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SHOULD TRANSDERMAL RATHER THAN ORAL ESTROGENS BE USED IN MENOPAUSAL HORMONE THERAPY? A REVIEW

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ABSTRACT

The current evaluation of the benefit/risk ratio associated with menopausal hormone therapy (MHT) use is largely based on clinical trials which investigated the effects of oral treatments. Would MHT with transdermal estrogens be associated with a more favourable benefit/risk ratio? We reviewed the available epidemiologic evidence on that question. Epidemiologic studies were considered if they provided risk estimates of conditions which carry an important weight among menopausal women, and for which epidemiologic evidence of a possible link with MHT use is convincing: cardiovascular diseases, breast cancer, diabetes, colorectal cancer and hip fracture. We did not include studies with only surrogate measures. We found that the available information on the potential impact of the route of administration of MHT on the risk of our selected outcomes is limited. To date, epidemiologic data suggest that it has no impact on the risk of breast cancer and hip fracture. Results on the risk of coronary heart disease and colorectal cancer are inconsistent. Studies on stroke and diabetes risk are too few to allow meaningful conclusions. There is a suggestion that transdermal MHT may be less deleterious than oral MHT regarding venous thromboembolism which needs to be confirmed. The issue of the route of administration of MHT should remain an active area of research as part of an attempt to identify treatment modalities that would have the least potential for exerting adverse effects.

INTRODUCTION

Cardiovascular safety concerns demonstrated by the Women's Health Initiative (WHI) randomized controlled trial¹ together with the WHI and the Million Women Study reports of an increased breast cancer risk among estrogen-progestagen menopausal hormone therapy (MHT) users^{2;3} led the European Medicines Agency to restrict indications of MHT to the treatment of climacteric symptoms: it considered that, otherwise, risks outweigh benefits.⁴ The American WHI trial evaluated oral conjugated equine estrogens, used alone or associated continuously with oral medroxyprogesterone acetate, but many other types of MHT are used around the world: estrogens can also be administered through the skin, other estrogenic and progestagenic molecules can be used, with different doses and different numbers of days of use per month. One must of course consider that the risks observed in the WHI also apply to other types of MHT until the contrary is demonstrated. Meanwhile, one should aim at identifying the safest modalities of use of MHT.

The present review will focus on the route of administration of the estrogenic component of MHT: may transdermal MHT be associated with a more favourable risk/benefit ratio than oral MHT? Because of the often complex interplay of biologic mechanisms at work when MHT is administered, we generally need epidemiologic studies with clinical outcomes to appreciate the net effect of MHT on the risk of a given disease. We therefore performed a review of the epidemiologic evidence available to date on the impact of the route of administration of MHT on the risk of selected conditions.

METHODS

We chose to focus on conditions which carry an important weight among menopausal women, and for which epidemiologic evidence of a possible link with MHT use is convincing. Of these, ischaemic heart disease and cerebrovascular disease constitute a considerable burden among women aged 45 years or more in the established market economies, followed by breast cancer and diabetes mellitus, and then by colorectal cancer and hip fracture.^{5;6} We also considered venous thromboembolism together with ischaemic heart disease and cerebrovascular disease in a “cardiovascular disease” category because pulmonary embolism is a potentially fatal condition for which a link with MHT use is demonstrated.

We included epidemiologic studies (clinical trials, case-control and cohort studies) when they provided risk estimates of the considered condition. We did not include studies with only surrogate measures (such as bone mineral density) as outcomes, because variations in individual intermediate biomarkers may not directly translate into clinically relevant variations in the risk of the condition considered. Sample size, main characteristics of included women, risk estimates, 95% confidence intervals [CI] and results of the tests for homogeneity between estimates associated with oral and transdermal MHT are given when available.

In the following, the term “MHT” is used when estrogen-alone and estrogen-progestagen therapy are not distinguished; “E-MHT” designates estrogen-alone therapy; “EP-MHT” designates estrogen-progestagen therapy; “transdermal” MHT designates transdermal (i.e. in the form of gel or patch) estrogen, associated or not with a progestagen (whatever the route of administration of the progestagen).

For each condition, we begin with a brief reminder of what is known about its relation with MHT use and we then examine the epidemiological evidence available regarding the impact of the route of administration of MHT.

RESULTS

CARDIOVASCULAR DISEASE

Ischaemic heart disease

In the 1990s, based on consistent evidence from observational studies, MHT was thought to reduce the risk of coronary heart disease (CHD) by 30% or more.⁷ However, this was not confirmed in subsequent randomized controlled trials which even demonstrated an early harm of EP-MHT.⁸⁻¹¹ Potential explanations for these contradictory findings included methodological weaknesses that affect observational studies, such as their inability to properly identify events that occur soon after MHT initiation (in the case of cohort studies) and to properly eliminate confounding by socio-economic, health or behavioural parameters.^{12;13} As participants in randomized trials were in average several years older at treatment initiation compared with those included in observational studies, it was also postulated that CHD risk might be lessened when MHT is started soon after menopause rather than later.¹⁴ This “timing hypothesis” is however currently not confirmed.¹⁵ The effect of MHT on CHD risk therefore remains unclear.

Randomized trials which evaluated transdermal MHT provided no evidence that it is associated with a beneficial effect on CHD risk or that it differs from oral MHT concerning this risk.¹⁶ Results from observational studies comparing oral and

transdermal MHT are inconsistent (Table 1). Some found similar risk reductions associated with both oral and transdermal MHT,^{17;18} one case-control study showed transdermal MHT to be associated with a significantly elevated CHD risk compared with oral MHT¹⁹ whereas two record-linkage cohort studies suggested the contrary,^{20;21} and another study suggested increases in risk for both oral and transdermal MHT.²² Of note, only one of these studies excluded premenopausal women¹⁸ and only Løkkegaard *et al.*²¹ compared oral and transdermal MHT without progestagen.

The effect of MHT on CHD risk is therefore ambiguous, and there is currently no consistent evidence for an effect of the route of estrogen administration.

Cerebrovascular disease

Evidence from clinical trials shows MHT to be associated with a significant 30% increase in risk of total stroke,^{16;23} with no difference between E-MHT and EP-MHT.¹⁶ It is further suggested that, among subjects who have stroke, those in the MHT groups have a worse outcome,^{16;23} and that the deleterious effect of MHT is limited to ischaemic stroke.²³ A meta-analysis of nine cohort studies published in 2002 also points toward a significant increase in ischaemic but not haemorrhagic stroke with MHT ever-use compared with never-use.²⁴ Of the largest recent observational studies evaluating the risk of stroke in relation to MHT use, three are concordant with these conclusions,²⁵⁻²⁷ whereas both Lemaitre *et al.*²⁹ and Prentice *et al.*²⁸ found no evidence of an elevation in the risk of stroke with MHT use.

The possibility of a differential effect between transdermal and oral MHT regarding stroke risk has been rarely investigated. In the meta-analysis of trials performed by Sare *et al.*,¹⁶ subgroup analyses showed no difference in

cerebrovascular events for oral versus transdermal administration (but the number of trials using transdermal administration was small). Only two observational investigations compared transdermal and oral MHT in this regard. The first one is a nested case-control study using data from the UK General Practice Research Database, which included 920 women 50-69 years old with a diagnosis of first ischaemic stroke, haemorrhagic stroke or transient ischaemic attack and 10,000 controls.²⁵ Regarding transient ischaemic attacks, and compared with MHT never-use, there was a suggestion of a greater risk associated with oral MHT (multivariable-adjusted odds-ratio [OR] 1.47; 95% CI 1.09-1.97) than with transdermal MHT (multivariable-adjusted OR 0.86, 95% CI 0.43-1.73) but the CIs largely overlap, which is compatible with no difference between the two types of MHT. The small number of users of transdermal preparations precluded a similar assessment for ischaemic and haemorrhagic stroke risks, which were non-significantly slightly increased with current MHT use. The second study investigating oral and transdermal MHT concerning the risk of stroke is an Italian record-linkage study which examined the effect of the persistence with MHT.²⁰ It included 76,875 women aged 45-65 years who received at least one MHT prescription during 1998-2000, of whom 298 experienced hospitalization for cerebrovascular disease. Compared with women who took oral MHT for ≤ 6 months, those exposed for 2-3 years and >3 years showed multivariable-adjusted Hazard-Ratios (HRs) of 0.73 (95% CI 0.18-2.93) and 0.54 (95% CI 0.08-3.86), respectively; compared with women who took transdermal MHT (mainly patches) for <6 months, those exposed for 2-3 years and >3 years showed multivariable-adjusted HRs of 0.50 (95% CI 0.29-0.87) and 0.39 (95% CI 0.18-0.82), respectively.

It can be concluded that the very few data exploring the effect of the route of administration of MHT on the risk of stroke do not suggest any strong effect of that parameter.

Venous thromboembolism

Evidence from both clinical trials and observational studies is consistent in indicating current use of MHT to be associated with a two- or three-fold increased risk of venous thromboembolism (including deep vein thrombosis and pulmonary embolism), with the highest risks occurring in the first year of use.^{16;24;30} Trials further suggest that the risk is less elevated with the use of E-MHT rather than EP-MHT.¹⁶

Studies evaluating the risk of venous thromboembolism with transdermal MHT are not numerous. Sare *et al.*¹⁶ noted no significant difference between oral and transdermal MHT in their meta-analysis of clinical trials, but the number of trials using transdermal administration was small. The earliest observational studies evaluating the risk of venous thromboembolism with transdermal MHT included very few cases among transdermal MHT users (Table 2). They found no significant difference between oral and transdermal MHT.³¹⁻³³ In an Italian population-based record-linkage study including 171 women aged 45-79 years with an idiopathic venous thromboembolism episode and 10,000 controls, 79% of exposure was with transdermal EP-MHT; the multivariable-adjusted OR associated with MHT current-use was 2.3 (95% CI, 1.0-5.3; six cases among MHT users) compared with MHT never-use.³⁴ The most recent observational studies comparing the risk of venous thromboembolism associated with oral and transdermal MHT have been performed in France, where use of transdermal estrogens is

predominant.^{35;36} Both found oral but not transdermal estrogen associated with a significant increase in venous thromboembolism risk. In the cohort study, the HRs associated with oral and transdermal estrogens differed significantly.³⁶

In conclusion, there is a recent suggestion from observational studies that transdermal MHT may be less deleterious than oral MHT regarding the risk of venous thromboembolism. This finding needs to be confirmed in future studies, which should carefully: (i) disentangle the effects of route of administration and progestagen molecule, since the French studies suggested that different progestagens may have different effects on the venous thromboembolism risk^{35;36}; (ii) limit incomplete capture of early events (which is likely to have happened in the French prospective cohort study) since the highest risks are seen in the first year of use¹³; and (iii) compare oral and transdermal MHT within homogeneous strata of time since treatment initiation, for the same reason.

BREAST CANCER

The relation between MHT use and breast cancer risk has been investigated in many epidemiological studies, whose results have led to the conclusion that EP-MHT is carcinogenic to the human breast.³⁷ Evidence comes from clinical trials and observational studies which suggest a \approx 30-70% increase in risk with EP-MHT current use,^{38;39} which would disappear a few years after treatment discontinuation.^{39;40} MHT use as a breast cancer risk factor gained additional support from the concomitant reductions in breast cancer incidence and in the use of MHT recently observed in several countries.⁴¹ EP-MHT use has been found associated with a greater breast cancer risk than E-MHT, but whether the latter is associated with an increase in breast cancer risk compared with MHT never-use is still the subject of

intense debate: use of estrogen-alone was associated with a decreased risk in the WHI trial⁴² but not in observational studies.^{38;39}

The impact of the route of administration of MHT on breast cancer risk began to be investigated lately (Table 3). To our knowledge, the UK Million Women Study investigators are the first to have done so, and their prospective cohort is the largest on the question.³ In this study, there was no significant difference between HRs associated with oral and transdermal E-MHT. Then, in Finland, Lyytinen *et al.*⁴³ reached the same conclusion after having compared oral and transdermal E-MHT with similar doses and durations of use. In another study focusing on EP-MHT, they found that oral and transdermal EP-MHT showed similar trends in the risk elevation.⁴⁴ The same authors were then able to compare oral and transdermal EP-MHT for a given progestagen (i.e. norethisterone acetate) in a further case-control study.⁴⁵ Again, they found no large difference between oral and transdermal EP-MHT regarding the risk of breast cancer. In the French E3N cohort study, no significant difference was found between the effect estimates associated with oral and transdermal MHT, for a given associated progestagen.^{46;47} In a study based on the UK General Practice Research Database, Opatrny *et al.*⁴⁸ found that oral but not transdermal MHT ever-use was associated with a significant increase in risk; however, CIs associated with oral and transdermal MHT overlap, which is compatible with no difference in risk estimates. Finally, only one study found a significant difference in the estimated effects of oral and transdermal MHT. That cohort study investigated the effect of the persistence with MHT and included only women who had received at least one MHT prescription during 1998-2000.⁴⁹ Compared with women who took oral MHT for <6 months, those exposed for >2 years showed an age-adjusted HR of 2.14 (95% CI 1.43-3.21) whereas, compared

with women who took transdermal MHT (mainly patches) for <6 months, those exposed for >2 years showed age-adjusted HR of 1.27 (95% CI 1.07-1.51).

The best observational evidence regarding the impact of the route of administration of MHT on the risk of breast cancer comes from studies that have evaluated E-MHT, since there is serious suggestion that the risk of breast cancer is also influenced by the progestagen component of EP-MHT and its modalities of use.⁵⁰ The best observational evidence to date therefore suggests that there is no differential effect of oral and transdermal MHT on the risk of breast cancer.

DIABETES

Use of MHT is likely to decrease the risk of type 2 diabetes, as suggested by a meta-analysis of clinical trials evaluating oral MHT, which showed a 30% reduction in risk for women in the MHT groups.⁵¹ Observational studies on the relation between MHT use and risk of diabetes are scarce. Two prospective observational studies both including ≈1200 cases of type 2 diabetes found the risk to be significantly reduced among MHT users compared with never-users.^{52;53} Among prospective studies of much more limited size, two found no significant association between MHT use and risk of diabetes,^{54;55} whereas a third one found a significant decrease in risk among MHT users compared with never-users.⁵⁶

The latter study evaluated exclusively transdermal EP-MHT but is based on only six cases of diabetes among users. To our knowledge, the only study that directly compared oral and transdermal MHT is the French E3N prospective cohort, which included 63,624 postmenopausal women among whom 1220 new-onset diabetes cases were identified.⁵³ Use of oral MHT was associated with a significantly greater decrease in diabetes risk than use of transdermal MHT

(compared with MHT never-use, multivariable-adjusted HR 0.68, 95% CI 0.55-0.85, 125 cases among oral MHT users; HR 0.87, 95% CI 0.75-1.00, 425 cases among transdermal MHT users; *P* for homogeneity between these two HRs 0.028).

However, the authors explain that some progestagens were preferentially combined with either oral or transdermal estrogens, which makes possible that the difference between the two HRs in fact reflected differences between progestagens. They did not observe significant differences in oral and transdermal effect estimates within homogeneous categories of progestagen, but the number of cases may have been too low.

In conclusion, the single observational study evaluating the impact of the route of administration of MHT on the risk of diabetes provides a weak suggestion that oral MHT may have a more marked protective effect than transdermal MHT.

COLORECTAL CANCER

Epidemiological evidence for a link between MHT use and colorectal cancer risk is equivocal, but in aggregate, it points toward a possible protective effect. A meta-analysis of observational studies indicates a ≈20% reduction in colorectal cancer risk with MHT ever-use, with much of the apparent reduction limited to recent use.⁵⁷ These results mainly pertain to E-MHT, since the studies included in the meta-analysis were mostly performed before use of EP-MHT became widespread. The largest recent observational studies generally suggest a similar protective effect of EP-MHT.⁵⁸⁻⁶⁰ However, one case-control study found the risk reduction to be limited to users of EP-MHT,⁶¹ whereas one cohort study concluded the contrary⁶²; another large cohort study even found no link between MHT use and colorectal cancer risk.⁶³ In the WHI trials, E-MHT was not significantly associated

with colorectal cancer risk,⁶⁴ while EP-MHT conferred a statistically significant reduction in risk.⁶⁵ The latter reduced incidence was however offset by the finding that colorectal cancers tended to be more advanced, with more likelihood of lymphatic or metastatic involvement. Although based on a low number of cases, which limits interpretation, the WHI results therefore cast doubts on the colorectal cancer benefit with MHT.

Whether this possible protective effect of MHT on colorectal cancer risk varies according to its route of administration has been investigated in five observational studies (Table 4). Three found both oral and transdermal MHT associated with decreases in colorectal cancer risk^{49;66;67}; there was no evidence of a difference between the risk estimates associated with oral and transdermal MHT in two of them,^{49;67} while Csizmadi *et al*⁶⁶ found transdermal MHT associated with a significantly greater decrease in risk than oral MHT, but only when the analyses were restricted to women with exclusive use of one route of administration. In another observational study, ever-use of MHT via oral or transdermal routes of administration both showed no significant association with colon cancer.⁶⁸ Finally, a population-based case-control study found oral but not transdermal MHT associated with a significant decrease in risk, but the difference between the two routes of administration was not significant.^{60;67}

Results of these five observational studies are not consistent and generally based on low number of cases among transdermal MHT users (no more than 26 cases, when the information was available). Taken together, they do not provide convincing evidence of an impact of the route of administration on the still debated colorectal cancer benefit of MHT.

HIP FRACTURE

Evidence from clinical trials concerning the relation between MHT use and the risk of hip fracture derives mainly from the WHI: both WHI trials (E-MHT and EP-MHT) found a statistically significant 30-40% reduction in risk for women in the treated groups.^{69;70} In the Heart and Estrogen/progestin Replacement Study (HERS) trial however, no protective effect of MHT was observed and the unblinded extension of this trial even showed a statistically significant increased risk in the MHT group, but the authors attributed this finding to chance.⁷¹ Before the release of the HERS and WHI results, a meta-analysis of randomized trials showed MHT to be associated with a 40% significant decrease in the risk of hip/wrist fracture.⁷² Evidence from observational studies points toward the same direction: pooled data from three cohort studies indicate a HR of hip fracture of 0.64 (95% CI 0.32-1.04) for current MHT use versus never-use.²⁴ More recent observational studies also support such a protective effect.⁷³⁻⁷⁵

Investigations of a possible differential effect of oral and transdermal MHT on the risk of fracture, in particular hip fracture, are scarce. One of these is a Swedish population-based case-control study which included 1327 women aged 50-81 years with hip fracture and 3262 controls.⁷⁶ Compared with MHT never-use, oral E-MHT ever-use was associated with an OR of 0.63 (95% CI 0.45-0.88; 59 cases among MHT users) and patches of E-MHT with an OR of 0.73 (95% CI 0.38-1.40; 15 cases among MHT users); oral EP-MHT was associated with an OR of 0.46 (95% CI 0.32-0.67; 55 cases among MHT users) and patches of EP-MHT with an OR of 0.49 (95% CI 0.24-1.00; 12 cases among MHT users). The prospective Million Women Study, which included 138,737 postmenopausal women from the UK aged 50-69 years of whom 5197 reported one or more fractures, found similar results.⁷³

Compared with MHT never-users, multivariable-adjusted HRs of fracture were 0.60 (95% CI 0.53-0.68; 290 cases among MHT users) for current use of oral E-MHT and 0.75 (95% CI 0.65-0.86; 197 cases among MHT users) for current use of transdermal E-MHT. Finally, in a Danish record-linkage case-control study which included 64,548 women with fracture and 193,641 controls, multivariable-adjusted ORs were very close for oral and transdermal MHT in the age groups 50-59 years and ≥ 60 years (where women were most likely postmenopausal).⁷⁴

The epidemiologic evidence to date therefore suggests that oral and transdermal MHT would have a similar protective effect on the risk of hip fracture.

CONCLUSION

Available information on the potential impact of the route of administration of MHT on the risk of clinically important outcomes is limited. To date, epidemiological data suggest that it has no impact on the risk of breast cancer and hip fracture. Results on the risk of CHD and colorectal cancer are inconsistent. Studies on stroke and diabetes risk are too few to allow meaningful conclusions. There is a suggestion that transdermal MHT may be less deleterious than oral MHT regarding venous thromboembolism which needs to be confirmed.

The issue of the route of administration of MHT should therefore remain an active area of research as part of an attempt to identify treatment modalities that would have the least potential for exerting adverse effects. To date, limited statistical power and a lack of comprehensive data collection have hindered the ability of most studies to simultaneously take into account several aspects of MHT use, and future studies should now be designed so as to be able to disentangle the

effects of various MHT parameters: molecules, doses, regimens, and route of administration.

Table 1. Risk of coronary heart disease - Results of observational studies comparing oral and transdermal MHT

First Author and publication year	Country and characteristics of participants	Design and size of the study	Risk estimates (95% CI; No of exposed cases)	Other
Varas-Lorenzo (2000) ¹⁷	United Kingdom, women aged 50-74 years	Population-based case-control study using the General Practice Research Database 1013 women with myocardial infarction and 5000 controls	<i>ORs for recent use versus MHT never-use:</i> Oral MHT: 0.66 (0.50-0.88; 63 cases) Transdermal MHT: 0.75 (0.47-1.21; 22 cases)	ORs are multivariable-adjusted The effect of oral and transdermal MHT has been assessed in recent users with duration >1 year
Chilvers (2003) ¹⁹	United Kingdom, women aged 35-65 years	Case-control study 559 women with non fatal myocardial infarction and 1118 controls 198 women with fatal myocardial infarction and 393 controls	<i>ORs of non-fatal events for ever-use versus MHT never-use:</i> Oral MHT: 0.68 (0.49-0.95; 139 cases) Transdermal MHT: 1.70 (0.58-4.98; 9 cases) <i>ORs of fatal events for ever-use versus MHT never-use:</i> Oral MHT: 0.40 (0.26-0.63; 29 cases) Transdermal MHT: 1.31 (0.47-3.68; seven cases)	ORs are multivariable-adjusted for non fatal events, and only age-adjusted for fatal events. ORs associated with oral and transdermal MHT are heterogeneous for fatal events
Hippisley-Cox (2003) ²²	United Kingdom, no age limit	Population-based case-control study using practice computer records 417 women with coronary heart disease (angina, myocardial infarction or coronary artery surgery) and 2435 controls	<i>ORs for current use versus MHT never-use:</i> Oral MHT: 1.27 (0.88-1.84; 50 cases) Transdermal MHT: 1.61 (0.76-3.39; 10 cases)	ORs are multivariable-adjusted
De Vries (2006) ¹⁸	United Kingdom, peri/postmenopausal women aged 40-74 years	Population-based case-control study using the General Practice Research Database 4537 women with myocardial infarction and 27,220 controls	<i>ORs for current use versus MHT never-use:</i> Oral MHT: 0.77 (0.66-0.90; 268 cases) Transdermal MHT: 0.66 (0.49-0.88; 62 cases)	ORs are multivariable-adjusted <i>P</i> for homogeneity between oral and transdermal MHT: 0.25
Corrao (2007) ²⁰	Italy, women aged 45-65 years who received at least one MHT prescription during 1998-2000	Record-linkage cohort study 76,875 women of whom 473 experienced hospitalization for ischaemic heart disease	<i>HRs for use >3 years versus <7 months:</i> Oral MHT: 1.80 (0.66-4.88) Transdermal MHT: 0.59 (0.33-1.05)	HRs are multivariable-adjusted
Løkkegaard (2008) ²¹	Denmark, healthy women aged 51-69 years	Record-linkage cohort study 698,098 women of whom 4947 experienced a myocardial infarction	<i>HRs for current use versus MHT never-use:</i> Oral E-MHT: 0.98 (0.67-1.12; 264 cases) Transdermal E-MHT: 0.62 (0.42-0.93; 24 cases) Oral EP-MHT: 1.08 (0.98-1.19; 523 cases) Transdermal EP-MHT: 0.95 (0.63-1.43; 23 cases)	HRs are multivariable-adjusted <i>P</i> for homogeneity between oral and transdermal E-MHT: 0.04 <i>P</i> for homogeneity between oral and transdermal EP-MHT: 0.33

CI, confidence interval; E-MHT, estrogen-alone therapy; EP-MHT, estrogen-progestagen therapy; HR, hazard-ratio; MHT, menopausal hormone therapy (estrogen-alone or estrogen-progestagen therapy); OR, odds-ratio

Table 2. Risk of venous thromboembolism - Results of observational studies comparing oral and transdermal MHT

First Author and publication year	Country and characteristics of participants	Design and size of the study	Risk estimates (95% CI; No of exposed cases)	Other
Daly (1996) ³¹	United Kingdom, women aged 45-64 years	Hospital-based case-control study 103 cases of venous thromboembolism and 178 controls	<i>ORs for current use versus MHT non-use:</i> Oral MHT: 4.6 (2.1-10.1; 37 cases) Transdermal MHT: 2.0 (0.5-7.6; five cases)	ORs are multivariable-adjusted
Perez (1997) ³²	United Kingdom, no age limit	Population-based case-control study using the General Practice Research Database 292 cases of venous thromboembolism and 10,000 controls	<i>ORs for current use versus MHT never-use:</i> Oral MHT: 2.1 (1.3-3.6; 20 cases) Transdermal MHT: 2.1 (0.9-4.6; seven cases)	ORs are multivariable-adjusted
Hoibraaten (1999) ³³	Norway, women aged 44-70 years	Population-based case-control study 176 cases of venous thromboembolism and 352 controls	?	No difference in risk between oral and transdermal MHT, but there was only two cases among users of transdermal MHT
Canonico (2007) ³⁵	France, postmenopausal women aged 45-70 years	Case-control study 271 cases of idiopathic venous thromboembolism and 610 controls	<i>ORs for current use versus MHT non-use:</i> Oral estrogen: 4.2 (1.5-11.6; 45 cases) Transdermal estrogen: 0.9 (0.4-2.1; 67 cases)	ORs are multivariable-adjusted Adjustment also includes the associated progestagen
Canonico (2010) ³⁶	France, postmenopausal women	Cohort study 80,308 women of whom 549 were diagnosed with an episode of idiopathic venous thromboembolism	<i>HRs for current use versus MHT non-use:</i> Oral estrogen: 1.7 (1.1-2.8; 81 cases) Transdermal estrogen: 1.1 (0.8-1.8; 174 cases)	HRs are multivariable-adjusted Adjustment also includes the associated progestagen HRs associated with oral and transdermal estrogens differ significantly

CI, confidence interval; E-MHT, estrogen-alone therapy; EP-MHT, estrogen-progestagen therapy; HR, hazard-ratio; MHT, menopausal hormone therapy (estrogen-alone or estrogen-progestagen therapy); OR, odds-ratio

Table 3. Risk of breast cancer - Results of observational studies comparing oral and transdermal MHT

First Author and publication year	Country and characteristics of participants	Design and size of the study	Risk estimates (95% CI; No of exposed cases)	Other
Beral (2003) ³	United Kingdom, women aged 50-64 years	Cohort study 1,084,110 women of whom 9364 were diagnosed with invasive breast cancer	<i>HRs for current use versus MHT never-use:</i> Oral E-MHT: 1.32 (1.21-1.45; 606 cases) Transdermal E-MHT: 1.24 (1.11-1.39; 324 cases)	HRs are multivariable-adjusted No significant difference between HRs associated with oral and transdermal E-MHT
Lyytinen (2006) ⁴³	Finland, women older than age 50 years who had bought E-MHT for at least 6 months during 1994-2001	Cohort record-linkage study 110,984 women of whom 2171 were diagnosed with breast cancer	<i>SIRs with the entire age-matched women Finnish population as the reference:</i> Low-dose oral E-MHT ≥5 years: 1.15 (0.71-1.75; 21 cases) Low-dose transdermal E-MHT ≥5 years: 1.60 (0.77-2.95; 10 cases) Medium-dose oral E-MHT ≥5 years: 1.38 (0.84-2.12; 20 cases) Medium-dose transdermal E-MHT ≥5 years: 1.32 (1.12-1.64; 104 cases) High-dose oral E-MHT ≥5 years: 1.49 (1.25-1.75; 130 cases) High-dose transdermal E-MHT ≥5 years: 1.44 (0.88-2.22; 20 cases)	The breast cancer incidence in the cohort was compared to that among the entire age-matched women Finnish population using SIR
Lyytinen (2009) ⁴⁴	Finland, women older than age 50 years who had bought EP-MHT for at least 6 months in 1994-2005	Cohort record-linkage study 221,551 women of whom 6211 were diagnosed with breast cancer	<i>SIRs with the entire age-matched women Finnish population as the reference:</i> Oral EP-MHT 0.5 to <3years: 1.05 (0.99-1.12, 931 cases) Transdermal EP-MHT 0.5 to <3years: 0.99 (0.79-1.23, 82 cases) Oral EP-MHT 3 to <5years: 1.27 (1.15-1.39, 440 cases) Transdermal EP-MHT 3 to <5years: 1.38 (1.01-1.85, 45 cases) Oral EP-MHT ≥5years: 1.81 (1.73-1.89, 1979 cases) Transdermal EP-MHT ≥5years: 1.60 (1.11-2.23, 34 cases)	The breast cancer incidence in the cohort was compared to that among the entire age-matched women Finnish population using SIR
Opatrny (2008) ⁴⁸	United Kingdom, women aged 50-75 years	Population-based case-control study using the General Practice Research Database 6347 women diagnosed with breast cancer and 31,516 controls	<i>ORs for ever-use versus MHT never-use:</i> Oral EP-MHT: 1.38 (1.27-1.48; 1120 cases) Transdermal EP-MHT: 1.08 (0.81-1.43; 60 cases)	ORs are multivariable-adjusted
Corrao (2008) ⁴⁹	Italy, women aged 45-75 years who received at least one MHT prescription during 1998-2000	Record-linkage cohort study 73,505 women of whom 1296 experienced hospitalization for breast cancer	<i>HRs for use >2 years versus <6 months:</i> Oral MHT: 2.14 (1.43-3.21) Transdermal MHT: 1.27 (1.07-1.51)	HRs are age-adjusted <i>P</i> for homogeneity between oral and transdermal MHT: 0.01
Fournier (2005) ⁴⁶	France, postmenopausal women	Cohort study 54,548 women of whom 948	<i>HRs for ever-use versus MHT never-use:</i> Oral EP-MHT: 1.5 (1.1-1.9; 80 cases)	HRs are multivariable-adjusted EP-MHT excludes MHT containing

		were diagnosed with breast cancer	Transdermal EP-MHT: 1.4 (1.2-1.7; 187 cases)	micronized progesterone
Fournier (2008) ⁴⁷	France, postmenopausal women	Cohort study 80,377 women of whom 2354 were diagnosed with breast cancer	<i>HRs for ever-use versus MHT never-use:</i> Oral E-MHT: 1.32 (0.76-2.29; 13 cases) Transdermal E-MHT: 1.28 (0.98-1.69; 56 cases) Oral estrogen+dydrogesterone: 0.77 (0.36-1.62; 7 cases) Transdermal estrogen+dydrogesterone: 1.18 (0.95-1.48; 90 cases) Oral estrogen+medrogestone: 2.74 (1.42-5.29; 9 cases) Transdermal estrogen+medrogestone: 2.03 (1.39-2.97; 28 cases) Oral estrogen+chlormadinone acetate: 2.02 (1.00-4.06; 8 cases) Transdermal estrogen+chlormadinone acetate: 1.48 (1.05-2.09; 35 cases) Oral estrogen+promegestone: 1.62 (0.94-2.82; 13 cases) Transdermal estrogen+promegestone: 1.52 (1.19-1.96; 69 cases) Oral estrogen+norgestrol acetate: 1.10 (0.55-2.21; 8 cases) Transdermal estrogen+norgestrol acetate: 1.60 (1.28-2.01; 91 cases)	<i>P</i> for homogeneity between oral and transdermal EP-MHT: 0.9 HRs are multivariable-adjusted No significant difference between oral and transdermal MHT for a given associated progestagen (or no progestagen)

CI, confidence interval; E-MHT, estrogen-alone therapy; EP-MHT, estrogen-progestagen therapy; HR, hazard-ratio; MHT, menopausal hormone therapy (estrogen-alone or estrogen-progestagen therapy); OR, odds-ratio; SIR, standardized incidence ratio

Table 4. Risk of colorectal cancer - Results of observational studies comparing oral and transdermal MHT

First Author and publication year	Country and characteristics of participants	Design and size of the study	Risk estimates (95% CI; No of exposed cases)	Other
Csizmadi (2004) ⁶⁶	Canada, women 50 years of age or older	Population-based nested case-control study using record-linkage data 1197 cases of colorectal cancer and 4669 age-matched controls	<i>ORs for ever-use versus MHT never-use:</i> Oral MHT: 0.82 (0.70-0.97; 251 cases) Transdermal MHT: 0.60 (0.39-0.92; 26 cases)	ORs are age-adjusted The difference between the estimates for oral and transdermal MHT is statistically significant when restricted to women with exclusive use of one route of administration (230 and five cases among oral and transdermal MHT users, respectively)
Dinger (2007) ⁶⁸	Germany, no age limit	Case-control study 354 cases of colon cancer and 1422 age-matched controls	<i>ORs for ever-use versus MHT never-use:</i> Oral MHT: 0.76 (0.54-1.08; 99 cases) Transdermal MHT: 1.17 (0.63-2.16; 24 cases)	ORs are multivariable-adjusted
Corrao (2008) ⁴⁹	Italy, women aged 45-75 years who received at least one MHT prescription during 1998-2000	Record-linkage cohort study 73,505 women of whom 383 experienced hospitalization for colorectal cancer	<i>HRs for use >2 years versus <6 months:</i> Oral MHT: 0.55 (0.13-2.21) Transdermal MHT: 0.81 (0.57-1.15)	HRs are age-adjusted <i>P</i> for homogeneity between oral and transdermal MHT: 0.45
Rennert (2009) ⁶⁰	Israel, peri/postmenopausal women	Population-based case-control study 1234 cases of colorectal cancer and 1226 age-matched controls	<i>ORs for ever-use versus MHT never-use:</i> Oral MHT: 0.68 (0.52-0.90) Transdermal MHT: 1.00 (0.46-2.18)	ORs are age-adjusted
Hoffmeister (2009) ⁶⁷	Germany, postmenopausal women	Population-based case-control study 546 colorectal cancer cases and 910 controls	<i>ORs for ever-use versus MHT never-use:</i> Oral MHT: 0.59 (0.39-0.90; 56 cases) Transdermal MHT: 0.40 (0.17-0.90; nine cases) Oral E-MHT: 0.44 (0.15-1.30; six cases) Transdermal E-MHT: 0.36 (0.14-0.97; six cases)	ORs are multivariable-adjusted <i>P</i> for homogeneity between oral and transdermal MHT: 0.37

CI, confidence interval; E-MHT, estrogen-alone therapy; EP-MHT, estrogen-progestagen therapy; HR, hazard-ratio; MHT, menopausal hormone therapy (estrogen-alone or estrogen-progestagen therapy); OR, odds-ratio

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