the total cohort) had received prescriptions for combined post-menopausal hormonal therapy consisting of 2 mg oestradiol and 250 mg levonorgestrol for 10–21 days. They had an age-adjusted relative risk of 0.6 (95% CI, 0.4–1.0) for colon cancer and 0.8 (95% CI, 0.4–1.3) for rectal cancer. The rate of mortality from colorectal cancer was marginally decreased (relative risk, 0.6; 95% CI, 0.2–1.1).

In the North American cohort described in detail in the monograph on 'Post-menopausal oestrogen therapy' (Troisi *et al*., 1997), the age-adjusted relative risk associated with use of combined oestrogen and progestogen therapy (i.e. 16% of woman–years of hormone therapy use) for colon cancer was 1.4 (95% CI, 0.7–2.5); there were insufficient numbers of exposed cases to evaluate the risk for rectal cancer or for cancers of the colon at subsites.

2.5.2 *Case–control study*

Only one case–control investigation (Newcomb & Storer, 1995), described in detail in the monograph on 'Post-menopausal oestrogen therapy', included detailed information on the influence of recent use of post-menopausal hormonal therapy on the risk for colon cancer. The relative risk, adjusted for age, alcohol, body mass index, family history of cancer and sigmoidoscopy, was 0.54 (95% CI, 0.28–1.0; 11 cases) and that for rectal cancer was 1.1 (95% CI, 0.51–2.5; 8 cases). Use of this formulation had been reported by 18% of hormone users, and the risk estimates were close to those for use of post-menopausal oestrogen therapy of any type.

2.6 Cutaneous malignant melanoma

2.6.1 *Cohort study*

In the study of Persson *et al*. (1996) (see section 2.4), an age-adjusted relative risk of 0.6 (95% CI, 0.3–1.1) was found for cutaneous malignant melanoma, with nine cases.

2.6.2 *Case–control study*

Østerlind *et al*. (1988) (see Table 11 of the monograph on 'Post-menopausal oestrogen therapy') reported a multivariate relative risk adjusted for age, naevi and sunbathing for any use of oestrogens and opposed progestogens of 1.5 (95% CI, 0.8–2.8), on the basis of 28 users among cases and 45 among controls.