COMBINED ESTROGEN–PROGESTOGEN MENOPAUSAL THERAPY

These substances were considered by a previous Working Group, in June 1998 (IARC, 1999), under the title 'Post-menopausal hormonal therapy'. Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Introduction

Estrogen–progestogen menopausal therapy involves the co-administration of an estrogen and a progestogen to peri- or menopausal women. While it is indicated most clearly for control of menopausal symptoms, the use of estrogens with or without progestogens has expanded to include the treatment or prevention of a range of chronic conditions that are associated with ageing. Such widespread, long-term use was often perceived as a 'replacement', in that it physiologically reconstituted vital functions that were lost with menopausal ovarian failure. This pattern was propitiated by the 'medicalization' of the menopause, which was perceived as pathological rather than as an expected and natural event in life. Evidence from the Women's Health Initiative, which showed a clearly harmful effect of the use of estrogen–progestogen combinations, has modified this attitude; as a result, use of the term 'replacement' has diminished. Patterns of exposure are also changing rapidly as the use of hormonal therapy declines, the indications are restricted and the duration of the therapy is reduced.

Combined estrogen–progestogen formulations are available for oral and transdermal administration, although separate administration of each component is still frequent. Progestogens are available orally, while estrogen may be administered orally, transdermally or transvaginally. The timing of exposure to these hormones may be continuous (both estrogen and progestogen at set daily doses), sequential (estrogen daily with progestogen for the last 10–14 days of the cycle) or cyclical (as with sequential, but including 7 days without hormonal exposure).

Chemical and physical data and information on the production and use of individual ingredients used in formulations of combined estrogen–progestogen therapy are given in Annex 1. Trade names and composition of combined products used in hormonal menopausal therapy are presented in Annex 4.

1.2 Historical overview

The earliest forms of hormone used for the treatment of the effects of natural ovarian failure or surgical removal of the ovaries were natural extracts of ovarian tissue, placenta and urine from pregnant women. These extracts contained both estrogen and progestogen, as well as other substances. Experiments in the late nineteenth century demonstrated the clinical benefit of injecting these extracts to alleviate menopausal symptoms, particularly in women who had premature natural or surgically induced menopause (IARC, 1999).

The identification and purification of ovarian hormones in the late 1920s and 1930s enabled wider clinical use of hormonal menopausal therapy. Esterone, estriol and progesterone were identified in 1929, followed by estradiol in 1936 (IARC, 1979). Progesterone was isolated in crystalline form in 1934. Although the use of estrogen and progesterone injections was reported in the 1930s (Hirvonen, 1996), for several subsequent decades, menopausal symptoms were treated mainly with estrogen alone rather than with combined estrogen–progestogen therapy. The extraction of conjugated estrogens from the urine of pregnant mares led to the marketing in 1943 of Premarin, the first orally active and readily available estrogen (IARC, 1999).

Further developments followed the production of the orally active progestogens, norethisterone (also known as norethindrone in the USA) in 1950 and norethynodrel in 1952, which were ultimately used in combined oral hormonal contraceptives (see the monograph on ‘Combined estrogen–progestogen contraceptives’). During the 1960s and early 1970s, hormonal menopausal therapy was most common in the USA and usually comprised estrogen therapy without a progestogen (Davis *et al.*, 2005). Estrogen–progestogen therapy was used by some clinicians, particularly in Europe, primarily for better control of uterine bleeding during treatment (IARC, 1999). Doses in hormonal menopausal therapy at that time were relatively high compared with current standards, and 1.25 mg conjugated equine estrogens were reportedly used in the USA (Pasley *et al*., 1984). Use of hormonal menopausal therapy increased through the 1960s until the mid-1970s, particularly in women who experienced natural menopause.

An association between estrogen therapy and endometrial cancer described in 1975 (Smith *et al*., 1975; Ziel & Finkle, 1975) led to a rapid decline in levels of estrogen use, and by 1980 reached those noted in the mid-1960s (Kennedy *et al.*, 1985). Many clinicians and researchers advocated that a progestogen be added to estrogen when treating menopausal women with a uterus to offset the proliferating action of estrogen with the differentiating action of progestogen. Studies that began in 1979 (Thom *et al*., 1979; Whitehead *et al*., 1981) demonstrated that progestogens attenuated the risk for endometrial cancer associated with the use of estrogen alone. In the early 1980s, the use of combined estrogen–

progestogen became more common, while greater attention to endometrial monitoring was recommended for users of estrogen only (American College of Physicians, 1992).

Ultimately, prescriptions for menopausal estrogens began to rise again with a significant increase in the use of combined estrogen–progestogen that continued throughout the 1990s. However, regional differences persisted; for example, combined therapy remained less common in the USA compared with the United Kingdom (Kennedy *et al.*, 1985; Townsend, 1998).

As use expanded in the 1980s and 1990s, the menopause was increasingly defined as a hormone deficiency that could be treated through 'replacement' of the missing hormones. Not only was estrogen established as a preventive therapy for osteoporosis in oophorectomised women (Aitken *et al*., 1973; Lindsay *et al*., 1980), but it was suggested that 'hormone replacement therapy' could reduce the risk for a range of related conditions, including cognitive decline (Campbell & Whitehead, 1977) and cardiovascular disease (Ross *et al*., 1981; Greendale *et al.*, 1999). A variety of social and medical factors stimulated an increase in use, including evidence of supporting benefits, corporate promotion of hormonal therapy (Palmlund, 1997) and increasing interest in women's health issues.

Estrogen–progestogen therapy became increasingly used for longer periods by older women and for indications far removed from menopausal symptoms. Combined therapy also became the norm for women with a uterus whereas estrogen therapy alone was largely limited to women who had surgically induced menopause. Use continued to increase despite reports of a greater risk for breast cancer associated with hormonal therapy (Hoover *et al*., 1976; Colditz *et al*., 1993), perhaps because of uncertainties in the estimation of the magnitude of this risk (Grady *et al*., 1992).

During this time, prevalence of current use remained lower in non-white women and lower socioeconomic groups (Stafford *et al.*, 1998). Increase in the use of hormonal therapy was greater outside of than within the USA (IARC, 1999).

In response to the increase in use of concomitant estrogens and progestogens, a number of combined formulations were developed in the mid-1990s, including both continuous combinations (fixed daily dose of estrogen and progestogen) and cyclical combinations (fixed daily dose of estrogen with a progestogen component on a given number of days per month). Intermittent administration of progestogen, as with the cyclical formulations, generally results in withdrawal uterine bleeding, whereas continuous administration does not. A transdermal patch that contained estrogen and progestogen was marketed in 1998.

There were some indications that the benefit of hormonal therapy was uncertain, and observational studies that suggested this benefit were unable to rule out confounding. The assumptions that were fundamental to the expansion of hormonal therapy came under particular scrutiny following the publication of the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998. HERS showed no protective effect against recurrent events of cardiovascular disease in women with known cardiovascular problems who were randomized to conjugated equine estrogens and medroxyprogesterone (Hulley *et al*., 1998). The initial suggestion of a temporal pattern of early harm and later benefit that emerged in this study was not confirmed on further follow-up (Grady *et al*., 2002a). As a result of dampened

enthusiasm for hormonal therapy, levels of use peaked in 2000 and plateaued in subsequent years (Hersh *et al*., 2004).

A more dramatic change in patterns of practice followed the results of the Women's Health Initiative (WHI) trial in July 2002. Women with no history of known cardiovascular disease were randomized to receive combined hormonal therapy. Contrary to expectations based on observational data, WHI showed that rates of cardiovascular events were higher in women exposed to conjugated equine estrogens and medroxyprogesterone than in those exposed to placebo (Rossouw *et al*., 2002; Manson *et al*., 2003; Majumdar *et al*., 2004). In addition, it was reported that conjugated equine estrogens and medroxyprogesterone increased the risk for other adverse events (Chlebowski *et al.*, 2003; Rapp *et al*., 2003; Shumaker *et al*., 2003; Wassertheil-Smoller *et al.*, 2003) that were not offset by reduced risks for fractures and colorectal cancer. Furthermore, overall quality of life was not improved by treatment compared with placebo (Hays *et al*., 2003a). While the results were not as dramatic, publication of the second WHI trial that involved administration of estrogen alone (Women's Health Initiative Steering Committee, 2004) reinforced a new consensus on the increase in adverse vascular outcomes associated with hormonal menopausal therapy.

Although some doubts were raised regarding the reliability and generalizability of the WHI results (Shapiro, 2003; Strickler, 2003), practice patterns changed tremendously. Prescriptions in the USA fell by 50% during the 18 months that followed the results of the WHI (Hersh *et al*., 2004; Majumdar *et al*., 2004). Internationally, similar reductions occurred in western Europe and most of the Western Pacific (Table 1). The decline in the use of hormonal therapy was particularly marked for combined estrogen–progestogen therapy.

Use has begun to shift towards lower-dose formulations (e.g. 0.30 mg conjugated equine estrogens and 1.5 mg medroxyprogesterone). Simultaneously, there is less use of hormonal menopausal therapy among older women. Patterns of use will probably change further as numerous professional organizations continue to recommend the use of lower doses, shorter durations of use and limiting use to more severe menopausal symptoms (US Preventive Service Task Force, 2002; North American Menopause Society, 2004; Wathen *et al*., 2004).

1.3 Preparations of estrogen–progesterone menopausal therapy

A variety of products are available for use in combined estrogen–progestogen menopausal therapy, either as individual estrogen and progestogen components that can be co-administered or as a combined product. The use of individual components may allow better tailoring compared with combined products. A number of combined formulations are described in Annex 4.

Available estrogen products can be defined by their estrogen form, dose and mode of delivery. The most common estrogens available for hormonal menopausal therapy are conjugated equine estrogen, conjugated plant-based estrogen, estradiol and ethinylestradiol. A range of three to five different doses are often available for each product, varying from

low-dose (0.3–0.5 mg orally) to high-dose (2.5–5 mg). Estrogen products are available in oral form, transdermal patches and intravaginal rings. These products can be used either for estrogen-only therapy (e.g. in women who have had a hysterectomy) or in conjunction with a progestogen to provide combined hormonal therapy.

Table 1. Trends in sales of combined estrogen–progestogen menopausal therapy products for selected years (millions of standard units[a])

Regions[b]	1994	1999	2004
Africa	21.0	29.9	27.7
South Africa	20.0	28.9	26.7
West Africa	1.1	1.0	1.1
Eastern Mediterranean	8.9	21.5	27.7
Europe	1 269.5	1 858.3	1 078.4
Eastern Europe	36.2	184.8	159.8
Western Europe	1 233.3	1 673.5	918.6
North America	39.7	1 089.4	421.8
South America	100.2	284.5	190.4
South East Asia	20.0	36.9	67.5
India	0	0	1.2
Korea	7.8	16.8	43.9
Rest of South East Asia	10.5	17.3	20.5
Western Pacific	100.8	219.7	107.0
Australia/New Zealand	17.5	75.8	34.3
China/Hong Kong	0.8	10.8	4.5
Japan	67.6	54.6	36.9
Taiwan, China	4.6	58.5	24.3
Rest of Western Pacific	10.4	20.0	7.1
Total	1 560.1	3 550.2	1 920.6

From IMS Health (2005)

[a] Standard units are sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule

[b] *West Africa* includes: Benin, Burkina, Cameroon, Congo, Gabon, Guinea, Ivory Coast, Mali, Senegal, Togo;

Eastern Mediterranean includes: Egypt, Jordan, Kuwait, Lebanon, Morocco, Saudi Arabia, Tunisia, United Arab Emirates;

Eastern Europe includes: Belarus, Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russian Federation, Slovakia, Slovenia, Ukraine;

Western Europe includes: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, UK;

North America includes: Canada, Central America (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama), Mexico, Puerto Rico, USA;

Rest of South East Asia includes: Indonesia, Pakistan, Thailand;

South America includes: Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Peru, Uruguay, Venezuela;

Rest of Western Pacific includes: Malaysia, Philippines, Singapore.

A range of progestogens are available for use in combined hormonal therapy. Those most commonly used are medroxyprogesterone acetate, norethisterone and levonorgestrel. Several doses of each progestogen are usually available. For example, medroxyprogesterone acetate is often available in doses of 1.5, 2.5, 5 and 10 mg. While oral forms predominate, progestogens also are available as a vaginal pessary, a systemically absorbed vaginal gel, a transdermal patch and an intrauterine device. Administration of progestogen may follow one of three types of schedule. In continuous combined therapy, the same dose of both estrogen and progestogen is administered each day. In sequential therapy, 10–14 days of progestogen is provided per cycle in addition to daily estrogen. In cyclical therapy, a cycle consists of estrogen alone, followed by progestogen with estrogen and then 5–7 days with no hormones.

Combined oral products that contain both estrogen and progestogen provide greater convenience to users, as only one rather than two tablets are taken. The various preparations available differ in their estrogen component, their progestogen component, the dose of these components, and the schedule and mode of drug administration. Despite the potential for a plethora of combinations, a relatively small number are manufactured. Continuous dose schedules during which the same doses are taken on a daily basis are most common. Less commonly, progestogens may be delivered for only a portion of a monthly cycle (e.g. Premphase). Combined products are frequently available at two dose levels. Oral forms of combined therapy predominate, but a combined transdermal patch and a vaginal ring are also available.

The selection of a specific regimen for menopausal therapy depends on the preferences and needs of each women. Further, evidence regarding long-term risk may motivate physicians to recommend a specific formulation. A number of the products available for hormonal menopausal therapy have only recently been introduced and their long-term effects have not been evaluated fully.

1.4 Patterns of use

A number of studies have provided information on patterns of use of hormonal menopausal therapy, most of which is related to women in developed countries and does not differentiate between use of estrogen alone or in combination with progestogen. Data from individual studies are summarized in Table 2. Most of the available information reflects use in the late 1990s when hormonal therapy had reached its peak. Another set of studies examined more recent use and provided an indication of the extent to which use has declined since the results of the WHI Study.

1.4.1 *Patterns of use in 1990–2000*

Table 2 summarizes the prevalence of current use of estrogen–progestogen menopausal therapy during the years 1997–2003. The section below details those studies that provide additional information on patterns of use during this period.

Table 2. Selected studies of the prevalence of current use of estrogen–progestogen menopausal therapy, 1997–2003

Reference	Country	Year(s) of study	Age group (years)	Prevalence of current use		Comments
				Combined estrogen–progestogen therapy	Any current hormonal therapy	
Pre-2002						
MacLaren & Woods (2001)	USA	1998	40–65	NR	39%	
Progetto Menopausa Italia Study (2001)	Italy	1997–99	45–75	NR	8.5%	
Banks *et al.* (2002) (EPIC)	Denmark Germany Greece Italy Netherlands Spain United Kingdom	1993–97	50–64	NR	29.0% 38.6–40.7% 2.1% 4.4–11.5% 14.3% 4.5–11.5% 28.1–30.3%	 2 centres 2 centres 2 centres 2 centres
Benet Rodriguez *et al.* (2002)	Spain	1989–99	≥ 40	NR	> 3.19%	Detail by 5-year age group and by year
Merom *et al.* (2002)	Israel	1998	45–74	NR	16.8%	
Million Women Study Collaborators (2002)	United Kingdom	1996–2000	50–64	17%	33%	
Mueller *et al.* (2002)	Germany	1985 1990 1995	45–64	0.1% 4.0% 13.9%	3.0% 8.8% 22.6%	
Bakken *et al.* (2004)	Norway	1996–98	Postmenopausal 45–54	24%	35%	

Table 2 (contd)

Reference	Country	Year(s) of study	Age group (years)	Prevalence of current use		Comments
				Combined estrogen–progestogen therapy	Any current hormonal therapy	
Buist *et al.* (2004)	USA	1999	40–80	14.6%	27.2%	
Heng *et al.* (2004)	Singapore	1994–97	45–69	NR	21%	Ever use
Hersch *et al.* (2004)	USA	1995 2001	50–74 50–74	 16%	33% 42%	
Lundberg *et al.* (2004)	20 countries	1989–97	45–64	NR	0–56%	
Manzoli *et al.* (2004)	Italy	1999–2001	50–70	2.9%	6.9%	
Rachoñ *et al.* (2004)	Poland	April 2002	45–64	[9.3%]	12%	
Carney *et al.* (2006)	USA	1996–99	> 40	13%	43%	
Post-2002						
Strothmann & Schneider (2003)	France Germany Spain United Kingdom	2003	45–75	NR	23% 19% 5% 19%	
Bilgrami *et al.* (2004)	New Zealand	December 2002	45–64	3%	11%	
Buist *et al.* (2004)	USA	December 2002	40–80	8%	17%	
MacLennan *et al.* (2004)	Australia	2003	> 50	7%	19%	

NR, not reported

Based on sales data, Jolleys and Olesen (1996) compared the use of hormonal therapy in the USA and Europe and found three strata of prevalence of use: the USA were in the highest stratum (20% of women); the United Kingdom and Scandinavian countries were in the intermediate group (9–16%); and continental Europe had the lowest prevalence (< 5%). The authors noted that use in France, however, was increasing towards levels found in the intermediate group. A later review on the use of hormonal therapy and risk for cancer by Beral *et al.* (1999) estimated that at least 20 million women in developed countries were currently using hormonal therapy.

Based on sales data, Benet-Rodriguez *et al.* (2002) estimated that prevalence of the use of hormonal therapy among women aged 40 years or over increased from 0.7% in 1989 to 3.4% in 1999. In 1998, prevalence was highest in the age group 50–54 years (10.8%) and was below 1% in women over 65 years of age.

Buist *et al.* (1999) examined patterns of long-term use of hormonal therapy in women aged 50–80 years in Seattle, WA, USA. Long-term users (> 10 years) and short-term users were significantly younger than never users. Compared with never users, long-term users were also more likely to be married, to have had surgically induced menopause, to have experienced menopausal symptoms, to see their family doctor and have mammograms and were less likely to smoke. Estrogen alone was the predominant therapy; combined therapy was more common among short-term (< 10 years) users than among long-term users.

Donker *et al.* (2000) reported on first-time users of hormonal therapy in a survey in the Netherlands. The number of prescriptions for such therapy increased from 2 to 3% between 1995 and 1998. Between 1987–88 and 1995–98, sequential therapy was prescribed more frequently than continuous therapy, but there has been a gradual shift from sequential to continuous therapy in the last few years. There was also a trend in prescriptions from estrogen towards combinations of estrogen and progestogen.

MacLaren and Woods (2001) found that, among peri- or postmenopausal women aged 40–65 years in the USA, use of hormonal therapy was lower among women who experienced natural menopause (31%) than among those who had surgically induced menopause (56%). The median duration of use was 5 years, and 25% reported taking hormones for 10 years or more.

In a study of over 40 000 women aged 45–75 years in Italy (Progetto Menopausa Italia Study Group, 2001), 12% were ever users, among whom 74% were current users. Mean duration of use was approximately 20 months in both current and former users. Ever users were more likely to have a higher education, be nulliparous, have had an early menopause, have ever used oral contraceptives and have a history of osteoporosis, and less likely to have cardiovascular disease or diabetes.

The EPIC [European Prospective Investigation into Cancer and Nutrition] Working Group (Banks *et al.*, 2002) examined the patterns of use of hormonal therapy in women aged 50–64 years in several European countries. Current use varied from 2% in Greece to 41% in Heidelberg, Germany, and ever-use varied from 7 to 55%, respectively. In all centres (except in Germany), the most frequent duration of use among ever users was less than 1 year; long-term use (> 10 years) varied from 26% in Denmark to 2% in southern Italy.

Merom *et al.* (2002) examined Israeli women aged 45–74 years in 1998 who had had a natural menopause, among whom 17% were current users and 13% were past users. The prevalence of current use was higher among post- than among perimenopausal women (15% versus 7%). The rates of current and ever use were highest in the 55–59-year age group and lowest in the 70–74-year age group. Current users were more likely to be more highly educated, to work outside the home and be married (compared with divorcees or widows), to have used contraceptives, to make regular visits to a gynaecologist, to be lean, to have regular physical activity and ever to have smoked.

The Million Women Study Collaborators (2002) examined patterns of use in women in the United Kingdom aged 50–64 years in 1996–2000. Of this cohort, 50% had ever used hormonal therapy, of whom 33% reported current use and 17% reported past use. Average age at initiation of therapy was 49.1 years; 38% started at 45–49 years and 37% started at 50–54 years of age. The most common duration of treatment was 1–4 years (37%) followed by 5–9 years (33%); the mean duration of use was 4.9 years.

Mueller *et al.* (2002) reported trends in use of hormonal therapy in Germany in 1984–95, based on a survey of women aged 45–64 years who were included in the WHO Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study. The highest prevalence of use (29.8%) was among women aged 55–59 years. Use of combined hormonal therapy increased from almost non-existent levels in 1985 to 4.0% in 1990 and 13.9% in 1995.

Ekström *et al.* (2003) examined patterns of use of hormonal therapy in women aged 45, 50, 55 and 60 years in Sweden and found that 50–52% of women aged 55 and 60 years had ever used hormonal therapy; the mean length of treatment was 4.4 years. Current users were more likely to be on antidepressive medication and/or cardiovascular drugs, to report psychological and physical menopausal symptoms and to have visited a psychotherapist.

Bakken *et al.* (2004) reported on over 35 000 postmenopausal women aged 45–64 years from the Norwegian Women and Cancer (NOWAC) cohort study, among whom 80% of ever-users of hormones were current users.

From a sample of women in the USA, Haas *et al.* (2004) found that use of hormones in 1997 was highest among white women (53%) and lowest among African-American, Latina, Chinese and Philipina women (30–34%); it was also much higher among women who had had a hysterectomy (60% versus 36%).

By 2001 in the USA, almost half (42%) of all postmenopausal women under the age of 65 years were being treated with hormonal therapy (Hersh *et al.*, 2004). It was reported that 38% of users were taking combined therapy, either as a single preparation or as separate estrogen and progestogen components.

Based on a sample population for a case–control study, Newcomb *et al.* (2002) reported that 25–28% of all postmenopausal women in the USA had ever used hormonal therapy in 1992–95. Of these users, 30% had used combined therapy.

Bromley *et al.* (2004) reported on the proportion of women who used hormonal therapy from 1992 to 1998. Women who started hormonal therapy during this period were less likely to have a history of a range of diseases but were more likely to have a history

of osteoporosis, hysterectomy, hyperlipidaemia and prior oral contraceptive use than non-users.

Lundberg *et al.* (2004) reported data collected from the MONICA study. Prevalence of current use in women aged 45–64 years varied enormously from 0% in Moscow, Russian Federation, to 42% in Newcastle, Australia, and Canada. Low prevalence of use (< 10%) was noted for central, eastern and southern Europe, the Russian Federation and China, while the highest prevalence of use was reported in populations in western and northern Europe, North America and Australia. Ever use in Perth, Australia, was estimated at 66% of women aged 50–54 years. Regional differences within the same country were generally modest compared with inter-country variations. The highest prevalence was in the age group 45–49 years in 12 populations, in the age group 50–54 years in nine populations and in the age group 55–59 years in four populations.

Rachon *et al.* (2004) examined use of hormonal therapy among Polish women over 45 years of age in April 2002. Overall current use was 12% in women aged 45–64 years and was 16% in the age group 45–54 years; ever use was in the range of 25 and 20% for women aged 45–54 years and 55–64 years, respectively. Women with a medium or higher level of education were more likely to be current users than those who had had a basic education.

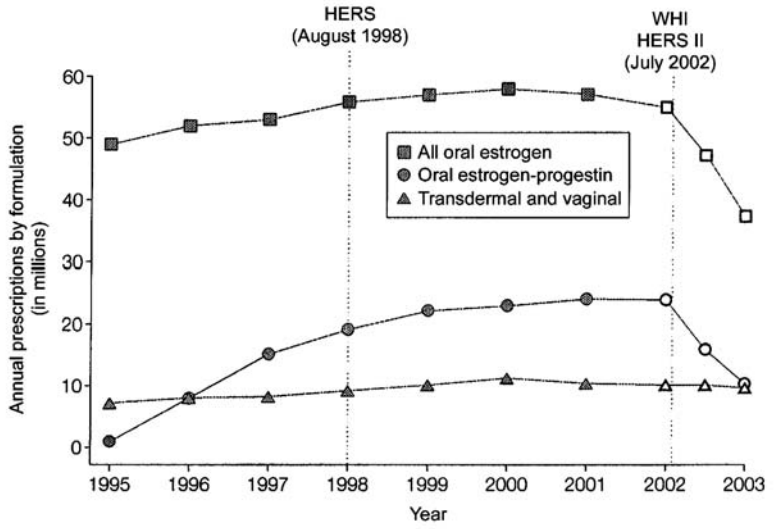
Fournier *et al.* (2005) reported that, among women born between 1925 and 1950 and followed-up between 1990 and 2000, users were more likely than non-users to have had an early menarche, an early menopause, to be parous, to have a personal history of benign breast disease, to have no familial history of breast cancer in first-degree relatives, to be lean, to have a higher level of education, to have used oral contraceptives and to have used oral progestogens before the menopause.

1.4.2 *Recent trends in hormonal menopausal therapy*

Large and rapid changes in the use of combined hormonal menopausal therapy took place in 2002 as a consequence of the publication of the results of the WHI. International data (IMS Health, 2005) suggest that sales of combined hormonal therapy (estrogen and progestogens in a single preparation) declined substantially worldwide (Table 1). Decreases between 1999 and 2004 were noted in Europe (42% decline), North America (61%), South America (33%) and the western Pacific (51%). Increased or stable sales of combined hormonal therapy were noted in Africa, the eastern Mediterranean and South-East Asia during the same period.

In the USA, overall use of hormonal therapy fell by about 38% and that of combined estrogen–progestogen therapy by 58% between 2001 and the first half of 2003 (Hersh *et al.*, 2004) (Figure 1). As use continued to decrease 18 months after the WHI results (Rossouw *et al.*, 2002), sales of Prempro (conjugated equine estrogens plus methoxyprogesterone acetate) had fallen by 80% (Majumdar *et al.*, 2004). Haas *et al.* (2004) found similar time trends from survey data.

Figure 1. Annual number of US prescriptions for hormonal therapy by formulation, 1995–July 2003



Modified from Hersh *et al.* (2004)
HERS, Heart and Estrogen/Progestin Replacement Study; WHI, Women's Health Initiative
Data for January to June 2002, July to December 2002 and January to July 2003 are included (open symbols). Data are from the National Prescription Audit Plus, IMS Health.

Strothmann and Schneider (2003) analysed data from France, Germany, Spain and the United Kingdom in women aged 45–75 years in 2003 and found that in all four countries the number of former users was relatively similar to that of current users.

Bilgrami *et al.* (2004) presented data from New Zealand. Based on survey information, current use of hormone therapy dropped from 15% in June 2002 to 11% in December 2002. The majority of women who had stopped using hormonal therapy specifically identified the results of the WHI trial as their reason. Further data from the New Zealand Pharmacy Management Agency (Metcalfe, 2004) showed a decline of 65% in use of hormonal therapy between 2001 and 2004. Examination of monthly data showed a continued decline through to March 2005.

MacLennan *et al.* (2004a) specifically examined changes in use patterns in Australia and found that prevalence of current use had declined from 22.5% in 2000 to 14.4% in 2003 among women aged > 40 years. Over the same period, duration of use decreased by an average of 10 months among current users. Unlike in studies in the 1990s, the number of past users exceeded the number of current users.

No data were available to the Working Group on changes in use in developing countries.