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D. A. Tan & A. R. B. Dayu

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REVIEW

Menopausal hormone therapy: why we should no longer be afraid of the breast cancer risk

D. A. Tan and A. R. B. Dayu

Section of Reproductive Medicine, Department of Obstetrics and Gynecology, St. Luke's Medical Center – Quezon City, Quezon City, Philippines

ABSTRACT

The threat that women may develop breast cancer is the major reason why both physicians and women are afraid to use menopausal hormone therapy (MHT). The fear pertains to estrogen–progestin replacement therapy (EPRT) as estrogen-alone replacement therapy has no, or even a reduced, breast cancer risk. We reviewed the way breast cancer risk with EPRT was reported in some major publications since 2002 and tried to put the use–risk association in context. We hope this will make it easier for the physician and the menopausal woman to understand the risk involved and allow more confident and more informed decision-making regarding MHT use. We conclude that there are five interrelated reasons why physicians and women should no longer be afraid of the breast cancer risk with EPRT. We submit that breast cancer related to EPRT use is rare because the risk is very low; the reported increase in breast cancer risk with EPRT is not relevant to current practice; modifiable lifestyle factors, not EPRT, are the real risks for breast cancer; breast cancer-specific mortality is reduced in women who develop breast cancer while on EPRT; and avoiding MHT use when indicated puts a woman in harm's way.

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Menopausal hormone therapy; breast cancer; categories of risk; attributable risk; baseline risk

Introduction

Fear makes the wolf bigger than he is (German proverb)

The threat of breast cancer is the major reason why physicians are afraid to recommend the initiation or continuation of menopausal hormone therapy (MHT) and why women are afraid to start or adhere to it [1].

In 2002, the estrogen–progestin arm of the Women's Health Initiative (WHI) was stopped after a mean of 5.2 years of follow-up mainly because the 'test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect' [2,3,p.321]. Many times during the next two decades, women and physicians were regularly reminded, frequently with exaggeration and misinterpretation, of the increase in breast cancer risk with MHT use by the researchers themselves [2–7] and by the media [8,9]. Whether intended or not, this is a failure in straightforward risk communication that distorted the perception of how MHT is really linked to breast cancer. The exaggerated fear of MHT that followed is the main element that led to the 'perfect storm' [9] that caused the precipitous decline in MHT use [10]. This decline has so far remained very difficult to reverse.

It is now clear that there are divergent effects of estrogen–progestin replacement therapy (EPRT) and estrogen-alone replacement therapy (ERT) on breast cancer risk. The reports from the WHI showed significant, albeit very small, increases in the risk of breast cancer with EPRT (specifically, conjugated equine estrogens [CEE] + medroxyprogesterone acetate [MPA]) compared to ERT (CEE alone).

Of the five WHI reports on CEE + MPA (Table 1), one showed no difference [3] and four showed a significant small increase [4,11–13] in the risk of breast cancer among users compared to non-users. On the other hand, of the six WHI reports on CEE alone, three showed no difference [14–16] and three showed a significant small decrease [12,13,17] in the risk of breast cancer among users compared to non-users.

The concern for breast cancer should be directed to women with an intact uterus who need estrogen and also a progestin for endometrial protection and not to hysterectomized women who need estrogen alone. Unfortunately, these divergent effects are not well known and women, as well as physicians, continue to fear MHT regardless of the type of regimen.

Review

This review looked at the way breast cancer risk with MHT was reported in some major publications since 2002. The objective is to put this use–risk association in context and make it easier for both the physician and the menopausal woman to understand the actual risk involved, and allow

CONTACT D. A. Tan datan@info.com.ph Section of Reproductive Medicine, Department of Obstetrics and Gynecology, St. Luke's Medical Center, Quezon City 1104, Philippines

Table 1. Divergent effects of EPRT and ERT on the risk of breast cancer among users versus non-users: WHI reports.

MHT regimen	*Authors, year*	*HR*	*95% CI*	*Reference*
EPRT	Rossouw et al., 2002	1.26	1.00–1.59	[3]
(CEE + MPA)	Chlebowski et al., 2003	1.24	1.02–1.50	[4]
	Chlebowski et al., 2010	1.25	1.07–1.46	[11]
	Bhupathiraju and Manson, 2014	1.28	1.11–1.48	[12]
	Chlebowski et al., 2020	1.28	1.13–1.45	[13]
ERT	Anderson et al., 2004	0.77	0.59–1.01	[14]
(CEE alone)	Stefanick et al., 2006	0.80	0.62–1.04	[15]
	LaCroix et al., 2011	0.75	0.51–1.09	[16]
	Anderson et al., 2012	0.77	0.62–0.95	[17]
	Bhupathiraju and Manson, 2014	0.79	0.65–0.97	[12]
	Chlebowski et al., 2020	0.78	0.65–0.93	[13]

CEE, conjugated equine estrogen; CI, confidence interval; EPRT, estrogen–progestin replacement therapy; ERT, estrogen-alone replacement therapy; HR, hazard ratio; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

more confident and more informed decision-making regarding MHT use.

Results

This review demonstrated five interrelated reasons why physicians and menopausal women should no longer be afraid of the breast cancer risk with EPRT use. We submit that breast cancer related to EPRT use is rare because the risk is really low; the reported increase in breast cancer risk with EPRT is not relevant to current practice; modifiable lifestyle factors, not EPRT, are the real risks for breast cancer; breast cancer-specific mortality is reduced in women who develop breast cancer while on EPRT; and avoiding MHT use when indicated puts a woman in harm's way.

Breast cancer related to EPRT use is rare because the risk is really low

How breast cancer risks are reported

Breast cancer risks with MHT use are reported in various ways in the literature. The initial 2002 WHI CEE + MPA article [3] reported breast cancer risk as hazard ratios (HRs) (95% confidence interval [CI]) and as absolute excess risks per 10,000 person-years attributable to CEE + MPA. Using the latter measure, the investigators concluded that women on CEE + MPA for a mean of 5.2 years, compared to those who were not, had 'eight more invasive breast cancers per 10,000 person-years per year' [3,p.321].

The 2020 WHI article [13,p.369] used HRs with 95% CIs and reported that women on CEE + MPA who stopped after a median 5.6 years and were followed for 18.9 years have a 'HR of 1.28 and 95% CI from 1.13 to 1.45' compared to controls.

The 2019 Collaborative Group on Hormonal Factors in Breast Cancer review [6,p.1159] reported on the probability of developing breast cancer at ages 50–69 years. The study projected that 'for women of average weight in developed countries, 5 years of MHT, starting at age 50 years, would increase breast cancer incidence by about 1 in every 50 users of estrogen plus daily progestogen'.

Table 2. World Health Organization (WHO) Council for International Organizations of Medical Sciences (CIOMS) categorization of adverse drug reactions [18].

	Frequency	
CIOMS III category	N	%
Very common	≥1/10	≥10
Common (frequent)	≥1/100 to <1/10	≥1 to <10
Uncommon (infrequent)	≥1/1000 to <1/100	≥0.1 to <1
Rare	≥1/10,000 to <1/1000	≥0.01 to <0.1
Very rare	<1/10,000	<0.01

These terms and numbers indicating levels of risk convey complex data and are often difficult for many women and even for physicians to comprehend.

Putting reported breast cancer risk in context

The World Health Organization (WHO), through the Council for International Organizations of Medical Sciences (CIOMS), provides strict categorization for describing risk levels for adverse drug events [18] to assist health-care professionals and the public when interpreting risk.

Using the CIOMS categories (Table 2), the eight extra cases of breast cancer per 10,000 person-years in CEE + MPA users compared to non-users, as reported by the WHI in 2002 [3], will be categorized as a rare adverse drug reaction. This risk is also equivalent to 0.08% which is less than a tenth of 1% per year.

Absolute risk, relative risk and attributable risk

Whether a woman is on MHT or not, she can develop breast cancer over a period of time [19]. The increase in breast cancer risk with MHT should be differentiated from that which happens because of aging [20].

In the 2020 WHI article [13], the reported long-term risk of breast cancer for CEE + MPA users (HR 1.28, 95% CI 1.13–1.45) is interpreted as a 28% significant increase in risk. The question is 28% of what? The answer is 28% of the absolute (or baseline) risk of breast cancer for non-users. This number, however, was not available from this WHI paper.

For women not using MHT, the baseline risk for breast cancer can be obtained from the Surveillance, Epidemiology, and End Results Program (SEER) Cancer Statistics Review [21]. Based on the 2012–2014 SEER data for US women, Table 3 presents the 10-year, 20-year and 30-year risks of developing breast cancer. For a 50-year-old, cancer-free woman followed for 10 years, the absolute risk of developing breast cancer is 2.31%.

The absolute risk for breast cancer for CEE + MPA users, then, is calculated by multiplying the absolute risk for breast cancer among non-users by the relative risk for users, 2.31 multiplied by 1.28, and is equal to 2.95 per 100 women.

The attributable risk for breast cancer among CEE + MPA users would therefore be the difference between the absolute risk for users and the absolute risk for non-users, 2.95 minus 2.31, which is equal to 0.64 per 100 women.

Therefore, the breast cancer risk attributable to CEE + MPA after 5.2 years of use is only 0.64%.

Table 3. Ten-year, 20-year and 30-year risk of developing breast cancer [21].

Current age (years) (cancer-free)	Risk (%)		
	10 years	20 years	30 years
30	0.45	1.90	4.11
40	1.47	3.70	6.84
50	2.31	5.54	8.81
60	3.45	6.93	8.91
70	3.95	6.18	N/A

Based on 2012–2014 Surveillance, Epidemiology, and End Results (SEER) data for US women.

Predicted risks

The 2019 Collaborative Group on Hormonal Factors in Breast Cancer review [6] reported a 6.3% baseline risk, which means that '3 out of 50 women without MHT would be expected to develop breast cancer anyway' [22,p.175]. Thus, if 5 years of MHT use would increase breast cancer by '1 in every 50 users of estrogen plus daily progestogen' as stated in the Collaborative Group paper, the number of breast cancer cases expected in women with MHT would be three (baseline) plus one (extra), which add up to 4 per 50 users.

To put the predicted risk in perspective, it was submitted in a commentary to the Collaborative Group review [22] that the article's statement '5 years of use would increase breast cancer incidence by 1 in every 50 users of estrogen + daily progestogen' [6] should be restated as '5 years of use would increase breast cancer incidence from 3 of 50 non-users to 4 of 50 users of estrogen plus daily progestogen' [22,p.176].

Other risk factors

In determining an individual woman's risk for breast cancer, the effect of aging should always be included in the calculation. Increasing age is one of the strongest unmodifiable risk factors for breast cancer [23]. The breast cancer risk increases with age and the reported risk in the WHI studies was for women in later menopause with a mean age of 63.2 (±7.1) years [3], and is not appropriate reference for breast cancer risk when counseling a woman in early menopause.

It is equally necessary to remember that breast cancer risk is affected strongly by ethnicity [24], and the results of a study in one population of women cannot be generalized to another. The risks reported from the WHI and the Collaborative Group studies, derived from white western women, may not be applicable to a woman of different ethnicity.

The reported increase in breast cancer risk with EPRT is not relevant to current practice

The 2019 Collaborative Group on Hormonal Factors in Breast Cancer review [6] analyzed the risk of breast cancer from studies from 1 January 1992 to 1 January 2018. Forty percent of the data in this review were from the 2003 Million Women's Study [25]. The Collaborative review (Table 4) presented significantly increased risks for breast cancer with estrogen–progestogen preparations which contain levonorgestrel, norethisterone acetate or MPA. These increased risks pertain to progestins which are not currently preferred nor recommended. The results are historical and are no longer relevant to current practice [26].

Table 4. Risk (relative risk, 95% CI) of breast cancer in current EPRT users versus non-users during 5–14 years (mean 9 years) of use [6].

Regimen	Adjusted relative risk	95% CI
All EPRTs	2.08	2.02–2.15
By progestin constituent		
Levonorgestrel	2.12	1.99–2.25
Norethisterone acetate	2.20	2.09–2.32
Medroxyprogesterone acetate	2.07	1.96–2.19

CI, confidence interval; EPRT, estrogen–progestin replacement therapy.

Table 5. Increases in breast cancer risk with EPRT compared to those with modifiable lifestyle factors.

Factor	Range (%)	References
CEE + MPA, all WHI studies	24–28	[3,4,11,12,13]
Physical inactivity	7–33	[31,32,33]
Alcohol consumption	32–46	[34]
Obesity	26–152	[32,33,35]

CEE, conjugated equine estrogens; EPRT, estrogen–progestin replacement therapy; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

Progestins currently preferred as components of EPRTs are micronized progesterone and dydrogesterone.

A 2017 review of 14 studies [27] concluded that the use of estrogen combined with micronized progesterone (odds ratio [OR] 1.00, 95% CI 0.8–1.2) and dydrogesterone (OR 1.1, 95% CI 0.89–1.36) carries no risk for breast cancer. This review reaffirmed the higher breast cancer risk with EPRTs which contain levonorgestrel (OR 1.47, 95% CI 1.17–1.85), norethisterone acetate (OR 1.44, 95% CI 1.26–1.65) and MPA (OR 1.19, 95% CI 1.07–1.33) [27].

A 2016 Cochrane review on the use of tibolone in postmenopausal women [28] found no increased risk of breast cancer among users of tibolone (OR 0.52, 95% CI 0.21–1.25) in four randomized trials with very low-quality evidence.

Modifiable lifestyle factors, not EPRT, are the real risks for breast cancer

Certain modifiable lifestyle factors can contribute more substantially to the development of breast cancer than hormone therapy: 'Even if EPRT did cause an increase in breast cancer risk, the magnitude of that risk is small, and less than that risk seen with many lifestyle factors' [29,p.633].

EPRT (CEE + MPA) increased the risk for breast cancer (Table 5) from 24% to 28% in users compared to non-users [3,4,11–13]. These risk levels are lower than those associated with modifiable lifestyle risk factors [30]. Physical inactivity increases breast cancer risk by 7–33% [31–33], regular alcohol consumption by 32–46% [34] and obesity by 26–152% [31,32,35]. Certainly, these modifiable factors should be given greater consideration when women want to reduce breast cancer risk.

Breast cancer-specific mortality is reduced in women who develop breast cancer while on EPRT

In contrast to the possible increased risk for breast cancer with MHT use, almost all of the studies since the 1990s have

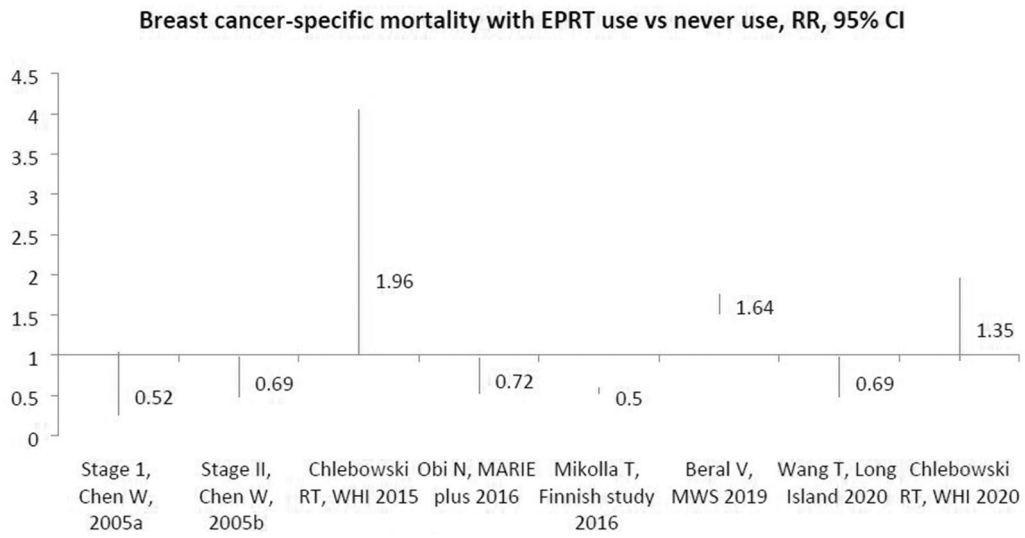

Figure 1. Forest plot showing breast cancer-specific mortality for seven studies [45,49,46,47,50,48,13]. CI, confidence interval; EPRT, estrogen–progestin replacement therapy; MARIE, Mamma Carcinoma Risk factor Investigation; MWS, Million Women Study; WHI, Women's Health Initiative.

indicated that women who develop breast cancer while using MHT have a reduced risk of dying from it [36].

Eight studies [37–44] from 1990 to 2001 showed the relative risk of mortality from breast cancer consistently to be <1.0 among MHT users compared to non-users.

Figure 1 demonstrates the risk (relative risk, 95% CI) of breast cancer-specific mortality in EPRT users versus never users in seven studies published from 2005 to 2020. One study [45] divided patients into those with stage I and those with stage II disease. Four studies showed statistically significant reductions in breast cancer-specific mortality [37,46–48]. Three studies, which included two WHI reports, showed no effect of EPRT use [13,37,49] and only one study, the Million Women Study [50], showed a statistically significant increase in breast cancer-specific mortality.

Avoiding MHT use when indicated puts a woman in harm's way

Following the initial WHI report [3], a number of publications have claimed that stopping or not initiating MHT in women with indications for its use has caused unnecessary harm and suffering.

A study using a claims database for multiple health-care plans [51] showed that the incidence of presumed osteoporotic fractures increased significantly following the decline in MHT use despite a concurrent increase in the use of other bone-modifying agents. Age-adjusted incidence of fractures remained stable at 28 per 10,000 from 2000 through 2002 before the WHI and rose during the subsequent 3 years, reaching 40 per 10,000 in 2005 with statistically significant trends for virtually all fracture types.

A longitudinal observational study [52] from the Southern California Kaiser Permanente health management organization concluded that, after 6.5 years of follow-up, women who discontinued MHT were at 55% greater risk of hip fracture compared with those who continued using MHT (HR 1.55; 95% CI 1.36–1.77) and the risk incrementally increased with longer duration of cessation (p for trend < 0.0001).

An analysis using US census data [53] claimed that many thousands of excess deaths resulted in women who had undergone hysterectomy without adequate estrogen-alone therapy. The avoidance of estrogen-only use was attributed to concerns generated by the results of the WHI estrogen plus progestin study. It was estimated that estrogen-only therapy in women aged 50–59 years declined nearly 79% between 2001 and 2011. During that time, a minimum of 18,601 and a maximum of 91,610 excess deaths were attributed to estrogen avoidance [53].

Using MHT may carry risk, but not using MHT carries the greater disadvantage of being denied its benefits. A 2019 editorial called for an increase in the use of hormone therapy to prevent disease in symptomatic postmenopausal women:

> Millions of women who could be safely treated hormonally are not and as result have menopause symptoms affecting their quality of life; adverse effects on the cardiovascular system, bone, mood, sexual health, and cognition, and increased risk of dying before age 70. [54,p.573]

Discussion

Historically, the association of MHT with breast cancer has always been a serious and controversial issue in menopause management.

In 2001, a qualitative review of 65 observational studies from peer-reviewed journals published from 1975 to 2000 found 'little consistency among studies that estimated the risk of breast cancer in hormone users compared with nonusers' [55,p.498]. As shown in Figure 2, of 20 published studies of EPRT, 80% found no increased risk, 10% found a significantly increased risk and 10% found a significantly decreased risk. Of 45 published studies on ERT, 82% found no increased risk, 13% found a small increased risk (none greater than 2.0) and 5% found a significantly decreased risk.

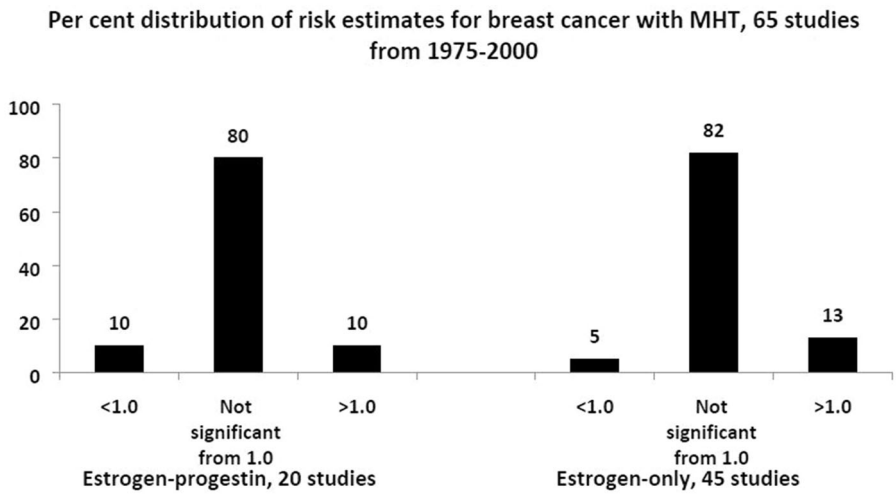

Figure 2. Breast cancer risks in 65 observational studies prior to the Women's Health Initiative (WHI) [55]. MHT, menopausal hormone therapy.

The authors commented that 'the distribution of risk estimates is what would be expected if there were no association' [55,p.502]. They also expressed the hope that randomized clinical trials like the then ongoing WHI 'could clarify the association between ERT or HRT and breast cancer' [55,p.504]. As the events of the last 20 years showed, however, the WHI did not clarify but, rather, obfuscated the association between MHT and breast cancer in the minds of physicians and menopausal women alike.

It is difficult to accept that the major reason for the decline in MHT use is fear of breast cancer generated by failure to communicate risk in a straightforward manner. If only the breast cancer risk (HR 1.26, nominal 95% CI 1.00–1.59, adjusted 95% CI 0.83–1.92) reported in the initial WHI article [3] was interpreted as a 26% statistically insignificant increase because the 95% CIs, both nominal and adjusted, included the number 1.0, the value of 'no effect' [56], then there would have been no fear and no uproar. But to declare in a press conference [2,p.1–2] that 'a 26% increase in breast cancer risk is too high a price to pay, even if there were a heart benefit' and that this 'increased risk applied to all women regardless of age, ethnicity, and family history of breast cancer' was certainly an invitation to an upheaval that cannot be justified by an insignificant breast cancer statistic.

Risk for the individual against risk for the population

The risks of MHT have been also extrapolated to potential effects for the population.

In the 2002 initial WHI report, looking at overall risks and benefits, the authors admitted that 'the absolute excess risk (or risk reduction) attributable to estrogen plus progestin was low' [3,p.331]. However, they argued that:

> if the current findings can be extrapolated to even longer treatment duration, the absolute risks and benefits associated with estrogen plus progestin … … … could be substantial and on a population basis could account for tens of thousands of conditions caused, or prevented, by hormone use. [3,p.331]

Likewise, the 2019 Collaborative group review, looking only at breast cancer, concluded that 'in western countries there have been about 20 million breast cancer diagnosed since 1990, of which about 1 million would have been caused by MHT use' [6,p.1168].

These strongly dramatic references to the effects on populations may be important from a public health perspective, but they only misrepresent risk and heighten the fear of MHT for the individual patient. They are, 'strictly speaking, irrelevant when it comes to an individual making a decision about her treatment' [22,p.176].

Neglect of menopause education

The most serious consequence of the negative attitude toward MHT is the neglect of menopause education and training. This is responsible for the current lack of physicians' competency, skill and experience in the care of menopausal women [57,58]. At present, residency programs in primary care, internal medicine and even obstetrics–gynecology do not provide adequate education in menopause [59].

It is obvious that this situation will have grave repercussions on postmenopausal health care in the years to come. By 2030, the world population of menopausal women is projected to increase to 1.2 billion, with 47 million new entrants each year [60]. Who will take care of them?

Even if we are now, as claimed [61,p.306], witnessing 'a rebirth of MHT' because women 'have had enough of putting up with tough menopausal symptoms and want effective treatment', the question is 'whether physicians are prepared for this new beginning' [61].

We have already lost a generation of physicians; there is an urgent need to get 'clinical care back on track' [59,p.803]. We need to 'train and equip the next generation of healthcare providers with the skills to address the current and future needs' [59,p.805] of women at midlife.

The Women's Health Initiative

The sad state of menopause management is in large measure due to 'over-interpretation and misrepresentation' [62,p.215] of the results of the WHI, the largest ever

randomized placebo-controlled trial evaluating MHT use. The parade of WHI articles for most of the last 20 years constituted a 'campaign of fear' [63,p.535] especially directed at breast cancer. The consequent reluctance to use MHT has 'derailed and fragmented clinical care, creating a large and unnecessary burden of suffering' [59,p.805] for women worldwide.

In a surprising turnaround for the media, the *Los Angeles Times* stated that the WHI results were 'misread and miscommunicated … and the investigators generated fears where they were not warranted – indeed, where they were flat wrong. Unfortunately, their misbegotten 17-year old claims continue to reverberate' [64].

Wolf Utian recalled, in a 2018 editorial [65,p.125], that '15 years [after the initial WHI report in 2002] the WHI investigators have tried to back track on those initial exaggerations but of course the damage has already been done'. He consequently named the WHI 'the greatest misdirection in science in the history of women's health' [65,p.125].

Conclusion

Currently, a great divide exists between what is real and what is not in the perception of risks and benefits of MHT. Unfortunately unwarranted mistrust and fear of MHT have become deeply rooted and prevail among health practitioners, women, and the media.

There is an urgent 'need to bridge the gap in risk perception with evidence-based common-sense advice' [9,p.13]. To recommend or not to recommend MHT is a multidimensional issue. Risk levels should be put in context and considered together with other factors that may affect decision-making. They should be presented in terms understandable to the menopausal woman who will eventually make the decision to take MHT or not. Informed decision-making by the menopausal woman, however, requires counseling from her informed physician:

> Preventing a woman from the sound benefits of a properly instituted hormonal medication, just for the fear of rare side-effects, is not satisfactory medicine. [66,p.323]

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