Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 1.5 million women over age 65: a retrospective observational study

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Abstract (250 out of 250 max)

Objectives: To examine the effects of estrogen on all-cause mortality, cancers, cardiovascular (CV) conditions, and dementia.

Design: Retrospective observational study

Setting: United States 2007-2018

Population: 1.5 million women aged over 65 in Medicare.

Method: Cox regression with time-varying estrogen type, route, and strength as well as patient's characteristics.

Main Outcome(s): all-cause mortality; 5 cancers- breast, lung, endometrial, colorectal, ovarian cancers; 6 CV conditions- ischemic heart diseases, heart failure, venous thromboembolism, stroke, atrial fibrillation, acute myocardial infarction; and dementia.

Results: Compared to counterparts, estrogen monotherapy (ET) exhibited a significant, 21% (HR=0.79; 95% CI 0.77-0.81), reduction in mortality risk. The reduction was greater with estradiol (HR=0.76; 95% CI 0.73-0.78) than conjugated estrogen (HR=0.83; 95% CI 0.80-0.86), and with topical (HR=0.69; 95% CI 0.66-0.71) than oral preparations (HR=0.86; 95% CI 0.83-0.89). ET also exhibited significant risk *reductions* for all study cancers, breast (HR=0.83; 95% CI 0.80-0.85), lung (HR=0.89; 95% CI 0.85-0.93), endometrial (HR=0.68; 95% CI 0.63-0.73), colorectal (HR=0.87; 95% CI 0.82-0.92) and ovarian (HR=0.86; 95% CI 0.80-0.92). Different dose levels exhibited similar risk reduction in mortality and cancers. ET slightly increased the overall CV risk, mostly risks of ischemic heart diseases and stroke. However, such risks occurred with CEE, oral, and high dose ET. Both combination therapy (HR=1.19; 95% CI 1.08-1.31) and progestogen monotherapy (HR=1.16; 95% CI 1.08-1.26) exhibited a significantly increased risk of breast cancer. No HT exhibited an increased risk of dementia.

Conclusions: Among senior female Medicare beneficiaries, the effect of hormone therapy varies by type, route, and strength of estrogen.

Keywords: hormone replacement therapy, mortality, cancers, cardiovascular conditions.

Tweetable Abstract: Women sans uterus and their providers should be more open to the use ET and its continuance after age 65**.**

Introduction

In 2002, the Women's Health Initiatives (WHI) study used combined estrogen and progestogen therapy (EPT) for menopause and reported a "significant" increase in invasive breast cancer, stroke, and coronary heart disease. However, after corrected for multiple testing both of these results lost significance.[1] The second WHI study examined the use of estrogen replacement therapy (ET) on these outcomes and reported a modest and nearly significant *reduction* in breast cancer.[2] Regardless, the use of any Hormone Therapy (HT) for menopause plummeted.[3,4] Many women prefer how they feel while on it,[5] the American College of Obstetrics and Gynecology (ACOG) and the North American Menopause Society (NAMS) accept the use of ET in older women[6] and the 20 year cumulative follow-up of WHI reported that ET *reduced* breast cancer risk by a significant 22%.[7] However, the FDA applied a black box warning to EPT and ET[8,9] and the National Committee for Quality Assurance (NCQA), the American Geriatric Society, some insurance companies[6] and others oppose its use especially in older women.[10]

The U.S. Centers for Medicare and Medicaid Services (CMS) Virtual Research Data Center (VRDC)[11] carries records for the majority of women age 65 and over including 13 years of prescription claims (since 2006), and 20 years of encounter claims (since 1999).[12] It also included death records. Thus, VRDC provides HT exposure data as well as CV, cancer, and death, like the exposures and events studied by WHI studies. Furthermore, about 7% of elderly women use HT,[13] enough that VRDC data might shed light on the consequences of HT use in older women and answer questions about the effect of dose size, routes and types of estrogens (E) that WHI studies could not address. We implemented extended Cox regression analyses[14–16] to assess the association of these factors with outcomes similar WHI study outcomes. Here we report the results of these analyses.

Methods

Study population

We took a 20% random sample of Medicare Prescription Drug Program (Part D) enrollees and constrained it to women first entitled in Medicare near age 65 (± 1 month) during the full years of Part D benefits, i.e., from 2007 through 2018. We only included enrollees with at least 6 months of data –to assure enough follow-up time, and

those continuously enrolled in Medicare's Part A (hospital) and Part B (medical) insurance, to assure complete records of inpatient/outpatient claims.

We report usage trends broken down by year, HT type and route. The denominator for each year's data was the number of senior female Part D enrollees in that year.

We report descriptive analysis of patients' demographics, socio-economic status, the prevalence of 49 chronic conditions, and the associated crude outcomes rates.

HT exposures

We classified HT into 6 drug types, 3 dose strengths and 2 routes, as applicable. The drug types included estradiol (E2) alone, conjugated estrogen (CEE) alone, progestogen (P) alone, E2+P combined, CEE+P combined and ethinyl estradiol (EE)+P combined. The routes included oral and topical. We defined three estrogen dose ranges relative to a "standard" which was 625, 1000, and 5 µg, for oral CEE, E2, and EE, respectively and 200 and 50 µg for topical, CEE and E2, respectively. EE was always delivered in product combined with a progestogen. When HT was prescribed in different regimens (e.g. 21 days on and 7 days off or every day), we developed an average daily estrogen dose based on DailyMed[17] dosing instructions for each distinct product (Supplementary material, Table S1). For each drug type, we categorized the average daily doses into: high, those greater than 1.45 times the standard; low, those less than 0.45 times the standard; and medium, those between the high and low bounds. We considered each combination of HT type, dose strength, and route as separate covariates (24 of them). We did not distinguish among the different progestogen products in any analysis. We considered subjects to be exposed to study drug if they had a prescription for that drug before an outcome event.

We ignored prescription of injectable CEE because it was prescribed rarely and indicated for uterine bleeding. We did include injectable E2 because it's indicated for menopausal symptoms.[18,19] We treated Injectable E2 like a topical E2 in our analysis because it also avoided 1st pass liver metabolism and we did not want to make separate category for the smallish numbers of patients taking it. To be sure this decision did not distort the results, we also ran a sensitivity analysis with all injectable estrogens ignored.

We did not count Megestrol as a progestogen in our primary analyses because of its special cancer uses but did include it our descriptive analysis.

Outcomes

Our goals were to describe the usage of HT in women age ≥65 and determine their influence on survival, and the occurrence of 5 cancers, 6 cardiovascular (CV) condition, and dementia, similar outcomes of the WHI studies.[1,2] The cancer outcomes included breast, lung, endometrial, colorectal, and ovarian, cancers. The CV outcomes include ischemic heart diseases (IHD), heart failure (HF), venous thromboembolism (VTE), stoke, atrial fibrillation (AFB), and acute myocardial infarction (AMI). For all but ovarian cancer and VTE, the occurrence and the onset date of the conditions were predefined by algorithm in Medicare's Chronic Condition Data Warehouse (CCW).[20] We examined all claims of ovarian cancer (ICD-9/10-CM codes of 183.0 and C56) and for VTE (ICD-9/10-CM codes of 415.1, 451, 453, I26, I80, I82) to define the occurrence and onset date of each. In order to avoid survivor's bias,[21] we created incident cohorts for each outcome by washing out patients diagnosed with that outcome within their first Medicare year.[22]

Statistical analysis

We explored the independent effect of each HT drug on all-cause mortality, on each of the 5 cancer, 6 CV, and dementia outcomes, for a total of 13 separate extended Cox regression analyses. In each regression analysis, we included 24 combinations of HT drug type (CEE, E2, P, or E+P), routes (topical, oral), and dose ranges (low, medium, or high) as covariates. However, in Tables 3 and 4, we only present marginal effects of type, route and dose of estrogen compared to no use of the given drug controlling for the use of other HT drugs. To adjust the effects of HT drugs for patient's characteristics, we also included race, degree of low-income-subsidy (LIS) (a surrogate for income), rural residence indicator, calendar year of Medicare Part D enrollment (for secular trends), and subsets of the 47 CCW chronic conditions with >1% prevalence, to adjust for overall medical burden. We treated all covariates except race, gender and rural status as time-varying to avoid the risk of, an immortal time

bias and, a violation of proportional hazard assumption.[14–16] When death was the outcome, we excluded both cancer and CV conditions from the list of chronic conditions. When a cancer or CV condition or dementia was the outcome, we excluded all other cancer, CV conditions or dementia, respectively.

Subjects became eligible for the study at the time of their Medicare entitlement, but prescription records were unavailable until their Part D enrollment. We followed these subjects from their entry to Part D (while accounting for left truncation[23]) until they 1) experienced as an outcome of interest, 2) switched to a capitated plan, 3) disenrolled from Medicare or 4) reached 12/31/2018, the end of our data availability, whichever came first. In order to mitigate selection bias toward use of the study drugs, we developed *time-varying* propensity score (PS)[24] separately for estrogens as a class and for progestogens as a class using logistic regressions. The PS was the likelihood of receiving an estrogen (or a progestogen), conditional on patient's characteristics (demographics, socioeconomics, and presence of the 47 chronic conditions). We iteratively estimated the PSs every 6 months among the patients who remain in follow-up considering all covariates that preceded the end of a given 6-month cycle[25] and ran all Cox regression analyses with time-varying PSs as additional adjustments.

Our data did not meet the strict requirement for a Fine-Gray competing risk analysis.[26] However, to be sure it would not be important, we also ran sensitivity analyses for non-fatal outcomes treating death as a competing risk.

Results

Study population and Secular trends

From our 20% random sample of Part D senior female enrollees, nearly 1.5 million satisfied our selection criteria (see Figure S1 Cohort Diagram). The death cohort (full cohort) without washout included all 1,522,256 study subjects. A notable proportion, 17.1%, of subjects in this cohort used some type of HT at least once during our study (Table S2). The disease specific incident cohorts had similar proportions of HT users.

Over the 12 years of follow-up (2007-2018), the proportion of senior Medicare women taking any HT containing estrogen dropped by half, from 11.5% to 5.8%. Those taking ET declined by 40%, from 10.3% to 5.6%. E2

tended to replace CEE, EPT plummeted from 1.3% to a minuscule 0.2% (Figure S2a), and topical forms tended to replace oral forms (Figure S2b).

We used Medicaid eligibility as a proxy for the subject's income level. In the full cohort, 16.4% were Duals (eligible for both Medicare and Medicaid) with income below 135% Federal Poverty Line (FPL)[27] or annual income below $25,000[28]; 2.6% were non-dual but eligible for low-income subsidy (LIS) with incomes between 135% and 150% FPL; and 81% had standard Medicare with incomes above 150% FLP. The proportions of non-Hispanic White and rural resident were 82.3% and 22.5% respectively. Among the chronic conditions, hyperlipidemia (72.1%), hypertension (69.0%), and cataract (56.6%), were the three most common (Table 1). Hysterectomy data was only available for 12.6% of our full cohort, because we lacked claims data before age 65 when most hysterectomies occur. So most (82%) of our information about uterine absence come from the ICD diagnosis codes for "acquired absence of uterus/cervix" (Z90.710 and Z90.711) (Table S3).

Starting with Part D enrollment, the median follow-up duration in the full (death) cohort was 4.9 years (total of 7,853,249 person-years) ranging from 11.3 years for the 2007 enrollment "class" to 0.9 years for the 2018 "class". The number of subjects, follow-up duration and number censored patients varied across incident cohorts because of different, end points, and one-year washouts, by outcome. Follow-up ended when subjects first developed the targeted outcomes, died, switched to a capitated plan, disenrolled from Medicare or reached the end of our study on 12/31/2018. For the full cohort, these rates were, 16.6%, 2.5%, 17.2%, <0.03% and 63.7%, respectively (Table 2). During the study period, participation in Part D increased from 55% to 70%,[29] and the shift to Medicare advantage increased from 19% to 34%.[30]

Primary Analyses

In Tables 3 and 4, we report the hazard ratios (HRs) of outcomes as the percent greater or less than one along with confidence intervals (CI). Table 3a includes the number (percent) of patients by type, route, and dose of estrogen in full cohort. More women were on ET (n=237,320) than on EPT (n=32,886) or P (25,215); more on topical ET (n=178,541) than oral ET (n=77,133); and more on medium dose (n=128,345) than low (n=81,344) or high

(n=88,339) dose ET. These figures were similar across all incident cohorts. ET use was associated with a significant, 21% (HR=0.79; 95% CI 0.77-0.81), reduction in mortality risk versus counterparts (Table 3b). The reduction was greater with E2 (24%, HR=0.76; 95% CI0.73-0.78) than with CEE (17%, HR=0.83; 95% CI 0.80-0.86), and greater with topical (31%, HR=0.69; 95% CI0.66-0.71) than with oral preparations (14%, HR=0.86; 95% CI0.83-0.89). There was no significant difference in mortality risk between different ET dose levels though medium dose exhibited numerically less risk than high or low dose. The HRs for EPT and progestogen alone for mortality were close to 1 and insignificant.

Breast/lung/endometrial/colorectal/ovarian cancers occurred in 55,828, 18,354, 14,010, 13,628 and 9,214 subjects, respectively. Compared to no ET use, ET use was associated with significant *reductions* in risk for all study cancers, breast (17%, HR=0.83; 95% CI 0.80-0.85), lung (11%, HR=0.89; 95% CI 0.85-0.93), endometrial (32%, HR=0.68; 95% CI 0.63-0.73), colorectal (13%, HR=0.87; 95% CI 0.82-0.92) and ovarian (14%, HR=0.86; 95% CI 0.80-0.92). For each cancer, the reductions tended to be similar or slightly greater with CEE than E2, and with oral than topical preparations, the opposite of what we saw for mortality risk (Table 3c-g). EPT was associated with a significant 19% *increase* (HR=1.19; 95% CI 1.08-1.31) in breast cancer, and a significant 29% decrease (HR=0.71; 95% CI 0.57-0.88) in endometrial cancer, risk. These results parallel the WHI study results for both cancers.[1] Progestogen alone significantly increased the risk of breast (16%, HR=1.16; 95% CI 1.08-1.26), ovarian (85%, HR=1.85; 95% CI 1.56-2.20) and endometrial (316%, HR=4.16; 95% CI 3.73-4.63) cancers.

ET increased the risk of combined CV outcomes overall, by a small, 2% (HR=1.02; 95% CI 1.01-1.03 data not shown). However, no increase in combined CV risk occurred with use of either E2 (HR=1.01; 95% CI 1.00-1.02) or topical E (HR=1.00; 95% CI 0.99-1.01) (data not shown) respectively. No increase in risk of any of the 6 CV outcomes occurred with either low or medium dose ET. Topical preparations reduced the risk of 5 of 6 CV outcomes (Table 4 b-e). But topical preparations and E2 increased the risk of IHD, by 2% (Table 4a). Overall, we saw no significant associations between EPT and CV outcomes, but the number of EPT users was 1/7th, that of ET users, reducing the power to see any effect. Progestogen alone significantly *increased* the risk of IHD by 6% (HR=1.06; 95% CI 1.02-1.11) (Table 4a).

Overall, no HT was associated with an increased risk of dementia (Table 4g). ET was associated with a small but significant 2% decrease in dementia risk (HR=0.98; 95% CI 0.96-1.00); E2 with 3% (HR=0.97; 95% CI 0.94-0.99), topical with 5% (HR=0.95; 95% CI 0.93-0.97) and low dose with 9% (HR=0.91; 95% CI 0.87-0.95) decreased risk. EPT and P exhibited null associations; only topical EPT exhibited any increased dementia risk, 11% (HR=1.11; 95% CI 1.02-1.21).

The results of the analysis that excluded all injectable estrogen was almost identical to the one that included only E2 injectables.

Table S4 shows the effects of all non-drug covariates on all-cause mortality, combined cancers, and combined CV conditions. Compared to the regular Medicare beneficiaries, dual eligible subjects (the poorest) had no increased risk of death (HR=0.75; 95% CI 0.73-0.77) or combined cancers (HR=1.01; 95% CI 0.99-1.04) but did exhibit significantly increased risk of combined CV conditions (HR=1.30; 95% CI 1.28-1.31). Being a rural resident had no effect on the risk of death, 5 cancers combined, or 6 CV outcomes combined.

Discussion

Main Findings

In this population-based retrospective observational study, we found significant reductions in the risk of, mortality, all 6 cancers, and small but significant reductions in 4 CV outcomes and dementia, among ET users. Risks of IHD and stroke increased (by 3% and 2% respectively) among such users, but risks were concentrated in CEE, oral preparations, and high dose. Across all CV outcomes, low or medium sized doses, topical routes and E2 had better outcomes than their alternatives.

Strengths and Limitations

Our study had the advantage of a very large sample, (1.5 million subjects and 7.8 million years of follow-up). It started with older women all close to age 65. We followed each subject for an average of 5.2 years in an extended

Cox regression analysis. We examined the effect of estrogen alone (ET), progestogen alone and combined (EPT), on all-cause mortality, the occurrence of 5 cancers, 6 CV conditions, and dementia using methods that minimized survival bias,[22] immortal time bias and deviations from the proportional hazard assumption of Cox regression,[14–16] and selection bias.[25] We meticulously categorized every HT drug by type, route and average daily dose (Table S2) and included all combinations of these three factors as covariates in our analyses in orders to ascertain their relative importance.

Some of our results might be explained by HT users practicing better health behavior. However, we took some healthy behaviors (or their inverse) into account by including diagnoses of tobacco, alcohol, and drug abuse as covariates in our analysis (Table S4). And the different direction in outcomes with ET use versus EPT use would be hard to explain if healthy behaviors were a dominant factor.

We depended solely on claims diagnoses and could not verify them with chart reviews. Our study has all the limits of observational studies. And the results do not apply to Medicare's Advantage enrollees for whom claims data were not generated. However, we have no reason to expect that HT effects would differ importantly by type of Medicare plan. We had very incomplete hysterectomy status information so could not fully separate the influence of hysterectomy versus HT on the study outcomes.

Interpretation

. Our significant 21% *decrease* in mortality risk among ET users stands out from the insignificant, 4% *increase* in mortality in the 2004 WHI report.[2] That became a 4% *decrease* in their 2013 report[31] and a near significant, 6%, *decrease* in their 2017 report,[32] still far less than what we observed. However, ET's effect in the WHI follow-up may have been attenuated by no ET use in the 10.8 years after the study stopped. The 10-year Danish Randomized Controlled Trial (RCT) also saw mortality reduction in two combined outcomes.[33]

Our results agree with all of WHI's significant cancer results. We reported a 17%, and WHI reported a 21%[31] decrease in breast cancer risk among ET users. The reduction in endometrial cancer, and increase in breast cancer, risk with EPT were similar in direction and magnitude in both our study and WHI's. Unique to our study were

significant reductions in lung cancer, and colon cancer, risks of 11% and 13% respectively, with ET use. Previous observational studies have also reported protective effects of HT against lung[34] and colorectal,[35,36] cancer.

Interestingly our significant HR for lung cancer risk was numerically identical to WHI's insignificant HR for lung cancer.[31] The number of cases in WHI's ET treatment arm, 35 colorectal, and 47 lung, cancer cases,[31] provided inadequate statistical power to detect modest sized effects (see Table S5).

Our follow-up began when women entered Medicare at about age 65, but we have to assume that women taking ET at that age had started it closer to menopausal for symptoms and continued it into their Medicare years. If so our positive results align with the timing hypotheses[37] that asserts ET use early in menopauses is better than later, but extend it by reporting positive effects with usage into Medicare years.

The beneficial associations we saw between ET use and endometrial and ovarian cancer were probably artifacts of the guidelines that constrain the use of ET to women post hysterectomy, who lack endometrial and/or ovarian tissue to spawn such cancers. Studies suggest that progestogens might prevent ovarian cancer.[38] Progestogen alone in our study was associated with an *increases* in ovarian and endometrial cancer risk. These results are likely artifacts of progestogen's use to treat these two cancers.[39]

Conclusion

In summary, our results suggest that progestogens (and EPT) tend to be bad, and ET to be very good, for older menopausal women, yielding important reductions in mortality and all six cancers. With our very large sample size, we were able to separate the influence of type, route, and dose size of estrogen on mortality, cancer, CV, and dementia outcomes. Low and medium doses of ET, E2 and topical routes generally provide more benefits than the alternatives confirming current guidelines and usage trends.

According to some, including the Chairman of the WHI Observational Study Scientific Advisory Committee,[40,41] the first reports of the WHI studies cast the hormone replacement, including ET, in an overly harsh light that has stuck in the public and medical mind, and frightened away users (Figure S2).

However, little evidence exists from RCTs to indict ET of harms. The significance of CEE's negative effect on stroke and VTE in the second WHI study[2] disappeared in the post intervention follow-up study.[31] The WHI results for ET's effects on dementia were not significant. A more focused WHIs study[42] and a systemic view[43] found no evidence that ET contributed to dementia. On the positive side ET reduces fracture risk,[2] and breast cancer risk[31] and yielded a near significant 6%, reduction in mortality risk.[32]

With the new RCT evidence, we believe the balance of RCT evidence favors ET use, especially if started close to menopause. Patients and their providers should be more open to ET use in the right doses and routes and the FDA should soften or remove their black box warning for ET.[3] Our study, though purely observational, raises the possibility of multiple new benefits from ET use in menopause and research to explore these possibilities is needed.

Disclosure of interests: None declared.

Contribution to authorship

SB and CM conceived and designed the study. SB and CM formulated the research questions. SB was responsible for data management and statistical analysis. SB analyzed the data. SB and CM drafted and revised the paper. CM provided important clinical input.

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Table Legends

Table 1. Baseline Characteristics

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: IQR = Interquartile Range; AMI = Acute Myocardial Infarction; COPD = Chronic Obstructive Pulmonary Disease.

Table 2. Event/Censoring Points and Rates of Event/Death by Each Study Cohort

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: HMO = Health Maintenance Organization; IHD = Ischemic Heart Disease; HF = Heart Failure; VTE = Venous thromboembolism; AFB = Atrial Fibrillation; AMI = Acute Myocardial Infarction.

Table 3. Hazard ratios of various HT regimens on all-cause mortality and cancer outcomes

Notes: Data are presented as Hazard Ratio (HR) and its 95% Confidence Interval (CI).

↑= very significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05

↓= very significantly low with P-value < 0.001, ↓= significantly low with 0.001 ≤ P-value < 0.05

Table 4. Hazard ratios of various HT regimens on CV outcomes and dementia

Notes: Data are presented as Hazard Ratio (HR) and its 95% Confidence Interval (CI).

Abbreviations: IHD = ischemic heart diseases; HF = heart failure; VTE = venous thromboembolism; AFB = atrial fibrillation; AMI = acute myocardial infarction.

↑= very significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05

↓= very significantly low with P-value < 0.001, ↓= significantly low with 0.001 ≤ P-value < 0.05

Table 1. Baseline Characteristics

Age at Part D Entry, Median (IQR)	65.0(65.0-65.3)	**Lung Cancer**	26,405(1.7)
Age at The End of Follow-Up, Median (IQR)	70.5(68.3-73.1)	**Endometrial Cancer**	23,234(1.5)
White	1,248,513(82.0)	**Cervical Cancer**	7,418(0.5)
Black	110,000(7.2)	**Ovarian Cancer**	16,052(1.1)
Hispanic	84,391(5.5)	**Anemia**	570,261(37.5)
Asian	40,195(2.6)	**Asthma**	190,915(12.5)
Other	39,157(2.6)	**Hyperlipidemia**	1,098,123(72.1)
Ever Dual	249,633(16.4)	**Hypertension**	1,050,484(69.0)
Non-Dual LIS	38,854(2.6)	**Hypothyroidism**	445,758(29.3)
Non-Dual No LIS	1,233,769(81.0)	**Alcohol Use Disorders**	29,790(2.0)
Living in Rural Area	341,465(22.4)	**Anxiety Disorders**	377,990(24.8)
Pulmonary Embolism	36,597(2.4)	**Bipolar Disorder**	39,557(2.6)
Deep Vein Thrombosis	109,009(7.2)	**Major Depressive Affective Disorder**	360,994(23.7)
AMI	30,215(2.0)	**Drug Use Disorder**	41,191(2.7)
Atrial Fibrillation	105,802(7.0)	**Personality Disorders**	25,627(1.7)
Heart Failure	180,656(11.9)	**Schizophrenia and Other Psychotic Disorders**	29,008(1.9)
Ischemic Heart Disease	392,621(25.8)	**Epilepsy**	28,989(1.9)
Stroke/Transient Ischemic Attack	103,388(6.8)	**Cystic Fibrosis and Other Metabolic Developmental Disorders**	24,272(1.6)
Cataract	862,003(56.6)	**Fibromyalgia, Chronic Pain and Fatigue**	437,311(28.7)
Chronic Kidney Disease	327,712(21.5)	**Viral Hepatitis (General)**	15,815(1.0)
COPD	255,662(16.8)	**Liver Disease Cirrhosis and Other Liver Conditions**	128,570(8.4)
Diabetes	435,272(28.6)	**Leukemias And Lymphomas**	24,120(1.6)
Glaucoma	272,846(17.9)	**Migraine and Other Chronic Headache**	97,612(6.4)
Hip/Pelvic Fracture	21,300(1.4)	**Mobility Impairments**	34,792(2.3)
Depression	476,918(31.3)	**Obesity**	412,361(27.1)
Alzheimer's Disease or Senile Dementia	81,241(5.3)	**Overarching Oud Disorder**	29,185(1.9)
Osteoporosis	316,807(20.8)	**Peripheral Vascular Disease**	163,051(10.7)
Rheumatoid Arthritis/Osteoarthritis	752,965(49.5)	**Tobacco Use Disorders**	159,906(10.5)
Breast Cancer	135,887(8.9)	**Pressure Ulcers and Chronic Ulcers**	56,765(3.7)
Colorectal Cancer	24,475(1.6)	**Deafness and Hearing Impairment**	116,779(7.7)

Table 2. Event/Censoring Points and Rates of Event/Death by Each Study Cohort

Cohort	N	Event	Death	Censored at HMO Entry	Censored at Disenrollment	Censored at Dec 31 2018	Rate of Event, per 1000 person-years	Rate of Death, per 1000 person-years
Death	1,522,256	73,656(4.8)	73,656(4.8)	294,926(19.4)	385(0.0)	1,153,289(75.8)	N/A	9.38
Brest Cancer	1,442,197	55,828(3.9)	62,742(4.4)	277,707(19.3)	362(0.0)	1,045,558(72.5)	7.69	8.64
Lung Cancer	1,514,205	18,354(1.2)	61,536(4.1)	293,072(19.4)	383(0.0)	1,140,860(75.3)	2.36	7.90
Endometrial Cancer	1,513,032	14,010(0.9)	70,296(4.6)	292,356(19.3)	383(0.0)	1,135,987(75.1)	1.80	9.05
Colorectal Cancer	1,511,409	13,628(0.9)	69,192(4.6)	291,905(19.3)	380(0.0)	1,136,304(75.2)	1.76	8.91
Ovarian Cancer	1,515,418	9,214(0.6)	69,760(4.6)	293,322(19.4)	381(0.0)	1,142,741(75.4)	1.18	8.95
IHD	1,353,713	224,078(16.6)	33,976(2.5)	233,254(17.2)	325(0.0)	862,080(63.7)	35.57	5.39
HF	1,465,885	124,285(8.5)	40,154(2.7)	268,600(18.3)	373(0.0)	1,032,473(70.4)	17.11	5.53
VTE	1,485,389	88,956(6.0)	52,110(3.5)	279,198(18.8)	374(0.0)	1,064,751(71.7)	11.98	7.02
Stroke	1,495,013	76,145(5.1)	57,626(3.9)	280,564(18.8)	371(0.0)	1,080,307(72.3)	10.13	7.67
AFB	1,485,601	69,147(4.7)	58,175(3.9)	282,829(19.0)	374(0.0)	1,075,076(72.4)	9.23	7.77
AMI	1,516,466	24,425(1.6)	66,677(4.4)	291,382(19.2)	384(0.0)	1,133,598(74.8)	3.14	8.58
Dementia	1,506,264	65,249(4.3)	56,169(3.7)	284,498(18.9)	380(0.0)	1,099,968(73.0)	8.54	7.35

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477 **Table 3. Hazard ratios of various HT regimens on all-cause mortality and cancer outcomes**

478

	(a) N(%) for full Cohort	(b) Death	(c) Breast	(d) Lung	(e) Endometrial	(f) Colorectal	(g) Ovarian
ET vs. no	237,320(15.6)	0.79(0.77,0.81)↓	0.83(0.80,0.85)↓	0.89(0.85,0.93)↓	0.68(0.63,0.73)↓	0.87(0.82,0.92)↓	0.86(0.80,0.92)↓
By type							
CEE vs. no	106,043(7.0)	0.83(0.80,0.86)↓	0.76(0.72,0.80)↓	0.90(0.84,0.97)↓	0.67(0.59,0.76)↓	0.85(0.77,0.94)↓	0.80(0.70,0.91)↓
E2 vs. no	165,006(10.8)	0.76(0.73,0.78)↓	0.87(0.85,0.90)↓	0.88(0.83,0.93)↓	0.68(0.63,0.75)↓	0.88(0.82,0.94)↓	0.90(0.83,0.97)↓
By route							
Oral vs. no	77,133(5.1)	0.86(0.83,0.89)↓	0.78(0.75,0.82)↓	0.94(0.89,1.00)	0.60(0.53,0.67)↓	0.87(0.80,0.94)↓	0.80(0.72,0.89)↓
Topical vs. no	178,547(11.7)	0.69(0.66,0.71)↓	0.90(0.87,0.92)↓	0.81(0.77,0.86)↓	0.82(0.77,0.88)↓	0.87(0.82,0.93)↓	0.95(0.89,1.02)
By dose							
Low vs. no	81,344(5.3)	0.78(0.75,0.82)↓	0.87(0.84,0.91)↓	0.83(0.77,0.89)↓	0.70(0.64,0.78)↓	0.79(0.72,0.86)↓	0.90(0.81,1.00)↓
Standard vs. no	128,345(8.4)	0.76(0.73,0.79)↓	0.82(0.79,0.85)↓	0.89(0.84,0.95)↓	0.72(0.66,0.78)↓	0.89(0.82,0.96)↓	0.84(0.77,0.92)↓
High vs. no	88,339(5.8)	0.83(0.78,0.88)↓	0.79(0.73,0.86)↓	0.95(0.85,1.06)	0.61(0.50,0.74)↓	0.93(0.81,1.07)	0.83(0.69,1.00)
P vs. no	25,215(1.7)	1.05(0.96,1.14)	1.16(1.08,1.26)↑	0.91(0.76,1.08)	4.16(3.73,4.63)↑	1.00(0.83,1.21)	1.85(1.56,2.20)↑
EPT vs. no	32,886(2.2)	0.96(0.86,1.07)	1.19(1.08,1.31)↑	0.58(0.02,20.60)	0.71(0.57,0.88)↓	0.91(0.70,1.17)	0.90(0.69,1.17)
By E type of E							
CEE vs. no	15,299(1.0)	0.95(0.80,1.14)	1.15(0.94,1.40)	1.13(0.86,1.48)	0.72(0.49,1.05)	0.86(0.51,1.45)	0.81(0.48,1.36)
E2 vs. no	20,834(1.4)	1.00(0.89,1.11)	1.16(1.07,1.26)↑	1.04(0.86,1.25)	0.65(0.52,0.80)↓	0.88(0.70,1.11)	0.83(0.63,1.09)
EE vs. no	1,521(0.1)	0.90(0.63,1.30)	1.31(0.98,1.74)	0.08(0.00,100.52)	0.84(0.43,1.65)	1.02(0.50,2.08)	1.25(0.61,2.54)
By route							
Oral vs. no	27,226(1.8)	0.89(0.76,1.03)	1.21(1.06,1.39)↑	0.45(0.00,77.16)	0.68(0.51,0.92)↓	0.90(0.63,1.27)	0.88(0.61,1.27)
Topical vs. no	9,665(0.6)	1.15(1.02,1.30)↑	1.13(1.04,1.23)	1.05(0.85,1.31)	0.77(0.64,0.93)↓	0.93(0.72,1.18)	0.95(0.77,1.19)

					↑			
By dose								
	Low vs. no	17,403(1.1)	0.98(0.81,1.19)	1.08(0.94,1.25)	0.17(0.00,100.97)	0.69(0.48,1.00)	1.09(0.81,1.46)	1.14(0.86,1.52)
	Standard vs.			1.25(1.15,1.36)				
no		19,985(1.3)	1.00(0.88,1.13)	↑	0.97(0.80,1.19)	0.65(0.50,0.84)↓	0.78(0.57,1.08)	0.78(0.56,1.07)
	High vs. no	4,106(0.3)	0.89(0.68,1.18)	1.23(0.94,1.60)	1.04(0.58,1.86)	0.81(0.49,1.36)	0.90(0.46,1.76)	0.86(0.42,1.75)

Table 4. Hazard ratios of various HT regimens on CV outcomes and dementia

		(a) IHD	**(b) HF**	**(c) VTE**	**(d) Stroke**	**(f) AFB**	**(e) AMI**	**(g) Dementia**
		1.03(1.01,1.04)	0.96(0.94,0.97)			0.96(0.94,0.98)	0.90(0.87,0.93)	
ET vs. no		↑	↓	0.97(0.95,0.99)↓	1.02(1.00,1.04)↑	↓	↓	0.98(0.96,1.00)↓
By type								
		1.04(1.02,1.06)			1.07(1.04,1.10)			
	CEE vs. no	↑	0.98(0.96,1.01)	0.99(0.96,1.02)	↑	0.98(0.95,1.02)	0.96(0.90,1.02)	1.00(0.96,1.03)
			0.94(0.92,0.96)			0.95(0.92,0.98)	0.86(0.82,0.91)	
	E2 vs. no	1.02(1.00,1.03)↑	↓	0.96(0.94,0.98)↓	0.99(0.97,1.02)	↓	↓	0.97(0.94,0.99)↓
By route								
		1.03(1.02,1.05)			1.07(1.04,1.10)			
	Oral vs. no	↑	1.01(0.99,1.04)	0.98(0.95,1.00)	↑	0.99(0.96,1.02)	0.96(0.91,1.01)	1.00(0.97,1.03)
			0.88(0.86,0.89)		0.96(0.93,0.98)	0.92(0.90,0.94)	0.82(0.78,0.86)	0.95(0.93,0.97)
	Topical vs. no	1.02(1.00,1.03)↑	↓	0.96(0.94,0.99)↓	↓	↓	↓	↓
By dose								
			0.90(0.88,0.93)	0.92(0.89,0.95)	0.94(0.91,0.97)	0.93(0.90,0.96)	0.88(0.82,0.94)	0.91(0.87,0.94)
	Low vs. no	0.98(0.96,1.00)↓	↓	↓	↓	↓	↓	↓
	Standard vs.		0.93(0.91,0.95)			0.95(0.92,0.98)	0.88(0.83,0.93)	
no		1.01(0.99,1.03)	↓	0.97(0.94,1.00)↓	1.00(0.97,1.03)	↓	↓	1.00(0.97,1.03)
		1.10(1.07,1.13)			1.15(1.10,1.21)			
	High vs. no	↑	1.05(1.01,1.09)↑	1.02(0.97,1.07)	↑	1.02(0.96,1.07)	0.95(0.86,1.04)	1.03(0.97,1.08)
P vs. no		1.06(1.02,1.11)↑	1.04(0.97,1.10)	1.03(0.96,1.10)	1.06(0.98,1.14)	1.04(0.96,1.12)	0.89(0.77,1.04)	0.96(0.89,1.04)
EPT vs. no		1.00(0.95,1.05)	0.95(0.88,1.03)	1.00(0.91,1.09)	0.91(0.83,1.01)	1.00(0.91,1.09)	0.81(0.63,1.05)	1.01(0.91,1.12)
By type								
	CEE vs. no	1.03(0.95,1.13)	0.99(0.88,1.12)	1.00(0.87,1.15)	0.89(0.76,1.03)	0.95(0.81,1.12)	0.94(0.71,1.26)	0.96(0.80,1.16)

	E2 vs. no	0.97(0.92,1.01)	0.99(0.92,1.06)	1.00(0.92,1.07)	0.94(0.87,1.03)	0.96(0.88,1.05)	0.95(0.79,1.14)	1.07(0.99,1.16)
	EE vs. no	1.01(0.85,1.21)	0.83(0.63,1.10)	1.00(0.74,1.35)	0.89(0.63,1.26)	1.13(0.84,1.53)	0.49(0.19,1.27)	0.95(0.66,1.36)
By route								
	Oral vs. no	1.00(0.93,1.07)	0.91(0.82,1.02)	0.99(0.88,1.12)	0.89(0.77,1.02)	1.00(0.88,1.13)	0.80(0.56,1.13)	0.96(0.83,1.12)
	Topical vs. no	1.00(0.95,1.05)	1.05(0.97,1.14)	1.01(0.93,1.10)	0.97(0.88,1.06)	1.00(0.90,1.10)	0.85(0.68,1.07)	1.11(1.02,1.21)↑
By dose								
	Low vs. no	0.93(0.85,1.02)	0.95(0.83,1.08)	0.93(0.80,1.09)	0.97(0.83,1.14)	1.04(0.90,1.20)	0.73(0.44,1.22)	0.99(0.83,1.19)
	Standard vs. no	1.02(0.96,1.07)	0.88(0.81,0.97)↓	1.02(0.94,1.11)	0.93(0.84,1.03)	0.96(0.87,1.07)	0.92(0.74,1.14)	1.10(1.00,1.21)
	High vs. no	1.04(0.91,1.20)	1.05(0.86,1.28)	1.04(0.83,1.30)	0.84(0.64,1.09)	1.00(0.78,1.28)	0.77(0.43,1.40)	0.92(0.69,1.22)