

# Women's Health Initiative and menopausal hormone management

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This review discusses the findings of the Women's Health Initiative in 2002 and its updates in 2013. Risks and benefits of menopausal hormone therapy in terms of coronary heart disease, breast cancer, stroke, pulmonary embolism and venous thromboembolism, colorectal cancer, endometrial cancer, and hip fracture/osteoporosis are also discussed, as is prescription of menopausal hormone therapy to alleviate menopausal symptoms and optimise health.

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## Women's Health Initiative in 2002

Since 1960s, the use of hormones in women to relieve menopausal symptoms and reduce mortality and incidence of coronary heart disease (CHD) has become popular<sup>1-4</sup>. The Women's Health Initiative (WHI) is a long-term health study funded by the National Heart, Lung, and Blood Institute of the United States<sup>5</sup>. It aims to assess the effect of hormonal use on CHD and invasive breast cancer in healthy postmenopausal women. In 2002, the WHI reported increased risks of invasive breast cancer, CHD, stroke, and pulmonary embolism in women on menopausal hormone therapy (MHT) [Table]<sup>6</sup>. These results shook the media<sup>7</sup>. However, the 2002 WHI has limitations in terms of study design, interpretation<sup>8</sup>, statistical analysis<sup>9</sup>, and presentation of results to the public. It did not address the benefits of MHT to relieve menopausal symptoms. Nonetheless, the US Preventive Services Task Force recommended against MHT for preventing CHD<sup>10</sup>, and the numbers of users and new users of MHT worldwide decreased significantly<sup>11-13</sup>.

The clinical alert<sup>14</sup> of WHI drew widespread media attention. Some media misinterpreted 26% increase in relative risk (of invasive breast cancer) as 26% increase in absolute risk. To prevent misinterpretation, a short section on study results to the public is suggested<sup>15</sup>.

In the 2002 WHI, the mean age of women in the MHT arm was 63.2 years. Only one third aged 50 to 59 years, and most women commenced on MHT after 60 years of age. In addition, one third of women were obese (body mass index  $\geq 30$  kg/m<sup>2</sup>), one third were treated for hypertension, and only half were never-smokers. Age, obesity, hypertension, and smoking are risk factors for CHD<sup>16</sup>, and these are confounding factors of the 2002 WHI. Although the sample

was considered 'normal healthy population' in the US, the results may not be representative to other populations<sup>17,18</sup>. In addition, the high drop-out rate (42% from the MHT group and 38% from the placebo group) and the small absolute increase in invasive breast cancer (8 more per 10000 women-years) render little clinical significance. Furthermore, the WHI was not designed to and did not have enough statistical power to assess the effect of MHT in younger peri-menopausal women<sup>19</sup>. The decision of early termination of MHT was based on unadjusted relative risks of CHD and invasive breast cancer; however, after taking into account the confounding factors, the adjusted relative risks were not significant<sup>20</sup>.

In a 2012 study evaluating German patients' and gynaecologists' attitudes toward MHT before and after the 2002 WHI, 80% of patients became more critical about MHT after the WHI, but most of them were badly (43.9%) or moderately (44.5%) informed about WHI through the media<sup>21</sup>. MHT use decreased after the WHI; the decrease was smaller in women aged 60 to 69 years than in those aged 40 to 59 years<sup>22</sup>. Younger women with more vasomotor symptoms who are recommended to MHT showed the largest decrease in MHT initiation (owing to the risks of CHD and invasive breast cancer) and continuation (owing to doctor advice or media reports)<sup>23</sup>. Therefore, better education and understanding regarding the risks and benefits of MHT for patients and clinicians are needed, as is a more personalised treatment strategy. Without the option of MHT, peri- or early postmenopausal women may suffer from climacteric symptoms and lose the opportunity of cardio-protection and risk reduction of osteoporosis<sup>24</sup>.

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**Table. Findings of the 2002 Women's Health Initiative\***

Adverse outcome	Estimated hazard ratio for the menopausal hormone therapy group	Absolute risk change per 10 000 women-years
Coronary heart disease	1.29	7 more
Invasive breast cancer	1.26	8 more
Stroke	1.41	8 more
Pulmonary embolism	2.13	8 more
Colorectal cancer	0.63	6 fewer
Endometrial cancer	0.83	Not significant
Hip fracture	0.66	5 fewer

\* Compared with the placebo group, the menopausal hormone therapy group has an absolute excess risk of 19 adverse events per 10000 women-years but no overall increase in mortality

The 2002 WHI also affected physicians' clinical practice, counselling, and prescription behaviours of MHT<sup>25</sup>. Physicians were concerned about the ambiguity of health information the WHI brought to women; they became less likely to prescribe MHT<sup>25</sup>. Compared with general gynaecologists, specialised gynaecologists reported a smaller decrease in MHT prescription<sup>21</sup>.

### Updates on Women's Health Initiative

Since the 2002 WHI, new evidence has resulted in updated consensus statements and recommendations in different societies. The North American Menopause Society published the evidence-based position statement in 2010 and updated it in 2012, recommending the initiation of MHT around menopause to treat climacteric symptoms and to prevent osteoporosis in high-risk patients<sup>26</sup>. It states that the absolute risk to healthy women aged 50 to 59 years is low. Similarly, the International Menopause Society updated its recommendations in 2011 and states that the potential benefits of MHT, if given for a clear clinical indication, outweighs the risks, which are low if MHT is initiated within a few years of menopause<sup>27</sup>.

In 2013, cumulative 13-year follow-up data of WHI and subgroup analysis reported that the risk of CHD was neutral for MHT, but such risk increased significantly in women past 20 years of menopause, probably owing to other risk factors (age, hypertension, diabetes) rather than MHT<sup>28</sup>. The risks and benefits of MHT are complex.

### Risks and benefits of menopausal hormone therapy

#### Coronary heart disease

The effect of MHT on CHD is associated with patient age and time since menopause when MHT is initiated<sup>29</sup>.

Vascular response to oestrogen is affected by oestrogen receptor expression in artery<sup>30,31</sup>. Oestrogens are beneficial to younger women by delaying onset of atherosclerosis but are detrimental to older women who already have atherosclerosis<sup>32</sup>. The International Menopause Society and the North American Menopause Society updated their recommendations in 2016 and 2017, respectively<sup>33,34</sup>, based on the 2015 Cochrane review<sup>35</sup> and the 2013 WHI<sup>28</sup>. Both societies considered that MHT is safe and effective to treat menopausal symptoms, provided that MHT is initiated in healthy postmenopausal women aged <60 years or within 10 years of onset of menopause. They also acknowledged the increased risk of CHD if MHT is initiated >10 years since menopause.

#### Breast cancer

Association between MHT and invasive breast cancer remains controversial. In the 2002 WHI, the absolute excess risk of invasive breast cancer was low (<0.1% per year), and the excess risk was affected by various confounding factors (body weight, alcohol intake, and physical inactivity)<sup>36</sup>. Therefore, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommended up to 5 years of combined MHT<sup>37</sup>, after discussion with patients the potential small increased risk of breast cancer<sup>34</sup>.

#### Stroke

The risk of stroke does not increase if MHT is initiated in women aged <60 years and/or within 10 years since menopause<sup>28,35</sup>. However, stroke incidence is increased if MHT is initiated after age 60 years.

#### Pulmonary embolism and venous thromboembolism

Oral oestrogens but not transdermal oestrogens increase the risk of recurrent venous thromboembolism<sup>38</sup>.

Oral oestrogens may cause a significant increase in resistance to activated protein C and hence activating blood coagulation<sup>39</sup>. Such increase is much smaller in transdermal oestrogens. The International Menopause Society recommends the use of transdermal oestrogen therapy for obese women with menopausal symptoms and recommends against the use of oral oestrogen in women with a history of venous thromboembolism<sup>33</sup>.

### Colorectal cancer

A meta-analysis reported that MHT reduces the risk of colorectal cancer, with the benefit persisting up to 4 years of cessation of MHT<sup>40</sup>. In contrary, the 2013 WHI reported insignificant effect of MHT on colorectal cancer<sup>28</sup>. Thus, MHT should not be used solely as chemoprevention of colorectal cancer<sup>33</sup>. Rather than promoting MHT's benefit in reducing colorectal cancer risk, a healthy lifestyle together with more frequent colorectal cancer screening should be emphasised<sup>41</sup>.

### Endometrial cancer

The 2002 WHI reported a reduced risk of endometrial cancer after MHT; this benefit remains after 13 years<sup>28</sup>. However, oestrogen increases the risk of endometrial hyperplasia and cancer<sup>42</sup>.

### Hip fracture/osteoporosis

In the 2013 WHI, MHT reduces risks osteoporotic fracture at any age and is considered the most appropriate therapy in the early menopause for prevention of fractures<sup>33</sup>. The benefit of MHT in fracture prevention persists after 5 years of MHT discontinuation<sup>43</sup>.

## Prescription of menopausal hormone therapy

With better understanding of risks and benefits

of MHT, comprehensive assessment of patients should be performed before prescription. This includes initial consultation to initiate check-up and identify risk factors. Toolkits with algorithms regarding patient assessment, hormonal therapy initiation, and review strategies are developed for clinicians<sup>44</sup>. Clinicians should help women make informed decisions on MHT by providing adequate information on their profiles and online resources for patient education. MHT is the most effective therapy in alleviating vasomotor symptoms, whereas complementary therapies have limited efficacy<sup>33</sup>. Thorough discussion with patients enables them to understand their own risk-and-benefit profile<sup>45</sup>. MHT should be customised regarding starting and stopping of MHT as well as dose and route of administration<sup>46</sup>. Patients become more involved in management of their menopausal transition, and menopause counselling provides an opportunity to reinforce key preventative health measures.

## Conclusion

Most mainstream women's health regulatory and scientific bodies support appropriate use of MHT<sup>33,34,37</sup>. Future studies that compare different MHT regimens in terms of dose, route of administration, and duration of use are warranted. The second WHI extension study in 2020 may provide further insight into the health outcomes after long-term MHT<sup>5</sup>. A meta-analysis in 2019 concluded that MHT had at an excess risk of breast cancer even higher than that reported in the 2002 WHI<sup>47</sup>. However, the breast cancer risk under the current recommended MHT regimens is not addressed, as the regimens have changed substantially<sup>48</sup>. Further research is needed to address the impact of latest regimens.

## Declaration

The author has no conflict of interest to disclose.

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