Review



# Associations Between Menopausal Hormone Therapy and Colorectal, Lung or Melanoma Cancer Recurrence and Mortality: A Systematic Reviews and Meta-Analysis

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# Associations between Menopausal Hormone Therapy and Colorectal, Lung or Melanoma Cancer Recurrence and Mortality: A Systematic Reviews and Meta-Analysis

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**Abstract:** Objective: to create a set of eligibility criteria for the use of MHT in non-gynecological cancer patients. Methods: We conducted a comprehensive search of peer-reviewed journals until March 2021. We applied PICOS standards and the following selection criteria: menopausal women with a history of non-gynecological and non-breast cancer receiving hormone replacement therapy (HRT) using either oestrogens alone or in combination with a progestogen, tibolone, or tissue selective oestrogen complex. Different routes of administration (including oral, transdermal, vaginal, or intra-nasal) focused on randomized controlled trials, relevant extension studies or follow-up reports, reporting on recurrence and mortality outcomes. Results: Women who have survived colorectal cancer under hormone replacement therapy (HRT) experience a decreased risk of mortality from any cause compared to those who do not use HRT. Women who have survived skin melanoma and use HRT show longer survival rates compared to non-HRT users. There is insufficient evidence to suggest a difference in survival rates among women who have survived lung cancer and use HRT compared to non-users. Conclusion: MHT is safe in women who have suffered from colorectal, lung or skin melanoma cancers. The study was registered at www.prospero.org (CRD42020166658).

**Keywords:** cancer survival; hormonal menopausal treatment

## 1. Introduction

The information gathered over the past two decades regarding the impact of menopausal hormone therapy (MHT) holds promise for a more reliable and successful long-term approach to managing menopause symptoms and potential complications. These complications may encompass osteoporotic fractures, cognitive impairment, cardiovascular conditions, and an overall enhanced quality of life[1-4]. With these findings in mind, international organizations have determined that the benefits of MHT outweigh the associated risks for healthy postmenopausal women experiencing symptoms, particularly if the therapy commences within a decade of menopause or before the age of 60[5,6].

Nevertheless, there is currently a lack of guidelines that offer recommendations on prescribing MHT to postmenopausal women who have medical conditions that could affect its use. In the realm of contraception, a comprehensive resource known as the "WHO Medical Eligibility Criteria" provides guidance on various medical conditions, aiding the scientific community in ensuring the safe use of contraceptive methods[7].

Among the factors that significantly influence the suitability of any form of MHT is a history of non-gynecological cancers such as colorectal, lung, or melanoma. The concern lies in the potential

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recurrence of these diseases since there are evidences of a potential sensitivity to estrogens as clarified below Moreover, a considerable number of women who have survived these cancers have undergone treatments that intensify menopausal symptoms due to the effects of cancer therapies. This further underscores the importance of providing effective remedies for these individuals, with MHT being one of the noteworthy options[8]

In previous articles, we have addressed the impact of menopausal hormone therapy (MHT) on the evolution of gynecological cancer. However, we believe it is important to investigate this issue in other cancers that may be of interest due to their high prevalence and potential relationship with estrogens.

According to the Globocan 2022 study, colon cancer was the second most common cancer in women, with an incidence rate of 16.2 per 100,000 women [9]. The WHI study demonstrated a significantly lower incidence of colon cancer following MHT (HR 0.6, CI 0.43-0.92) [10]. However, the mechanism by which this reduction occurs remains unclear. It is currently known that estrogen action is mediated by two types of receptors, ERα and ERβ, which interact similarly. ERα interacts more frequently with c-Jun, c-Fos of the activator protein-1 (AP-1) complex, and specificity protein 1 (SP1) [11]. On the other hand, ERβ has been shown to have a suppressive effect on tumor progression in certain cancers and has demonstrated therapeutic potential in the management of these malignancies [12]. In the normal colon, ERβ plays a crucial role in maintaining physiology and immune response [13]. It has been described that estrogen stimulation of these receptors, even with flavonoids [14], can stimulate the tumor suppressor function in colon cancer, thus promoting a protective effect [15].

Lung cancer is the third most common cancer in women, with an incidence of 14.6 per 100,000 women [9]. While the relationship between lung cancer and tobacco use is well-established, some studies have also associated endogenous estrogen stimulation or hormonal treatments with the development of this neoplasia. This may be attributed to women's greater susceptibility to tobacco carcinogenesis, primarily due to the induction of the CYP1B1 enzyme, which interferes with estrogen metabolism and leads to increased formation of reactive oxygen species with oncogenic properties [17]. The Women's Health Initiative trial concluded that estrogen and progesterone treatment in postmenopausal women did not increase the incidence of lung cancer [10]. However, other investigators have demonstrated in vitro that estrogen induces the spread of lung cancer cells in non-small cell tumors, promoting tumor growth [18]. Conversely, anti-estrogen treatment strategies have shown potential in decreasing tumor size, cell growth, and proliferation [19].

While gender differences have been observed in the incidence of melanoma, the role of estrogenicity in this divergence remains uncertain. Molecular studies have described a greater presence of ERβ in the skin, inhibiting DNA transcription and significantly reducing tumor capacity, unlike the breast where ERα predominates[20]. Epidemiologically, the effects of hormonal treatment in women with melanoma have yielded initially divergent results. While some previous studies do not contraindicate hormonal contraception in this tumor [21,22], other authors have shown a higher risk associated with estrogen treatment in postmenopausal women, which is not observed when combined estrogen-progestogen therapy is administered [23].

Based on these biological and clinical considerations, we have selected colon, lung, and melanoma cancers as the focus of our review.

The objective of this report is to create a set of eligibility criteria for the use of MHT in non-gynecological (colorectal, lung or melanoma) cancer patients, similar to those established for contraceptive methods. A panel of experts from various Spanish scientific societies (Spanish Menopause Society, Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Oncología Médica) met in order to draw up a series of evidence-based recommendations.

## 2. Methods

The study was registered with www.prospero.org under registration number CRD42020166658 and is part of the "Eligibility Criteria for MHT Project" (Appendix 1).

### *2.1. Inclusion Criteria*

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The systematic review included randomized controlled trials, extension studies, or follow-up reports. Additionally, observational studies were included, with a special focus on population-based cohorts or large case-control studies that included a control group of non-users. Eligible studies involved menopausal women of any age who received MHT and were survivors of melanoma, colorectal cancer, or lung cancer. We considered studies that evaluated any MHT preparation (including estrogens alone or combined with a progestogen, tibolone, or tissue-selective estrogen complex) administered via any route (oral, transdermal, vaginal, or intra-nasal). The impact of MHT was compared to placebo or non-treatment controls.

*2.2. Study Selection*

We conducted a comprehensive literature search in the following databases: MEDLINE (via PubMed), The Cochrane Library (CENTRAL), and EMBASE (via embase.com), from their inception to the most recent available date. We developed a search strategy tailored to the requirements of each database, combining controlled vocabulary and search terms related to each specific cancer. Appendix 2 presents an exploratory search strategy for MEDLINE. Validated filters were employed when necessary to retrieve appropriate study designs. Two independent researchers screened the references retrieved from the search to reach a consensus on study inclusion. In case of discrepancies, a member of the expert panel was consulted to resolve them. The panel members were kept informed of this process to assess the suitability of included studies and suggest additional relevant studies if any were omitted. The study scope, along with the procedures, selection, and synthesis of the literature search, adhered to the a priori PICOS (Population, Intervention, Comparators, Outcomes, Study Design) criteria. The selection criteria were as follows:

Population: Menopausal women of any age with non-gynecological and non-breast cancer receiving MHT.

Intervention: Any MHT preparation (including estrogens alone or combined with a progestogen, tibolone, or tissue-selective estrogen complex) administered via any route (oral, transdermal, vaginal, or intra-nasal).

Outcome: Recurrence and mortality.

Study Design: Randomized controlled trials, extension studies, or follow-up reports. Any complete article meeting the inclusion criteria underwent a detailed review.

*2.3. Data Extraction, Synthesis, and Risk of Bias Assessment*

The panel, consisting of the study authors, reviewed the scientific literature following a predefined protocol based on methodological guidelines from the Cochrane collaboration [24]. The findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. For observational studies, the ROBINS-I tool was adapted to assess confounding variables, selection bias, outcome measures, and attrition[26]. The evidence synthesis followed the PRISMA guidelines, with a narrative synthesis of findings and effect estimates from the included studies focusing on the relevant outcomes to explore the association between MHT and cancer survivors. When appropriate, pooled analyses were conducted using the Mantel-Haenszel method and the random effects model within the RevMan software statistical package (v 5.3.5) [27]. Certainty of evidence for each outcome of interest was explicitly assessed using GRADE criteria [28]. Quality was classified as high (A), moderate (B), low (C), or very low (D), taking into account factors such as risk of bias, inaccuracy, inconsistency, lack of directionality, and publication bias. In systematic reviews where no direct evidence was identified, but plausibility existed based on clinical experience or publications with indirect evidence, the panel reached consensus and categorized the evidence as "Expert opinion."

*2.4. Evidence-to-Decision Framework and Eligibility Criteria*

To formulate explicit and reasoned recommendations, we employed an evidence-to-decision (EtD) framework to inform the panel about the most relevant aspects required for decision-making,

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facilitating justifications[29]. To establish a ranking of MHT eligibility criteria, the panel integrated findings from the reviews using a structured framework that considered the magnitude of MHT effects on recurrence and mortality, certainty ratings of the evidence, and data from other sources. To standardize the proposal, the following eligibility criteria have been defined in accordance with the WHO international nomenclature:

Category 1: No restriction on the use of MHT
Category 2: The benefits outweigh the risks.
Category 3: The risks generally outweigh the benefits.
Category 4: MHT Should not be used

## 3. Results

*Colorectal cancer*

Five observational studies on the use of MHT in women with colorectal cancer (CRC) were identified: two prospective[30,31] and three retrospective[32-34] cohorts totaling 5510 women receiving some form of MHT (table 1).

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**Table 1.** Study characteristics of included studies. Colorectal cancer.

| Study | Study Period | Country | Age | Number of Participants | Stage | Grade | HRT Type | HRT Recency | CRC Death HRT User vs no User | All-Cause Mean Death HRT User vs no User | Mean Follow Up Year |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Prospective cohort | | | | | | | | | | | |
| Slattery et al (1999)[18] | 1991-1998 | USA | 50-79 | 801 | 35.4% local, 53.2% regional, 11.4% distant | NR | E, E + P | Current to stop less than 5 years | 504 (62,9) 297 (37,1) 0.6 (0.4±0.9) | 0.7 (0.5±0.9) | 4 |
| Mandelson et al (2003)[16] | 1980-1998 | USA | 50–79 | 699 | NR | NR | E, E + P | Current | 0.59 (0.35–0.97) | 0.77 (0.54–1.09) | 5.33 |
| Ji et al (2018)[17] | 2006-2015 | Sweden | 45-69 | 5626 | 23.7% stage I, 27.8% stage II, 36.2% stage III, 12.3% stage IV | NR | E, E + P | Current | 0.74 (0.62-0.88) p= 0.0006 | 0.70 (0.60-0.82) p<0.0001 | 5.4 |
| Retrospective cohort | | | | | | | | | | | |
| Chan et al (2006)[14] | 1976-2004 | USA | 62.2–65.7 | 834 | 22.3% stage I, 26.1% stage II, 25.5% stage III, 15.6% stage IV, 10.5% unknown | 22.3% stage I, 26.1% stage II, 25.5% stage III, 15.6% stage IV, 10.5% unknown | E, E + P | Current former | Current 0.64 (0.47-0.88) former 1.05 (0.79-1.40) | Current 0.74 (0.56-0.97) former 1.00 (0.78-1.30) | 5-10 |
| Arem et al (2015)[15] | 1995-2001 | USA | 50,71 | 2053 | 30.5% localized, 31.3% | 12.0% well-differentiated, 57.5% moderate- | E, E + P | Current former | Current 0.76 (0.59, 0.97) | Current 0.79 (0.66, 0.94) | 7.7 |

| | | | | | |
|---|---|---|---|---|---|
| | | regional or distant, 38.2% unknown | differentiated, 0.9% undifferentiated, 29, 6% unknown | former 1.03 (0.72, 1.47) | former 1.13 (0.89, 1.43) |

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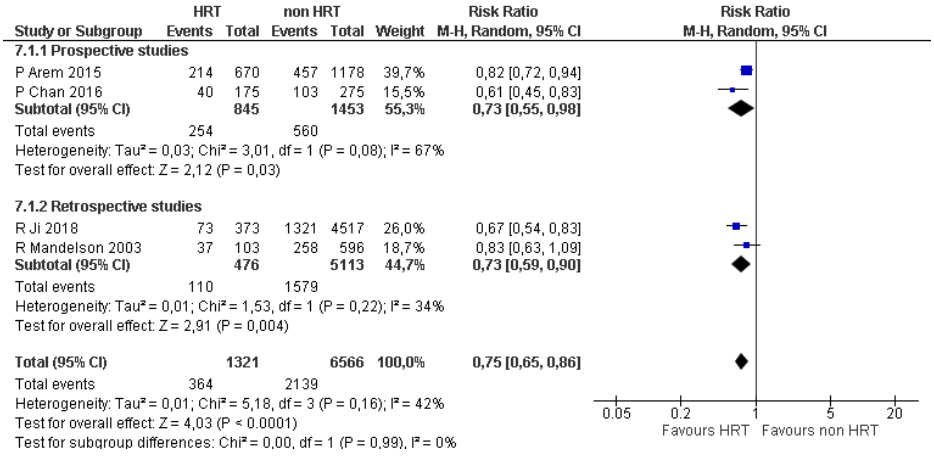
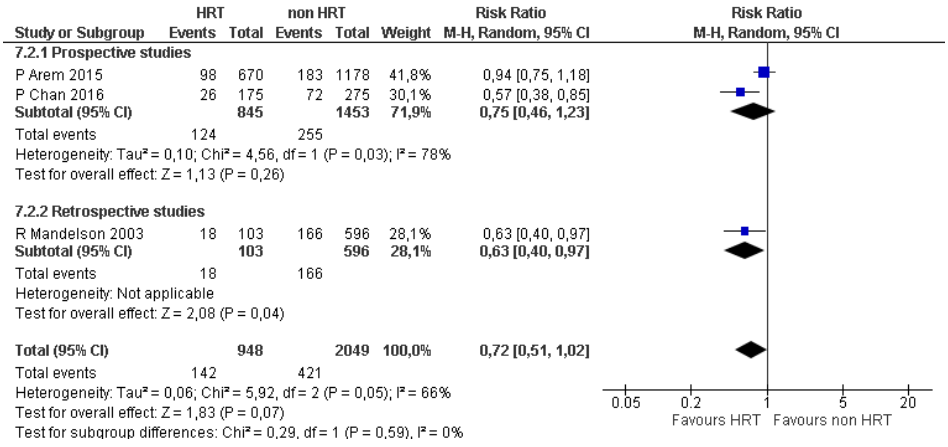
For this report, a combined evaluation was made of the results of four of these studies[30-33] which showed a significant reduction in the proportion of women who died of any cause among those who received MHT compared with those who were untreated (RR 0.75, 95% CI: 0.65 to 0.86; Figure 1a). The results were not statistically significant for the proportion of women with a cause of death attributable to CRC (RR 0.72, 95% CI: 0.52 to 1.02; Figure 1b), because of the discrepancy between estimates from prospective (RR 0.75, 95% CI: 0.46 to 1.23) and retrospective studies (RR 0.63, 95% CI: 0.40 to 0.97).




Summary of pooled risk estimates. The association between HRT use in women with colorectal cancer and all-cause mortality. Note. HR: hazard ratio, CI: confidence intervals, HRT: hormone replacement therapy

**Figure 1.** a. Colorectal cancer. Mortality from any cause (data from prospective and retrospective studies).




Summary of pooled risk estimates. The association between HRT use in women with colorectal cancer and colorectal cancer mortality. Note. HR: hazard ratio, CI: confidence intervals, HRT: hormone replacement therapy

**Figure 1.** b. Colorectal cancer. Mortality attributable to colorectal cancer (data from prospective and retrospective studies).

*Lung Cancer*

Five studies were included on the effect of MHT on lung cancer, three retrospective[35-38] and one prospective[39] collected in a meta-analysis[40] with a total of 1054 women with lung cancer who used MHT compared with 1528 who did not (table 2).

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**Table 2.** Study characteristics of included studies. Lung cancer.

| Study | Study period | Country | Age | Number of participants | Stage | Smokers | HRT Type | Median overall survival | Median overall survival with HTR Smokers/no smokers |
|---|---|---|---|---|---|---|---|---|---|
| Retrospective cohort | | | | | | | | | |
| Ganti et al (2006)[19] | 1994-1999 | USA | 31-93 | 498 | I 26 %<br>II 21 %<br>IIIA 11 %<br>IIIB 8 %<br>IV 28 % | 86 % | All types | Never used HRT 79 months; 95% CI, 65 to 95 months) HRT 39 months; 95% CI, 35 to 77 months<br>P 0 .02 | Smoke and HRT smoked and used / smoke and no HRT 39 v 73 months; P 0 .03).<br>No smoke and HRT / No smoke and not HRT 92 v 98<br>NS |
| Ayeni et al (2009)[20] | | | | | | | | | |
| Katkoff et al (2014)[21] | 2001-2005 | USA | 17-74 | 485 | Local 33,6 %<br>Regional 33,4 %<br>Distant 33,0 | Current or former 92,3 % | Estrogen only 99<br>Estroge plus progesterone 85 | Median survival time, HRT 80.0 m No HRT 37.5 m p<0.001 | Never smoker and HRT vs no HRT 17 (7.4) /<br>20 (7.9) Current smokers anh HTR vs no HRT 126 (54.8) / 165 (65.2)<br>NS |
| Huang et al (2009)[22] | 1995-2005 | USA | 37-90 | 648 | I 20.8 %<br>II 4.8 %<br>III 30.1 %<br>IV 37.4 %<br>Unknown stage 6.9 % | 61,9 % | All types | HRT / no HRT 16.4 v 10.5 NS | Smoke and HRT / no smoke and HRT 11.3 vs 16.9 months P 0,03<br>Smoke and HRT / No smoke and HRT<br>NS |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Prospective cohort | | | | | | | | |
| Clague et al (2014)[23] | 1995-1996 | USA | NR | 727 | Localized 153<br>Regional 51<br>Lymph nodes 73<br>Regional and lymph nodes 33<br>Distant 365<br>Unknown 52 | 543 (74,69%) | Estrogen 188<br>Estrogen + progesterone 176 | HRT 21.4 m<br>No HRT 15,6 m<br>p=0.002 | Ever MHT user vs never user (HR)<br>Never smokers 1.23 (0.58–2.63)<br>Former smokers 0.74 (0.50–1.10)<br>Current smokers 0.44 (0.26–0.75) |
| Meta-analysis | | | | | | | | |
| Li et al (2020)[24] | | | | No HRT 1054<br>HRT 1528 | | | | With HRT increased survival time for 5 years (ES=0.346; 95% CI 0.216 to 0.476; P<0.001). | |

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No publication bias was observed among these studies. The sensitivity analysis result showed that the overall results were stable. The meta-analysis revealed that in comparison with patients not treated with hormone replacement therapy, patients that received hormone replacement therapy had an increased survival of 5 years (RR=0.346; 95% CI: 0.216 to 0.476; p<0.001).

*Cutaneous Melanoma*

A prospective[41] cohort study was identified that analyzed the effect of MHT in 206 women with cutaneous melanoma (table 3). After 10 years of follow-up, adjusted analysis of the results showed increased survival among women who received MHT after melanoma surgery (HR 0.17, 95% CI: 0.04 to 0.62). An estimate of the data provided by the study showed a statistically significant reduction in the risk of death in those who received MHT (RR 0.06, 95% CI: 0.01 to 0.41; Figure 2).

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**Table 3.** Study characteristics of included studies Melanoma.

| Study | Study period | Country | Age | Number of participants | Type | HRT Type | CRC death/ HRT user | All-cause Mean death/HRT user | Mean follow up year |
|---|---|---|---|---|---|---|---|---|---|
| Prospective cohort | | | | | | | | | |
| MacKie et al (2004)[25] | 1990-1995 | Scotland | 46-59 | 206 | Ulceration<br>Yes 5 (6.2) 21 (17.8) 0.017*<br>Patients with tumours o1mm thick 42 (50.6) 58 (47.2) 0.627*<br>Patients with<br>Superficial spreading melanoma 60 (73.2) 84 (69.4) 0.846*<br>Nodular/polypoid melanoma 15 (18.3) 25 (20.7)<br>Lentigo maligna melanoma 4 (4.9) 4 (4.3)<br>Acral/mucosal melanoma 1 (1.2) 2 (1.7)<br>Other and unspecified melanoma 2 (2.4) 6 (5.0) | 21 oestrogen<br>62 oestrogen/progesrterone | HRT 1<br>No HRT 22 | HRT 0<br>No HRT 4 | 19 |

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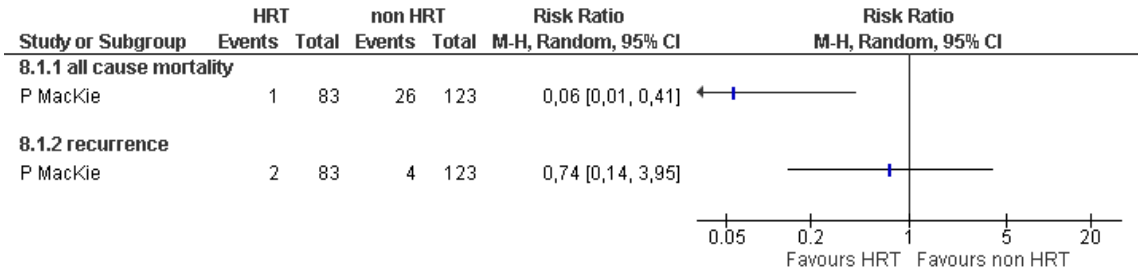


Summary of pooled risk estimates. The association between HRT use in women with melanoma and all cancer mortality. Note. HR: hazard ratio, CI: confidence intervals, HRT: hormone replacement therapy

**Figure 2.** Melanoma. Mortality (from any cause) and recurrence.

Regarding recurrences, this study showed no difference in the proportion of women with MHT who suffered recurrences (RR 0.74, 95% CI: 0.14 to 3.95; Figure 2). The quality of evidence for this outcome is very low due to the serious methodological limitations of the study and the inaccuracy of the estimate attributable to a small sample size.

## 4. Discussion

On the basis of a combined analysis of the researched literature, it is concluded that MHT is safe, in terms of recurrence and/or mortality, in patients who have suffered some of the most frequent non-gynecological cancers (colorectal, lung or melanoma).

*Why is This Report Important?*

There is considerable confusion regarding the appropriateness of MHT in women with cancer, primarily because of the fear of recurrence or increased mortality that may occur with its use.

Women who have suffered from cancer often present earlier and more intense menopausal symptoms, due to the effects of some of their treatments, which seriously affect their quality of life. On many occasions, the long-term risks overlap with those suffered by women with premature ovarian insufficiency, thus extending the suitability of MHT[8].

*Strengths*

This is the first published work to present a systematic review and meta-analysis to analyze the recurrence and mortality of MHT in women survivors of the most common non-gynecological cancers (colorectal, lung, and melanoma).

It is also the first time that categories of evidence (eligibility criteria) have been distinguished for the use of MHT in these patients, using the strictest methodological tools.

*Limitations*

The quality of evidence is low overall. Many studies include the generic use of MHT without distinguishing between dose, formulation, or route of administration.

*Clinical Evidence*

1 Colorectal cancer

The recommendation is based on analyzing five observational studies (two prospective cohorts[30,31]; and three retrospective studies[32,34]. There are no randomized studies, although the population studied is large, mainly due to the high prevalence of this tumor.

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The results point to an increased survival rate, although differences in the means do not reach statistical significance.

This risk reduction is evident during treatment but not after the end of treatment. Better outcomes appear to be associated with estrogens alone than with combined treatments.

There are many limitations, including lack of randomized studies, case collection, BMI, lack of knowledge of the socio-economic profile, and treatment variability.

Results regarding disease-free survival are not sufficiently consistent for drawing conclusions.

1. Lung cancer

The recommendation is based on analyzing five observational studies (three retrospective studies[35-38] and one prospective[39] pooled in a meta-analysis[40]

Although most of the results point to reduced survival in female MHT users, particularly smokers, other retrospective studies show better survival in MHT users, especially in female smokers.

The limitations include the absence of randomized studies, different dosages, low prevalence of the disease, and a low number of cases, along with a lack of knowledge of the socio-economic profile.

There are no available data on recurrence rates.

2. Cutaneous melanoma

The recommendation is based on a single cohort study[41] with a small sample of women (n=206) but a long follow-up (10 years on average).

There is evidence of longer overall survival in this single study with no differences in disease-free survival. In addition, no differences were found in the various histological types or the depth of the lesion. However, there were differences in tumor ulceration.

The main limitations are the absence of randomized studies, only one follow-up study, and the small sample size. There are no studies to either support or counter these data. Better evolution of the disease in younger women remains to be clarified.

*Cancer Risk in Healthy MHT Users*

Colorectal Cancer

The results of the WHI study show that the use of equine conjugated estrogens both alone and in combination with medroxyprogesterone was associated with a lower risk of colon cancer[10]. Further studies have confirmed these results with reductions in the risk of cancer (RR 0.81, p = 0.005) and the risk of death from this cancer (RR 0.63, p = 0.002)[42]. An 18-year follow-up of women in the WHI study has shown no difference in mortality between treated and untreated women[43].

Lung Cancer

Most of the studies aimed at assessing the risk of lung cancer in MHT users have reported positive results in reducing the risk of this type of cancer. Age, smoking, comorbidities and family history have been considered as risk factors in these comparisons, reporting a significant reduction among users compared with non-users (RR 0.80; 95% CI: 0.70-0.93; p=0.009) although no significant differences in mortality rates were found[44]. Another recent meta-analysis of 13 studies has also shown a reduced risk in users of MHT (RR: 0.95, 95% CI: 0.91-0.99, I = 30.8%, p=0.137)[45]. And whilst co-factor variability is a major limitation in this assessment, the evidence suggests a protective effect of MHT on the incidence of lung cancer.

Melanoma

After reviewing the literature, the use of MHT has been associated with a significantly increased risk of melanoma (RR, 1.28; 95% CI: 1.17-1.41)[46], for both estrogens alone (RR 1.37; 95% CI: 1.22-1.52) and estrogen-progestogen combinations (RR 1.23, 95% CI: 1.13-1.34; P = 0.15) after five years of use[47]. These same authors reported significant increases in risk of melanoma for both oral and vaginal estrogens, while no such relationship was found with estroprogestagen combination therapy (RR

0.91; 95% CI: 0.70-1.19)[23]. No differences were found when assessing estrogen doses, sun exposure, or age.

*Future Research*

Our report has, however, identified some important areas for improvement in future research. We expect that the results will contribute to the development of studies that further examine the safety and efficacy of MHT for treating menopausal symptoms in non-gynecological and breast cancer survivors. Larger RCTs should be conducted over a longer follow-up period to evaluate the various MHT strategies.

## 5. Conclusions

Female colorectal cancer survivors who use MHT have a lower risk of mortality from any cause than survivors who are non-users: **Category 1C.**

Female cutaneous melanoma survivors who use MHT have longer survival than non-users: **Category 2C.**

There is no evidence that female lung cancer survivors who use MHT have a different likelihood of survival than non-users: **Category 2C.**

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**Ethics approval and consent to participate:** AEEM is responsible for the investigation. It is a systematic review, so it has not required an ethics committee review.

**Consent for publication:** Spanish Menopause Society, Spanish Society of Medical Oncology and Gynecological Oncology Section of the Spanish Society of Gynecology and Obstetrics are directly involved and responsible of the content of this manuscript: All authors have reviewed and participated in the final writing.

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