# Cancers in Australia in 2010 attributable to and prevented by the use of menopausal hormone therapy

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Menopausal hormone therapy (MHT) is the use of exogenous sex hormones during the peri-menopause and menopause to alleviate symptoms (e.g. hot flushes, vaginal dryness) or other consequences (e.g. osteoporosis) of declining oestrogen levels.[1] Oestrogen is the component of MHT with most therapeutic benefit but, for women who have not had a hysterectomy, it is recommended that a progestogen also be taken (continuously or for at least 10–14 out of 28 days) to reduce the risks of endometrial cancer that result from oestrogen-only MHT.[2]

Until 2002, MHT was prescribed widely because it was believed that, apart from symptom relief, its use also prevented conditions such as cardiovascular disease and dementia. However, the Women's Health Initiative randomised placebo-controlled trial (RCT) published in 2002 found that the global harms (cancer and non-cancer outcomes) of taking MHT outweighed the benefits.[3] These results reduced the prevalence of MHT use among Australian women considerably,[4] but estimates suggest that more than 15% of Australian women aged between 50 and 65 currently use MHT.[5]

Associations between MHT and cancer vary according to body site and whether oestrogen is used alone or in combination with a progestogen. It is likely that at least

## Abstract

**Objectives**: To estimate the proportion and number of cancers occurring in Australia in 2010 attributable to menopausal hormone therapy (MHT) use.

**Methods**: We estimated the population attributable fraction for cancers causally associated with MHT (breast, endometrium, ovary), and the proportion of colorectal cancers prevented by MHT. We used standard formulae incorporating Australian prevalence data, relative risks of cancer associated with MHT and cancer incidence. We also estimated potential change in cancer incidence under two hypothetical scenarios whereby 25% fewer Australian women used MHT, or women exclusively used oestrogen-only MHT.

**Results**: An estimated 539 cancers in Australia in 2010 were attributable to MHT: 453 breast, 67 endometrial and 19 ovarian cancers equating to 3.4%, 3.1% and 1.6% of each cancer type, respectively. In contrast, MHT may have prevented 52 colorectal cancers. If 25% fewer women used MHT, then 141 cancers may have been avoided. If women exclusively used oestrogen-only MHT then 240 cancers may have been avoided.

**Conclusions**: MHT use caused more than 500 cancers in Australian women in 2010 and prevented ~50 colorectal cancers.

**Implications**: MHT use continues to cause an excess of cancers. The risks, benefits, regimen and treatment duration should be carefully considered for each woman before MHT is commenced.

**Key words**: population attributable fraction, cancer, risk factor, menopausal hormone therapy, potential impact fraction

some of the observed associations with cancer result from the effects of these hormones on cell proliferation in the various target tissues. The International Agency for Research on Cancer (IARC) first concluded that there was sufficient evidence that oestrogen-only MHT was carcinogenic to humans in 1999.[6] In a subsequent report published in 2012, IARC also concluded that there was sufficient evidence that oestrogen plus a progestogen (combined MHT) was carcinogenic; however, they additionally found that there was sufficient evidence that oestrogen-only MHT decreases the risk of colorectal cancer (CRC). There is no consistent evidence that either vaginal oestrogens or tibolone (a synthetic molecule with oestrogenic, progestogenic and androgenic properties used for MHT) cause cancer, and IARC has not published evidence summaries

relating these factors to cancers in humans. For these reasons, we reduced the prevalence estimate for MHT accordingly. Cancer associations by body site, MHT type and the level of evidence supporting them (according to IARC[7]) are summarised in Table 1.

This study aimed to estimate the number and proportion (population attributable fraction – PAF) of cancers diagnosed in Australian women in 2010 that could be attributed to the use of MHT and the number and proportion of cancers theoretically prevented by MHT use, according to MHT type.

## Methods

The population attributable fraction of cancers associated with MHT is the proportion of cancers diagnosed in a given period in a specified population that could potentially have been avoided if no one in the population had used MHT.[8] We have also calculated the prevented fraction of cancers to estimate the proportion of cancers that would otherwise have occurred in the absence of any MHT use, but were prevented through prevailing use of MHT by Australian women.

In our primary analysis, we included cancers for which IARC concluded there was sufficient evidence of a causal association. Where high-quality evidence published subsequent to the IARC report has strongly supported additional associations, we conducted supplementary analyses including these (see supplementary analysis section below). Analyses were conducted by type of MHT (oestrogen-only and combined). We estimated the proportion and number of breast cancers diagnosed in 2010 attributable to the use of combined MHT. We did not include endometrial cancer in the primary analysis because available Australian data do not provide estimates of the number of days per cycle that women were taking progestogens with oestrogen. We did, however, make a range of assumptions about the prevalence of progestogen use and modelled the likely effect of combined HRT on endometrial cancer in a supplementary analysis. For oestrogen-only MHT we estimated the proportion and number of endometrial and ovarian cancers diagnosed in 2010 attributable to its use and modelled the prevented fraction for colorectal cancer.

### Relative risk estimates

As IARC did not publish pooled or summary estimates,[7] relative risks for the

PAF calculations were sourced from meta-analyses, pooled analyses or from large cohort studies that published relative risks by MHT type and patterns of use reflecting the IARC conclusions (Table 1). Relative risks from the Women's Health Initiative (WHI) RCT were not used because the participants were, on average, older (mean age 63 years at study entry) than the average post-menopausal woman using MHT and the mean duration of MHT use was limited to five years.[3] Similarly, we did not use estimates from the largest pooled analysis of the association between MHT use and ovarian cancer,[9] because no estimates of risk of ovarian cancer by duration of use were presented separately for oestrogen-only and combined MHT. We did, however, conduct a sensitivity analysis using the estimates from this study for both types of MHT combined. To assess the effect on the PAF of alternative relative risk estimates we conducted a sensitivity analysis using relative risks from other large cohort studies (studies summarised in the supplementary file: Table S1, available with the online version of this article). The results of this analysis are presented in Table 3.

### Exposure prevalence estimates

No latent period was assumed in relation to MHT use, as current and recent use seem to confer the greatest risks. Risk also varies with duration of use and formulation; however, no single data source has captured nationally representative prevalence data cross-classified by these characteristics, so we used data from several different sources to derive prevalence estimates. We made several important assumptions in these derivations (described below).

The most recent nationally representative data on MHT use were reported in the Australian 2004-05 National Health Survey (NHS 2004-05).[10] In that survey, women were asked if they were *currently* using MHT prescribed by a doctor and, if so, for how long they had been using it. Estimates of prevalence of current MHT use by five-year age group (40 to 75+ years) and duration of use were obtained from the NHS 2004-05 Confidentialised Unit Record Files (CURF).[5] We made the assumption that MHT use remained relatively stable between 2005 and 2010 (the year we assessed cancers due to current use). More recent studies suffer from much lower response rates but report a similar prevalence,[11,12] suggesting this assumption is valid. The NHS prevalence data did not

include the type of MHT women were using or information about past use in women not currently using MHT.

To estimate the proportions of women using the different types of MHT (oestrogen-only or combined) we used data from *Australian Statistics on Medicines 2010* (ASM 2010).[13] That publication estimated aggregate community use of prescription medicines in Australia from two sources: the Pharmaceutical Benefits Scheme (subsidised prescriptions) and an ongoing survey of a representative sample of community pharmacies (non-subsidised prescriptions).[13] Prescription medicines dispensed to in-patients in public hospitals were not included in those datasets; however, such prescriptions were likely to contribute a negligible proportion of dispensed MHT. We grouped the MHT formulations included in the ASM 2010 to derive the proportion of prescriptions for vaginal oestrogens, systemic oestrogen-only and oestrogen plus progestogen MHT, and tibolone. Details of these calculations and the estimated distribution of MHT prescriptions in Australia by type are presented in the supplementary file: Table S2, available online. Because there is no evidence that vaginal oestrogens influence cancer risk and the evidence for an association between tibolone and cancer is conflicting, we have reduced the prevalence estimate for MHT by the proportion of women estimated to be using these preparations.

We assumed that each category was mutually exclusive such that, for example, women prescribed vaginal oestrogens would not also be taking systemic oestrogen. To estimate the proportion of all Australian women using each type of MHT, we multiplied the relative proportion of MHT prescriptions for each type of MHT (online supplementary file: Table S2) by the proportion of Australian women using MHT in each category of age and duration (NHS 2004-05 CURF data), see Table 2. We assumed that the distribution of MHT type did not vary by age. Our estimates of prevalence of systemic MHT use were dependent on the assumptions we made about the prevalence of vaginal oestrogen use. As there are no nationally representative data on this, we conducted sensitivity analyses using a range of prevalence estimates to determine the likely impact on the PAF (see online supplementary file: Table S3).

Women who have had a hysterectomy are usually prescribed oestrogen-only MHT because they are no longer at risk of

developing endometrial cancer. We wanted to remove this group of women from our calculations for endometrial cancer. There are no published population data that show how many women taking oestrogen-only MHT have or have not had a hysterectomy, so we used raw data from the population-based control group of the Australian Ovarian Cancer Study (AOCS)[14] to estimate these proportions. The AOCS was a population-based Australia-wide case-control study of epithelial ovarian cancer, which recruited women between 2003 and 2005. The response proportion among controls was 47%. In that study, 13% of women who reported using oestrogen-only MHT had not had a hysterectomy. We applied this proportion to the estimated number of Australian women (by age group) taking oestrogen-only MHT (online supplementary file: Table S1) to separate oestrogen users who had had a hysterectomy from those who had not. Because the response proportion among controls in the AOCS was lower than ideal, we also conducted sensitivity analyses in which we recalculated the PAF assuming that: a) a higher proportion of women using oestrogen-only HRT had an intact uterus (25%); and b) a lower proportion of women using oestrogen-only HRT had an intact uterus (5%).

An adjustment could not be made to account for women with a bilateral oophorectomy, who would not be at risk of ovarian cancer, as suitable data on oophorectomy prevalence were not available.

## Statistical analysis

To estimate the PAF, we used the standard formula:[8]

$$PAF = \frac{\sum(ERR_x * P_x)}{1 + \sum(ERR_x * P_x)}$$

where $ERR_x$ is the excess relative risk and $P_x$ is the prevalence of MHT use by age and/or duration category.

For cancers of the breast and endometrium, relative risks were available within strata of duration of use (<5 yrs, ≥5 yrs use). The excess relative risk for each stratum ($x$) was simply ($RR_x$-1).

To calculate the PAF for endometrial cancer associated with oestrogen-only MHT use, the estimated proportions of women with an intact uterus currently taking oestrogen-only MHT (<5 yrs, ≥5 yrs) were used, assuming the duration of use did not differ by hysterectomy status.

For ovarian cancer, where the relative risks were estimated per year of MHT use, we calculated the excess relative risk using the dose–response relative risk and the mid-point of each duration category (in years):

$ERR_x = EXP(RR * Mid\text{-}point \ of \ duration \ category) – 1$

where the dose–response relative risk was log-transformed to give the increased risk per year of use (1.046 per year of use – refer Table 1).

For colorectal cancer, MHT use is protective; hence, the Prevented Fraction (PF) was calculated:

$$PF_x = p_x (1 - RR)$$

where $p_x$ is the prevalence of MHT use by age category.

To estimate the number of cancers attributable to MHT use, the PAF was multiplied by the number of incident cancers occurring in 2010[15] in each age category (for women aged 40 years and over, as MHT use is rare below this age). The total number of cancers attributable to MHT (all sites combined) was also expressed as a percentage of the total number of all incident cancers (excluding basal cell and squamous cell carcinoma of the skin) in women aged over 40 years recorded in Australia in 2010.

To estimate the number of cancers prevented by use of MHT, the formula was:

$Est. \ number \ of \ prevented \ cancers = \Sigma \left( \frac{N_x}{1 - PF_x} \right) - N_x$

where $N_x$ is the number of observed cancers in 2010 in each age category and $PF_x$ is the prevented fraction in each age category.

The sum of the estimated number of prevented cancers across age categories was expressed as a percentage of the total observed plus total estimated prevented cancers.

## Supplementary analysis

Based on evidence published[16-21] since the 2008 IARC review, in our supplementary analyses we also estimated the proportion of breast cancers attributable to use of oestrogen-only MHT, the proportion of ovarian cancers attributable to use of combined MHT and the proportion of colorectal cancers prevented by use of combined MHT.[22] Risk of endometrial cancer is influenced by the number of days that progestogens are taken with oestrogen in combined MHT preparations and this may be either continuously (every day) or sequentially (usually 10-14 days per 28 day

cycle). There are no Australian data that provide information about the number of days per month that MHT users took a progestogen with oestrogen so, as in the UK PAF project,[23] we used data from the Million Women Study[24] suggesting that the ratio of oestrogen plus progestogen preparations prescribed as continuous-combined versus cyclic-(sequential) combined was 1:2.[24] A relative risk for all such preparations was obtained by weighting the RRs for current use from the Million Women Study (0.75 for continuous and 1.05 for cyclic) according to the 1:2 ratio, giving an overall RR of 0.95 for combined MHT use.[23,24]

Table1 summaries the relative risks used for these supplementary analyses.

## Potential impact of reducing MHT use by Australian women

It is unrealistic to expect that no women will use MHT in the future. We modelled a scenario whereby the number of women taking MHT (in each age and/or duration of use category) decreased from 2005 levels by 25%, keeping the same MHT type distributions and hysterectomy adjustment as per the primary analysis. We then calculated the potential impact fraction (PIF) using the formula from Morgenstern and Bursic:[25]

$$PIF = \frac{\sum_{x=1}^{n} p_x RR_x - \sum_{x=1}^{n} p_x^* RR_x}{\sum_{x=1}^{n} p_x RR_x}$$

where $p_x$ is the proportion of the population in category x, $RR_x$ is the RR for that category and $p_x^*$ is the population in category x after a 25% reduction in MHT use.

Briefly, for each cancer site, we calculated the number of cases that would have occurred in Australia in 2010 assuming that the alternative scenario of MHT use had prevailed. The PIF is then the proportional difference between the observed number of cancers and the number expected under the alternative prevalence scenario.

## Potential impact of women only being prescribed oestrogen-only MHT

In 2010, breast cancer was the most common cancer in Australian women, accounting for 28% of all cancers diagnosed in women. Combined MHT confers a greater risk of breast cancer than oestrogen-only MHT, so we modelled possible effects on cancer incidence if women were only ever prescribed oestrogen-only MHT; that is, progestogens were not prescribed, even in women with

an intact uterus. We assumed that the proportion of women estimated to have taken combined MHT instead took oestrogen-only preparations and calculated PAFs using the relative risks for oestrogen-only MHT and breast (assuming causality), endometrial and ovarian cancer, and calculated the prevented fraction for colorectal cancer.

## Results

Estimates of the prevalence of current MHT use, by type and age category, in Australian women aged over 40 years in 2004-05 (assumed to apply in 2010) are presented in Table 2. Prevalence of current use of MHT was highest among women in the 50-64 year age groups (peaking at 18% in the 55-59 year age group) but was reported by less than 5% of women in the youngest and oldest age groups. The estimated proportions of women using vaginal oestrogen only, systemic oestrogen-only MHT, or combined oestrogen and progestogen were similar at around 3% each. We estimated that 1% of women were currently taking tibolone. For all age groups over 55 years, the majority of current users had taken MHT for five years or more.

We estimate that 539 cancers (453 breast, 67 endometrium and 19 ovary) diagnosed in 2010 in women aged over 40 years were attributable to the current use of MHT. This was 1.1% of all cancers (excluding basal cell carcinoma and squamous cell carcinoma of the skin) diagnosed in women aged over 40 years (3.4%, 3.1% and 1.6% of breast, endometrial and ovarian cancers respectively) (Table 3). In contrast, an estimated 52 colorectal cancers were prevented in women aged 40+ years through use of oestrogen-only MHT (Table 3).

### Sensitivity analyses

The results of our sensitivity analyses are presented in Table 3. Under the various scenarios the proportion of all breast cancers attributable to use of combined MHT varied between 2.5% and 3.9%; the proportion of all endometrial cancers attributable to oestrogen-only MHT varied between 1.0% and 5.8%; and the proportion of ovarian cancers attributable to oestrogen-only MHT varied between 1.6% and 1.9%. Applying the relative risks for ovarian cancer from the recent pooled analysis[9] and using prevalence of both combined and oestrogen-only MHT users gave a PAF of 2.4%. The assumption that

| Table 1: Summary of conclusions from IARC on MHT-cancer associations and relative risk source and estimates by MHT type and cancer. | | | | | |
|---|---|---|---|---|---|
| **Cancer Site (ICD-10 codes)** | **IARC Conclusions** | | **Relative Risk Source and Estimates** | | |
| | **Level of evidence[7]** | **Relation between risk and usage patterns** | **Reference** | **Study type** | **Relative Risk** |
| **Oestrogen-only MHT – Primary analysis** | | | | | |
| Colorectum (C18-C20) | Evidence suggesting lack of carcinogenicity. An inverse relationship established between exposure to oestrogen-only menopausal therapy and cancer of the colorectum | Decreased risk in recent users, not related to duration of use | Lin et al[22] | Meta-analysis of 2 RCTs, 8 case-control studies and 8 cohort studies | Current versus never use RR = 0.70 (95%CI 0.57-0.85) |
| Endometrium (C54,C55) | Sufficient | Risk increases with duration of use, decreases with time since last use, but remains elevated for at least 10 years | Karageorgi et al[33] | Nurses' Health Study (US): prospective cohort study (778 endometrial adenocarcinomas) | Duration of use (current users) vs. never use <5 yrs : RR = 2.46 (95% CI; 1.56-4.06) ≥5 yrs : RR = 10.78 (95%CI 7.53-15.44) |
| Ovarian (C56) | Sufficient | Risk increases with duration of use | Pearce et al[20] | Meta-analysis of 8 population-based case-control studies, 5 cohort studies and 1 RCT | Duration of use Per 5 yrs: RR = 1.22 (95%CI 1.18-1.27) Assuming a log-linear relationship 1.0406 per year of use |
| **Oestrogen-only MHT – Supplementary analysis** | | | | | |
| Breast (C50) | Limited-suggestive | Increased risk seen in current users of at least five years duration | Beral et al[17] | Million Women Study (UK): large prospective cohort study (9364 incident invasive breast cancer cases) | Current versus never use RR = 1.30 (95%CI 1.22-1.38) |
| **Combined MHT– Primary analysis** | | | | | |
| Breast (C50) | Sufficient | Risk increases with duration of use, but is largely confined to current and recent users | Beral et al[17] | Million Women Study (UK): prospective cohort study (9364 incident invasive breast cancer cases) | Duration of use (current users) vs. never use <5 yrs : RR = 1.70 (95%CI 1.56-1.85) ≥5 yrs : RR = 2.21 (95%CI 2.06-2.37) |
| **Combined MHT– Supplementary analysis** | | | | | |
| Endometrium (C54, C55) | Sufficient | The increased risk for oestrogen-induced endometrial cancer decreases with the number of days/month progestogens are added to the regimen | Beral et al[24] | Million Women Study (UK): prospective cohort study (1320 endometrial cancer cases) | Derived RR = 0.95 (95%CI 0.78-1.16) [see text for calculation methods] |
| Colorectum (C18-C20) | Insufficient evidence | Evidence suggestive of a protective effect, but insufficient to draw a conclusion | Lin et al[22] | Meta-analysis of 2 RCTs, 8 case-control studies and 8 cohort studies | Current versus never use RR = 0.80 (95%CI 0.69-0.93) |
| Ovarian (C56) | Insufficient evidence | Unlikely to alter risk | Pearce et al[20] | Meta-analysis of 6 population-based case-control studies, 4 cohort studies | Duration of use RR = 1.10 (95%CI 1.04-1.16) per 5 years of MHT use Assuming a log-linear relationship 1.0192 per year of use |

resulted in the largest variation in the number of cancers attributed to MHT was whether women who used only vaginal oestrogen actually reported being current MHT users (539 in the primary analysis where we assumed all women using vaginal oestrogen reported being current users versus 631 cancers in the sensitivity analysis where we assumed only 50% did). For endometrial cancer the largest variation in estimated numbers of cancers resulted from varying the proportion of women using oestrogen-only MHT who had not had a hysterectomy from 13% to a low of 5% and a high of 25% (67 in the primary analysis; 31-127 in the sensitivity analysis).

### Supplementary analyses

If associations between oestrogen-only MHT and breast cancer and combined MHT and ovarian cancer are causal, then an additional 127 (0.9%) breast cancers and 8 (0.7%) ovarian cancers could be attributed to MHT use.

Similarly, assuming a protective effect of combined MHT use on colorectal cancer, we estimated an additional 36 cases of colorectal cancer were prevented in 2010 through the use of combined MHT. When we applied the same relative risk to the Australian data as was used in the UK PAF project for current use of combined MHT and endometrial cancer, an estimated four cases of endometrial cancer in 2010 were prevented through combined MHT use.

### Potential impact of reducing MHT use by Australian women

In 2010, 16,819 women were diagnosed with cancers of the breast, endometrium and

ovary, of which we estimated 539 (3.2% of all breast, endometrium and ovarian cancers) were attributable to MHT use. If the number of women using MHT had been 25% lower across all age categories and/or duration of use categories, we estimate there would have been 142 fewer cancers (PIF 0.8%) including 113 fewer breast cancers (a reduction of 0.8% in the total number of breast cancers), 24 fewer endometrial cancers (a 1.1% reduction) and five fewer ovarian cancers (a 0.4% reduction).

### Potential impact of women only being prescribed oestrogen-only MHT

Overall (in primary and supplementary analyses), we estimated that 670 cancers diagnosed in 2010 were attributable to the use of oestrogen-only or combined MHT. If women had only been prescribed oestrogen-only MHT, we estimate that the number of endometrial and ovarian cancers would have increased by 71 and 12 respectively; however, an estimated 323 fewer breast cancers would have occurred, and the overall total number of cancers attributable to use of MHT would be 430, a net reduction of 240 cancers.

## Discussion

Our analyses suggest that more than 500 Australian women – and perhaps as many as 675 women – developed cancer in 2010 as a consequence of using MHT. On the other hand, an estimated 50 colorectal cancers were prevented in 2010 by oestrogen-only MHT; and if combined MHT also has a protective effect, then a further 36 colorectal and four endometrial cancers were likely prevented. The PAF was highest for breast (3.4%) and endometrial cancer (3.1%). In absolute terms,

most of the cancers attributable to MHT use were breast cancers (n=453).

Other published studies have reported different PAFs for these hormonal exposures, reflecting different relative risk estimates and different prevalence of MHT use between countries. For example, the proportion of French women (45+ years) estimated to be using combined MHT (18.8%)[26] was much higher than that estimated for the Australian population (3.1%), leading to a much higher breast cancer PAF.[26] In contrast, the UK PAF project[23] reported lower PAFs for all cancers (3.2% for breast, 1.2% endometrium and 0.7% ovary) because prevalence of MHT use was lower.[23]

While the precise mechanisms through which MHT causes cancers in humans are not known with certainty, the likely pathway to carcinogenesis in breast, endometrial and ovarian cancer is through oestrogen-induced cell proliferation with consequent increased risk of DNA damage and neoplastic transformation.[27] In breast cells, the presence of a progestogen substantially increases the rate of proliferation. In endometrial tissue, progestogens have the reverse effect, which is why the number of days per cycle that a progestogen is given as part of a MHT regimen determines the overall effect on risk of endometrial cancer.[27,28] In ovarian cancer, the mechanisms are less clear, at least in part because the different histological subtypes may have different tissue origins and different associations with MHT.[29,30] High-grade serous ovarian cancers may arise from the fallopian tube and endometrioid ovarian cancers may arise from ectopic endometrial tissue (endometriosis). Progestogens induce atrophy in tubal epithelium[31] and stop oestrogen-induced proliferation in endometrial cells. How oestrogen reduces CRC risk is unknown, although several mechanisms have been suggested.[32] Bile acids may promote CRC by causing proliferation of colonic epithelium; oestrogens can decrease bile acid secretion. Insulin-like growth factor-1 (IGF-1) may also play a role in the development of CRC and oestrogens have been found to reduce serum IGF-1 levels.

The major limitation of these analyses was the lack of detailed prevalence data for MHT usage in Australian women. Ideally, we would have had access to current (2010) information about MHT use by age, MHT type, duration of use and hysterectomy status; however, such data were not available and this meant

| Table 2: Estimated proportion (%) of women, 40 years and over by categories of current MHT use and hysterectomy status. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age category (yrs) | | | | | | | | |
| | 40-44 % | 45-49 % | 50-54 % | 55-59 % | 60-64 % | 65-69 % | 70-74 % | 75+ % | All women 40+ yrs % |
| Oestrogen-only (vaginal delivery) | 0.5 | 1.8 | 4.6 | 5.5 | 4.6 | 4.4 | 2.4 | 1.3 | 3.1 |
| Systemic Oestrogen-only: | | | | | | | | | |
| Women without a hysterectomy[a] | 0.1 | 0.2 | 0.6 | 0.7 | 0.6 | 0.6 | 0.3 | 0.2 | 0.4 |
| Women with a hysterectomy[a] | 0.4 | 1.5 | 3.9 | 4.6 | 3.9 | 3.7 | 2.1 | 1.1 | 2.6 |
| Oestrogen + Progesterone | 0.5 | 1.8 | 4.7 | 5.5 | 4.6 | 4.4 | 2.5 | 1.3 | 3.1 |
| Tibolone | 0.2 | 0.6 | 1.5 | 1.8 | 1.5 | 1.4 | 0.8 | 0.4 | 1.0 |
| All current MHT USERS | 1.5 | 5.8 | 15.3 | 18.0 | 15.1 | 14.4 | 8.1 | 4.3 | 10.1 |
| Duration of use <5 yrs | 1.1 | 4.1 | 8.5 | 5.3 | 3.2 | 2.4 | 1.1 | 0.9 | |
| Duration of use ≥5 yrs | 0.4 | 2.2 | 6.9 | 12.7 | 11.9 | 12.0 | 7.0 | 3.4 | |
| Not current MHT USERS | 98.5 | 94.2 | 84.7 | 82.0 | 84.9 | 85.7 | 91.9 | 95.7 | 89.9 |

*a: Assuming 13% of women taking oestrogen-only tablets/patches have not had a hysterectomy (and 87% have had a hysterectomy)*

we had to make a number of assumptions about patterns of use by drawing on a several different data sources. The most recent population-based prevalence data available were from the 2004-05 NHS and we assumed that MHT use remained stable between 2005 and 2010. These data post-date the major decline in MHT usage that occurred in the wake of publication of findings from the WHI trial in 2002. However, the 2004-05 NHS did not provide any information on the type of MHT that women were using (oestrogen-only, oestrogen + progestogen, etc) and, as cancer risk varies by type of MHT, we had to make assumptions about the proportions of women using different types. These assumptions were based on prescription data from the *Australian Statistics on Medicine 2010* report,[13] which provides information on individual prescription items rather than on usage by individual women, so may not accurately reflect true usage patterns.

We also made assumptions about use by women who have had a hysterectomy. We assumed that women with a hysterectomy all used oestrogen-only MHT. We also assumed that use of oestrogen-only MHT by the control women who participated in the Australian Ovarian Cancer Study was representative of the general population in that 13% of oestrogen-only users had an intact uterus; the true figure may be higher or lower. Furthermore, we were unable to take into consideration the possibility that some of these women may have been using progestogen-releasing intrauterine devices, to reduce their risk of endometrial neoplasia. Finally, information on duration of MHT use was only available for current users. While that is appropriate for breast and endometrial cancer calculations because risk is not elevated among former users, the dose–response relative risk used for ovarian cancer was not restricted to current users, thus we may have underestimated the number of ovarian cancers attributable to former use.

The overall effect of the many assumptions that we made is difficult to quantify. However, the series of sensitivity analyses that we performed suggest relatively minor variations in the numbers of cancers attributable to MHT use under the various scenarios.

The largest change in the number of cancers attributable to use of MHT would occur if women were to use oestrogen-only MHT exclusively, rather than using combined oestrogen-progestogen MHT. Our calculations suggest that while this may result in a small increase in numbers of endometrial and ovarian cancers, these increases would be offset by a larger reduction in the numbers of breast cancers. Thus, recommendations that women with a uterus always be given combined MHT should be reassessed. It is possible that concomitant use of progestogen-releasing intrauterine devices would mitigate the proliferative effect of oestrogen-only MHT on the endometrium, but how these devices influence breast or ovarian cancer risk is not clear, although at least one study using linked data from Finland suggests their use may be associated with a small increase in risk of breast cancer.[12]

Notwithstanding the likely imprecision, our results indicate that more than 500 cancers could have been prevented in 2010 if women did not use MHT. The decline in use since 2002 has almost certainly reduced

| Table 3: Population Attributable Fractions (PAF) and estimated numbers of cancers diagnosed in Australia in 2010 attributable to exposure to menopausal hormone therapy, estimated number of colorectal cancers prevented in 2010 by use of menopausal hormone therapy; and results of sensitivity analyses. | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Breast (C50[a]) | | | Endometrium (C54, C55[a]) | | | Ovary (C56[a]) | | | All Cancers[b] | | Colorectal (C18-C20[a]) | | |
| | | PAF | Obs. | Exc. | PAF | Obs. | Exc. | PAF | Obs. | Exc. | Obs. | Exc. | PF | Obs. | Prev. |
| **Primary analysis** | Age Group | Combined MHT | | | Oestrogen-only MHT | | | Oestrogen-only MHT | | | | | Oestrogen-only MHT | | |
| | 40-44 yrs | 0.4 | 918 | 4 | 0.2 | 62 | 0 | 0.1 | 47 | 0 | 2,142 | 4 | 0.1 | 117 | 0 |
| | 45-49 yrs | 1.7 | 1,563 | 26 | 1.0 | 122 | 1 | 0.4 | 89 | 0 | 3,416 | 27 | 0.5 | 244 | 1 |
| | 50-54 yrs | 4.2 | 1,822 | 76 | 2.9 | 240 | 7 | 1.2 | 108 | 1 | 4,396 | 84 | 1.3 | 376 | 5 |
| | 55-59 yrs | 5.5 | 1,837 | 101 | 4.8 | 352 | 17 | 2.3 | 138 | 3 | 5,038 | 121 | 1.6 | 541 | 9 |
| | 60-64 yrs | 4.8 | 2,056 | 100 | 4.4 | 369 | 16 | 2.6 | 146 | 4 | 6,004 | 120 | 1.3 | 684 | 9 |
| | 65-69 yrs | 4.7 | 1,734 | 82 | 4.4 | 319 | 14 | 2.9 | 165 | 5 | 5,859 | 101 | 1.3 | 828 | 11 |
| | 70-74 yrs | 2.7 | 1,111 | 30 | 2.6 | 237 | 6 | 1.8 | 120 | 2 | 5,214 | 38 | 0.7 | 868 | 6 |
| | 75+ yrs | 1.4 | 2,372 | 34 | 1.3 | 494 | 6 | 0.9 | 398 | 4 | 14,986 | 44 | 0.4 | 2,794 | 11 |
| | Total[b] | | 13,413 | 453 | | 2,195 | 67 | | 1,211 | 19 | 47,055 | 539 | | 6,452 | 52 |
| | PAFaw | 3.4 | | | 3.1 | | | 1.6 | | | PAF$_{aw}$ = | | PF$_{aw}$ 0.8 | | |
| **Alternative relative risks** | | | | | | | | | | | | | | | |
| Saxena (2010)[21] California Teachers (Breast cancer) | | 2.5 | 335 | | | | | | | | [PAF$_{aw}$=0.9] | 423 | | | |
| Brinton (2008)[18] NIH-AARP (Breast cancer) | | 3.5 | 475 | | | | | | | | [PAF$_{aw}$=1.2] | 562 | | | |
| Razavi (2010)[34] California Teachers (Endometrial cancer) | | | | | 1.0 | 22 | | | | | [PAF$_{aw}$=1.0] | 493 | | | |
| Collaborative Group (2015)[9] Individual participant meta-analysis of 52 studies (ovarian cancer)[c] | | | | | | | | 2.4 | | 29 | [PAF$_{aw}$=1.2] | 549 | | | |
| **Adjustment for hysterectomy** | | | | | | | | | | | | | | | |
| 5% of oestrogen-only users w/out hysterectomy | | | | | 1.4 | | 31 | | | | [PAF$_{aw}$=1.1] | 502 | | | |
| 25% of oestrogen-only users w/out hysterectomy | | | | | 5.8 | | 127 | | | | [PAF$_{aw}$=1.3] | 598 | | | |
| **Assumptions about women using vaginal oestrogen** | | | | | | | | | | | | | | | |
| 50% of vaginal oestrogen users did not report using MHT | | 3.9 | 529 | | 3.6 | | 80 | 1.9 | | 23 | [PAF$_{aw}$=1.3] | 631 | 0.9 | | 61 |
| 10% of vaginal oestrogen users also use systemic MHT | | 3.5 | 474 | | 3.3 | | 72 | 1.7 | | 20 | [PAF$_{aw}$=1.2] | 565 | 0.8 | | 55 |

*Abbreviations: Obs. = observed cancers in 2010; Exc. = excess cancers in 2010 attributable to MHT use; Prev. = cancers prevented in 2010 through MHT use; PAF = population attributable fraction (expressed as a percentage); PF = prevented fraction (expressed as a percentage); PAF$_{aw}$ = Age-weighted population attributable fraction (expressed as a percentage) PF$_{aw}$ = Age-weighted prevented fraction (expressed as a percentage).*

*a: International Classification of Diseases (ICD-10) code.*

*b: excluding basal cell carcinoma and squamous cell carcinoma of the skin.*

*c: PAF calculations based on an overall relative risk for oestrogen-only MHT plus combined MHT users.*

cancer incidence, but a further reduction in use may be warranted especially in light of other known risks associated with MHT such as stroke and pulmonary embolus. MHT is now mostly indicated for relief of perimenopausal/menopausal symptoms and, while undoubtedly effective for those indications, our results – in combination with information from other studies and guideline recommendations[2] – suggest that use of these therapies requires careful appraisal of the risks and benefits, and that if MHT is used it should be at the lowest dose that helps symptoms and for the shortest time.

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### PAF Project

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## Supporting Information

Additional supporting information may be found in the online version of this article:

**Supplementary Table 1**: Summary of alternative relative risks used in sensitivity analyses.

**Supplementary Table 2**: Estimated distribution of MHT types dispensed in Australia in 2010.

**Supplementary Table 3**: Estimated proportions (%) of use of different MHT types using alternative scenarios for including vaginal oestrogen.