Hormone Replacement Therapy and Menopause: A Review of Randomized, Double-blind, Placebo-controlled Trials

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Hormone replacement therapy (HRT) is frequently prescribed to healthy women to ameliorate menopausal symptoms. HRT is used long term (≥ 1 year) to prevent chronic disease in older women. The objective of this study was to review the benefits and risks of HRT and studies of menopause or HRT in Taiwan via a MEDLINE search. Recommendations are provided for future HRT research in Taiwan. Randomized, double-blind, placebo-controlled clinical trials are considered the gold standard of scientific evidence. A MEDLINE literature search (January 1966–July 2002) identified 23 papers on trials (≥ 1 year) that met the inclusion criteria. The results showed that various HRT regimens used for more than 1 year caused more harm than good in healthy menopausal women and that there was no benefit for women with coronary artery disease, Alzheimer's disease, hysterectomy, hysterosalpingo-oophorectomy, and ischemic stroke. None of this research was conducted in Taiwan. A MEDLINE search using the key words "estrogen replacement therapy and menopause in Taiwan" identified 16 studies. There was only one, short-term, HRT trial. No evidence suggested benefits from long-term HRT in menopausal women in Taiwan.

Key Words: hormone therapy, menopausal women, randomized, double-blind, placebo
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Hormone replacement therapy (HRT) is frequently prescribed to healthy women as a preventative measure. Short-term (< 1 year) HRT use to ameliorate menopausal symptoms has been reported [1]. Healthy women also take long-term HRT with the purpose of preserving their health and to prevent disease [2].

On July 9, 2002, the National Heart, Lung, and Blood Institute of the US National Institutes of Health (NIH) announced that it had stopped a trial of estrogen-progestin versus placebo in healthy menopausal women [3]. The trial was one component of the Women's Health Initiative (WHI). In the part of the WHI study that was stopped, 16,608 postmenopausal women aged 50 to 79 years received one tablet of conjugated equine estrogens (CEE, 0.625 mg) plus medroxyprogesterone (MPA, 2.5 mg) or placebo. The trial was stopped after a mean of 5.2 years (planned follow-up, 8.5 years) because the risks outweighed the benefits. The WHI writing group cautioned that the combination used in the trial should not be initiated or continued. This step reveals the conscientiousness and integrity of the researchers.

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The number of studies relating to menopause have increased in the past decade in Taiwan. However, the response of the medical profession in Taiwan, primarily that of gynecologists, to the results of the WHI trial has generally been defensive, with continued insistence on the effectiveness of HRT. Medical professionals argued in the media that the absolute excess risks per 10,000 person-years in the WHI trial were too low to cause concern (*Liberty Times* 2002/7/13), and because the trial used one drug regimen only, it is doubtful whether the results can be applied to other lower dosages of these drugs or other formulations (*United Daily News* 2002/7/12; *Liberty Times* 2002/7/14).

The objective of this study was to provide evidence gathered from HRT research conducted outside Taiwan and to offer recommendations for future HRT research directions in Taiwan. Randomized, double-blind, placebo-controlled trials are considered the most comprehensive methods of investigating the effectiveness of a drug in most epidemiologic or public health studies. The approval of a drug for clinical use by the US Food and Drug Administration (FDA) largely depends on the results of these trials [4]. Thus, the authors selected randomized, double-blind, placebo-controlled HRT trials (≥ 1 year duration) through a MEDLINE search and reviewed the benefits and risks of HRT use in menopausal women.

Method

Data sources were selected from studies with English-language abstracts identified by a computerized MEDLINE search (January 1966–July 2002) using the key words estrogen replacement therapy, double-blind, clinical trials, and random allocation. Only long-term trials, in which participants had been randomized to at least 1 year of therapy, were included.

Results

Twenty-three papers on long-term (≥1 year) clinical trials from important journals of medicine and menopause met the inclusion criteria (Table 1). The samples were selected from healthy women and women with hysterectomy, hysterosalpingo-oophorectomy, coronary artery disease, Alzheimer's disease, or ischemic stroke. Most trials were conducted in the USA [3,5–20], with the remainder in Holland [21,22], Denmark [23,24], Australia [25], and Italy [26]; there were none conducted in Taiwan. Only 16 studies conducted in Taiwan, with English-language abstracts, were identified in a similar MEDLINE search using the key words estrogen replacement therapy and menopause [27–42] (Table 2).

Table 1. Number of papers on long-term (≥ 1 year) hormone replacement therapy clinical trials in MEDLINE journals

Journal	1966–2002, abstract, English*	+ key words†	Clinical trials ≥ 1 year	RCT
JAMA	9,099	13	9	9
Maturitas	1,215	36	9	5
Am J Obstet Gynecol	14,340	23	5	3
N Engl J Med	6,569	6	3	3
Climacteric	120	12	3	1
Menopause	205	16	2	1
Arch Intern Med	7,499	7	1	1
BJOG‡	164	1	1	0
Arch Gynecol Obstet	691	0	0	0
Psychosom Med	1,542	0	0	0
Am J Cardiol	13,958	5	0	0
J Nat Cancer Inst	6,945	2	0	0
Lancet	12,448	7	0	0
BMJ	6,166	2	0	0
Int J Cancer	10,908	0	0	0
Total			33	23

*Excluding review articles; †combined with key words (n = 452): estrogen replacement therapy, double-blind, clinical trials, random allocation, 1966–2002, abstract, English; ‡BJOG: an international journal of obstetrics and gynecology. RCT = randomized, double-blind, placebo-controlled trial.

Table 2. Menopause or hormone replacement therapy (HRT) research conducted in Asian countries in MEDLINE journals (1966–2002)

Country	A: Research done in Asia	Combined A with key words*
Taiwan	5,876	16
Japan	52,693	37
China	23,291	15
Korea	5,373	6
Malaysia	5,163	2
Singapore	4,722	5
Philippines	4,369	1
	Total	82

*Combined key words (n = 20,672): estrogen replacement therapy (ERT) and menopause; excluding review articles.

Randomized, double-blind, placebo-controlled trials (≥1 year)

Of the 23 studies, nine were part of long-term trials (3–13 years) [3,5–10,14,15] and 13 were multicenter studies [3,5–10,14–18,20].

For healthy women using estrogen (CEE 1.25, 0.625, 0.45, or 0.3 mg) or estrogen plus progesterone (CEE 0.625, 0.45, or 0.3 mg plus MPA 10, 2.5, or 1.5 mg), six papers reported that risks exceeded benefits and five reported benefits only (Table 3).

The risks of long-term estrogen or estrogen plus progesterone therapy (5.2 or 3 years) in healthy menopausal women were: an increase in coronary heart disease, stroke, pulmonary embolism, breast cancer [3], and mean triglyceride levels [8] and enhanced development of endometrial hyperplasia [9]. The benefits of long-term HRT use (1 to 5.2 years) in healthy menopausal women were: a decrease in the risk of colorectal cancer and hip fracture [3], an increase in bone mineral density [7,10,12], bone mineral content [10], and postcranial and oral bone mass [11], a slowing of bone loss [14], and decreases in the mean concentration of low-density lipoprotein cholesterol [6,8] and the risk of forgetfulness [5].

Benefits of long-term HRT use (3 years) in women with coronary artery disease were found in women with flushing, but there were risks in women without flushing [14]. Women with flushing who were assigned to HRT had improved mental health and fewer depressive symptoms during follow-up compared with those assigned to placebo. Women without flushing who were assigned to HRT had greater declines in physical function and energy/fatigue during follow-up (Table 4).

Among women with coronary artery disease, Alzheimer's disease and hysterectomy, three trials reported that long-term HRT (1 to 4 years) had no benefit in slowing the progression of Alzheimer's disease [15], in global cognitive or functional outcomes [15], and in the reduction of the overall rate of coronary heart disease [16,17] (Table 4).

Some trials with other HRT regimens were conducted in Europe as the particular hormone replacement combination investigated in the WHI is not available there (Table 5).

Among healthy women using various HRT regimens for 2 years, benefits were found with continuous norethindrone acetate-ethinyl estradiol (NA-EE2) combinations, 17 beta-estradiol, sequential estradiol/norethisterone acetate (E2/NETA) combinations, and continuous E2/NETA or E2/cyproterone acetate combinations: increased bone mineral density [18], bone loss prevention [19], and climacteric symptom relief [23,24]. No benefit was found with tibolone [22].

When women with hysterectomy, hysterosalpingo-oophorectomy, and ischemic stroke or transient ischemic attack used raloxifene, 17 beta-estradiol, and transdermal estradiol (1 to 2.8 years), no benefit was found in the systolic function of the left ventricle [21], in reducing the recurrence of stroke [20], and in modifying atrioventricular conduction and ventricular repolarization [26].

HRT and menopause research in Taiwan

We found 16 studies reporting on HRT and the menopause in Taiwan (Tables 6 and 7). They covered: the perception of menopausal women toward menopause [27,37]; the risk of osteoporosis [29], high-

Table 3. Effects of hormone replacement therapy (HRT) in healthy women in randomized, double-blind, placebo-controlled trials: conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) therapy

Author/location	Follow-up (yr)	Subjects*	Treatments (HRT dose, mg/d)	Main results
				Risks exceed benefits
Women's Health Initiative [3], USA: 40 centers	5.2	16,608 (50–79 y.o.): HRT 8,506, placebo 8,102	CEE 0.625/MPA 2.5	Risks: CHD, stroke, PE, breast cancer; benefits: colorectal cancer, hip fracture
PEPI trial [5–9], USA: 7 centers	3	875 (45–64 y.o.): 596 + uterus, 279 – uterus	CEE 0.625, CEE 0.625/MPA 10, CEE 0.625/MPA 2.5, CEE 0.625/MP 200	Estrogen increased BMD and mean TG, and decreased mean LDL-C; progestin decreased risk of forgetfulness; for women with a uterus, therapy enhanced development of endometrial hyperplasia
				Benefits
Lindsay et al [10], USA: 19 centers	2	822 (40–65 y.o.), + elemental calcium 600 mg/d	CEE 0.625, 0.45, or 0.3, CEE 0.625/MPA 2.5, CEE 0.45/MPA 2.5, CEE 0.45/MPA 1.5, CEE 0.3/MPA 1.5	BMD and bone mineral content increased
Civitelli et al [11], USA	3	135 (41–70 y.o.), + calcium 1,000 mg/d + cholecalciferol 800 IU/d	CEE 0.625, CEE 0.625/MPA 2.5	Postcranial and oral bone mass increased
Watts et al [12], USA	2	406, + calcium 1,000 mg/d	Esterified estrogens 0.3, 0.625, or 1.25	BMD increased
Riis & Christiansen [13], USA	1	17, + calcium 0.5 g/d	Estrogen/progestogen	Calcium potentiated bone-preserving effect of HRT
Prince et al [25], Australia	2	†120: exercise/calcium 39, exercise/HRT 40, exercise only 41	Estrogen/progesterone	Bone loss slowed or prevented by exercise/calcium or HRT

*Subjects randomly assigned to receive either treatments or placebo; †low forearm bone density. MP = micronized progesterone; CHD = coronary heart disease; PE = pulmonary embolism; BMD = bone mineral density; TG = triglyceride; LDL-C = low-density lipoprotein cholesterol.

Table 4. Effects of hormone replacement therapy (HRT) in women with infirmity in randomized, double-blind, placebo-controlled trials: conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) therapy

Author/location	Follow-up (yr)	Subjects	Treatments (HRT dose, mg/d)	Main results
				Risks exceed benefits
Hlatky et al [14], USA: 20 centers	3	2,763 (< 80 y.o.) with CAD: HRT 1,380, placebo 1,383	CEE 0.625/MPA 2.5	Benefits for women with flushing, risks for women without flushing*
				No benefits
Mulnard et al [15], USA: 32 centers	1.25	120 with AD and hysterectomy: 42 and 39 received estrogen, 39 placebo	CEE 0.625 or 1.25	Estrogen did not slow disease progression, and did not improve global, cognitive, or functional outcomes
Herrington et al [16], USA: 6 centers	2	309 (49–80 y.o., mean 66) with angiographically verified coronary disease: HRT 100, 104, placebo 105	CEE 0.625, CEE 0.625/MPA 2.5	No cardiovascular benefit
Hulley et al [17], USA: 20 centers	4	2,763 (mean 67 y.o.) with coronary disease and intact uterus: HRT 1,380, placebo 1,383	CEE 0.625/MPA 2.5	Treatment did not reduce overall rate of CHD

*Women with flushing who were assigned to HRT had improved mental health and fewer depressive symptoms over follow-up compared with those assigned to placebo. Women without flushing who were assigned to HRT had greater declines in physical function and energy/fatigue over follow-up. CAD = coronary artery disease; AD = Alzheimer's disease; CHD = coronary heart disease.

density lipoprotein cholesterol concentrations [31], and breast cancer factors [35,36,38] in menopausal women; increases in total cholesterol, low-density lipoprotein cholesterol, triglycerides, apoprotein B [28,32] and body fat [33,34]; age at menopause [30,40] and menopausal symptoms [30,39,41]; and the effectiveness of estrogen treatment for menopausal women [42].

Only one study was a short-term HRT trial [42]. Most of the studies were conducted in Taipei [28,30–32,35,36,38–42]. The studies included questionnaire surveys, case-control studies, clinical studies, interview-based studies, cross-sectional studies, and cohort studies [28,32]. No evidence suggested long-term benefits from HRT among menopausal women in Taiwan.

Discussion

This paper reviewed 23 reports on randomized, double-blind, placebo-controlled HRT trials (≥ 1 year duration) identified from a MEDLINE search of abstracts from January 1966 to July 2002. The results indicated that various HRT regimens used for more than 1 year caused more harm than good in healthy menopausal women, and that they had no benefit in women with coronary artery disease, Alzheimer's disease, hysterectomy, hysterosalpingo-oophorectomy, and ischemic stroke or transient ischemic attack. Large-scale epidemiologic research, such as cross-sectional and cohort studies, frequently form the basis of public health research. However, randomized, double-blind,

Table 5. Effects of hormone replacement therapy (HRT) on women in randomized, double-blind, placebo-controlled trials: other regimens

Author/location	Follow-up (yr)	Subjects*	Treatments	Main results
				Benefits
Speroff et al [18], USA: 65 centers	2	265 (≥ 40 y.o.) + uterus	†NA 0.2 mg/EE2 1 μg, NA 0.5 mg/EE2 2.5 μg, NA 1 mg/EE2 5 μg, NA 1 mg/EE2 10 μg, EE2 1, 2.5, 5, 10 μg	Increased BMD
Field et al [19], USA	2	127	17 beta-estradiol	Bone loss prevention
Obel et al [23], Denmark	2	151	‡E2 2 mg/NETA 1 mg, E2 2 mg 12 d + E2 2 mg/NETA 1 mg 10 d + E2 1 mg 6 d	Climacteric symptom relief
Marslew et al [24], Denmark	2	86 (45–54 y.o.)	Continuous combined estradiol + NETA or estradiol + cyproterone acetate	Climacteric symptom relief
				No benefits
Viscoli et al [20], USA: 21 hospitals	2.8	664 (46–91 y.o., mean 71) with ischemic stroke or TIA: estrogen 337, placebo 327	1 mg 17 beta-estradiol/d	Did not reduce mortality or the recurrence of stroke
Vogelvang et al [21], Holland	2	Study I: 60 with hysterectomy; Study II: 97 without hysterectomy	Study I: daily raloxifene§ 60, 150 mg or CEE 0.625 mg; Study II: daily raloxifene 60, 150 mg, or CEE 0.625 mg/MPA 2.5 mg	No effect on echocardiographic parameters of left ventricular systolic function
Berning et al [22], Holland	2	HRT 25 and 23, placebo 16	¶Tibolone 1.25 or 2.5 mg/d	No increase in cortical bone density
Siniscalchi et al [26], Italy	1	50 (42–59 y.o.) with hysterosalpingo-oophorectomy	50 μg/d transdermal estradiol	Atrioventricular conduction and ventricular repolarization not modified

*Subjects were randomly assigned to either treatments or placebo; †continuous norethindrone acetate (NA)–ethinyl estradiol (EE2) combinations; ‡estradiol (E2)/norethisterone acetate (NETA); §raloxifene hydrochloride has an estrogen-antagonistic effect on the breast and endometrium, and estrogen-agonistic effects on bone, serum lipids, homocysteine, and coagulation factors, but does not alleviate climacteric symptoms; ¶tibolone, a synthetic C-19 steroid with weak estrogenic, progestagenic and androgenic properties, has selective gonadomimetic effects on different hormonal receptors, behaving as an agonist or antagonist depending on the target tissue. BMD = bone mineral density; TIA = transient ischemic attack.

Table 6. Hormone replacement therapy and menopause studies in Taiwan (in reverse chronological order)

Authors	Institution(s)	Topic
Pan et al [27]	Department of Obstetrics and Gynecology, National Cheng-Kung University Hospital, Tainan	Perception of menopause among women in Taiwan
Torng et al [28]	Department of Obstetrics and Gynecology, National Taiwan University College of Medicine, Taipei	Effects of menopause on changes in serum lipids, blood pressure and body weight
Chen et al [29]	Department of Obstetrics and Gynecology, School of Medicine, China Medical College Hospital, Taichung	Relation of the estrogen receptor alpha gene microsatellite polymorphism to BMD and osteoporosis
Fuh et al [30]	The Neurological Institute, Taipei Veterans General Hospital	Menopausal study of a population aged 40–54
Lyu et al [31]	Graduate Program of Nutrition, National Taiwan Normal University, Taipei	Association of sex, adiposity, and diet with high-density lipoprotein subclasses in middle-aged Chinese
Torng et al [32]	Department of Obstetrics and Gynecology, National Taiwan University College of Medicine, Taipei	Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women
Chang et al [33]	Department of Family Medicine & Nuclear Medicine, National Cheng Kung University Hospital, Tainan	Relationships of age, menopause, and central obesity on CVD risk factors in Chinese women
Tsai & Chou [34]	Chang Gung Institute of Nursing, Taoyuan	Association of body fat distribution with lifestyle and reproductive factors
Huang et al [35]	Department of Surgery, College of Medicine, National Taiwan University, Taipei	Cytochrome P4501A1 polymorphism as a susceptibility factor for breast cancer
Huang et al [36]	Department of Surgery, National Taiwan University Hospital, Taipei	Association between N-acetyltransferase 2 genetic polymorphism and breast cancer
Chen et al [37]	Westminster College School of Nursing, Salt Lake City, Utah, USA	Chinese midlife women's perceptions and attitudes about menopause
Yang et al [38]	Mackay Memorial Hospital, Academia Sinica, Taipei	Breast cancer in Taiwan
Chang & Chang [39]	Institute of Health Policy & Management, National Taiwan University, Taipei	Experience of menopause and hormone use in women in Taiwan
Chang et al [40]	Institute of Health Policy & Management, and the Department of Obstetrics & Gynecology, National Taiwan University, Taipei	Age of menopause of women in Taiwan
Lin et al [41]	Department of Obstetrics and Gynecology, College of Medicine, National Taiwan University, Taipei	Clinical study of postmenopausal bleeding
Ouyang et al [42]	Department of Obstetrics and Gynecology, College of Medicine and the Hospital, National Taiwan University, Taipei	Total serum estrogen levels and urinary excretion of calcium and hydroxyproline in pre- and postmenopausal women

BMD = bone mineral density; CVD = cardiovascular disease.

Table 7. Hormone replacement therapy (HRT) and menopause studies in Taiwan

Authors	Design	Subjects (age range, yr)	Main results
			Perception
Pan et al [27]	Questionnaire	386 women	97% have heard of the menopause; 53% knew its definition; most common source of knowledge was reading material (43%), friends (22%); 71% thought they should receive therapy
Chen et al [37]	Questionnaire	168 women	92% perceived menopause as natural; 41% obtained menopause information from friends and printed materials
			Risk of osteoporosis
Chen et al [29]	BMD measurement	174 women	Estrogen receptor alpha gene microsatellite polymorphism may be a candidate genetic marker for risk of osteoporosis
			Cholesterol
Torng et al [28,32]	Cohort study	671 pre- and 872 postmenopausal women (45–54)	Menopause associated with increases in TC, LDL-cholesterol, TG, and apoprotein B levels
Lyu et al [31]	Interviews	203 women, 206 men	Women had higher concentrations of HDL-cholesterol than men
			Body fat
Chang et al [33]	Cross-sectional study	136 pre- and 193 postmenopausal women	Through aging and menopausal effects, women will have increased total body fat content
Tsai & Chou [34]	Cross-sectional study	1,310 women (45–54)	Overall obesity and menopausal status are determinants of body fat distribution
			Breast cancer
Huang et al [35,36]	Case-control study	150 breast cancer patients, 150 controls	N-acetyltransferase 2 polymorphism or cytochrome P4501A1 polymorphism are susceptibility factors for breast cancer in women
Yang et al [38]	Case-control study	244 breast cancer patients, 450 controls	Family history of breast cancer appears to be the most important risk factor for breast cancer
			Age and symptoms
Fuh et al [30]	Questionnaire	1,497 women (40–54)	Age at menopause did not differ from Western studies, but menopausal symptoms, especially vasomotor symptoms, are much lower than in the West
Chang & Chang [39]	Questionnaire	673 women (40–60)	Discomfort low compared with Western countries; most frequent discomforts: backache/lumbago, amentia, tiredness
Chang et al [40]	Interviews	771 women (40–60)	Mean menopausal age 49.8 ± 3.28 yr (median 50, range 38–55)
Lin et al [41]	Clinical study	381 postmenopausal women with abnormal vaginal bleeding	55.6% had normal histologic findings, 21.9% benign pathologic findings, 3.6% cervical intraepithelial neoplasia, 11% endometrial hyperplasia, 5% cervical cancer, 2.9% endometrial cancer, and obesity correlated with malignancy
			Treatment
Ouyang et al [42]	Premarin treatment (0.625 or 1.25 mg/d)	14 natural, 14 surgical, and 4 post-irradiation menopausal women	Premarin effectively treated menopausal syndrome

BMD = bone mineral density; TC = total cholesterol; LDL = low-density lipoprotein; TG = triglyceride; HDL = high-density lipoprotein.

placebo-controlled trials are considered the most comprehensive. The approval of a drug for clinical use largely depends on the results of such trials [4]. As the results are usually already convincing, further statistical analyses such as meta-analyses are not necessary to present additional credible scientific evidence.

We found no randomized, double-blind, placebo-controlled HRT trial (≥ 1 year) conducted in Taiwan. Only one short-term HRT trial was published [42], and there was no evidence to suggest long-term benefits from HRT use.

The trials reviewed in this paper were predominantly conducted in the USA and Europe; none were conducted in Asia. Therefore, research into the special coping strategies of menopausal women in Asia is essential. Eighty-two studies with English-language abstracts were selected from a computerized MEDLINE search using the key words estrogen replacement therapy and menopause in various Asian countries (Table 2). The main themes reported were: the occurrence of climacteric complaints or menopausal symptoms and menopausal age [43–56]; the effects of HRT treatment or compliance and the sale of estrogen replacement products [57–68]; the perception of menopause, depression, psychological distress, and the effects of counseling on climacteric symptoms [69–72]; the risk of Alzheimer's disease, menopause-related vascular changes, bone loss, bone density, contraceptive status and sexual function [73–102]; the pattern of postmenopausal bleeding, the measurement of normal ovaries and plasma lipid and lipoprotein levels [103–105]; and special diets [106–108].

These Asian studies do not provide any additional credible scientific evidence to that from the 23 reports on randomized, double-blind, placebo-controlled HRT trials conducted in the USA and Europe.

Recommendations

Three major propositions are recommended for future research in Taiwan. First, the purpose of healthy women taking long-term HRT is to preserve health and prevent disease [2]. Freedman et al argue that a single outcome is often not an appropriate paradigm for trials of disease prevention but the interventions often have potential effects on several diseases [109]. Thus, a major rationale for a trial may be to estimate all of these effects more precisely, thereby providing a basis for informed public health decisions [109]. Simply repeating the WHI trial or other similar HRT research with subjects in Taiwan is undesirable. It is more appropriate to investigate the effects of HRT on a wider range of diseases or disciplines. For instance, breast cancer in Taiwan occurs in younger women compared with the West. The question is whether the increase in HRT use will cause a rise in the incidence of breast cancer in Taiwan. This issue will require further research. A multidisciplinary research team composed of medical experts, public health experts, epidemiologists, and statisticians to carry out this research would be optimal. Furthermore, the experience of menopausal women, their health needs and medical demands, and long-term follow-up of women's health are essential in Taiwan.

Second, the NIH in the USA, responding to the demand of women's organizations and congress-women in 1991, initiated a large-scale estrogen-progestin versus placebo trial in healthy menopausal women [110]. However, there was little reaction from the National Health Research Institutes in Taiwan when the WHI study in the USA was stopped. Although the Department of Health in Taiwan has posted guidelines for HRT use on its website in response to the halted WHI study, they do not provide information on healthcare for menopausal women and alternatives when women do not want to use medication. In Taiwan, HRT resources offered to medical personnel and to the media are distributed predominantly by the pharmaceutical industry. To combat this, we propose that the National Health Research Institutes in Taiwan take responsibility for making HRT resources available. With respect to the health of the general public, there is a need for ethical management and responsibility from related medical societies in combating the over-marketing of medicines in the Taiwanese media. Additional research is needed to tackle this situation.

Third, regarding the use of HRT, gynecologists' or allied physicians' arguments over the different physical constitutions of women in the East and West have been increasing in Taiwan since the WHI trial was stopped. Instead of singling out HRT use, research attention should be focused on the effect of any type of medication on different physical constitutions. This kind of research is recommended to begin as soon as possible in order to avoid any possible overdosage side effects.

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