Health outcomes of hormone therapy initiated or continued after age 65

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Abstract

Objective: Menopausal hormone therapy (HT) is effective for alleviating vasomotor symptoms but remains controversial regarding long-term safety, particularly in women over 65. Despite guidelines recommending initiation before age 60, a notable proportion of older women continue or begin HT later in life. The health outcomes of HT in women aged 65 and older, especially those initiating therapy after 65, compared with younger users and nonusers were evaluated.

Methods: This retrospective cohort study included 83,147 women aged 50 years or older enrolled in Clalit Health Services (2000-2022). Women were categorized by age at HT initiation: never-users, initiators at 50-65 years, initiators 65 years or older, or initiators after 50 continuing beyond 65. Outcomes included malignancies, cardiovascular events, osteoporosis, and dementia. Group differences were evaluated using χ^2 tests, and time-to-event associations were examined using Cox proportional hazards models with age as the underlying time scale. To evaluate the health outcomes of HT in women aged 65 and older, especially those initiating therapy after 65, compared with younger users and nonusers.

Results: HT use was associated with increased risks of several malignancies, including both hormone-sensitive and non–hormone-sensitive cancers. In crude analyses, women initiating HT at 50-65 years had lower ischemic heart disease/myocardial infarction prevalence (3.6% vs. 9.2%) but higher hypertension (11.0% vs. 6.2%). In adjusted Cox models, initiation at 65 years or older was associated with increased hazards of any cancer (hazard ratio [HR]: 2.216, 95% confidence interval [CI]: 1.833-2.677) and cerebrovascular accident (HR: 2.695, 95% CI: 2.358-3.079). Among women initiating HT at 50-65 years, hazards were markedly elevated for cerebrovascular accident (HR: 16.692, 95% CI: 15.571-17.893), cancer (HR: 8.490, 95% CI: 7.281-9.900), and ischemic heart disease/myocardial infarction (HR: 9.169, 95% CI: 8.321–10.102); the crude cardiovascular advantage was not observed after adjustment.

Conclusions: Initiation of HT after age 65 is linked to significantly increased risks of cancer and vascular events, supporting current guidelines discouraging late initiation. While HT may offer some cardiovascular benefits when started earlier, use in older women should involve individualized risk-benefit assessment and close monitoring. These findings underscore the need to align clinical practice with evolving evidence and guideline recommendations. Given the retrospective design, incomplete pre-2000 medical history, and potential residual confounding, findings should be interpreted with caution.

Key Words: Age 65, Cancer risk, Cardiovascular risk, Menopausal hormone therapy, Older women, Risk-benefit, Vasomotor symptoms.

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Menopausal hormone therapy (HT) remains a subject of ongoing debate in women's health, particularly regarding its long-term use and safety, especially in older women.[1] While HT effectively alleviates vasomotor symptoms (VMS) such as hot flashes, there is limited high-quality evidence that HT provides meaningful benefit for most other menopausal symptoms.[2] Traditional medical guidance often discouraged HT use beyond age 65, assuming VMS would subside by then.[3] However, recent evidence indicates that a significant proportion of women aged 65 and older continue to experience these symptoms. Studies have shown that VMS can persist for many years after menopause, with some women experiencing them into their late 60s.[4,5]

Previous major studies, such as the Women's Health Initiative, have produced mixed results on HT's long-term effects. Some studies suggested potential benefits in reducing the risk of certain chronic diseases, while others highlighted potential risks, such as an increased risk of

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The study was approved by the Ethics Committee of Clalit Health Services (Beer-Sheva, Israel) (approval # 0214-17-COM1). The procedures followed were in accordance with the ethical standards of the committee responsible for human research. Informed consent forms were signed by all participants.

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breast cancer and cardiovascular events.[6] Liu and Li[7] found that HT use was associated with a smaller biological aging discrepancy, particularly in women with lower socioeconomic status (SES), suggesting potential health equity benefits. However, extended use of systemic HT, particularly initiation after age 60 or 10 years postmenopause, has been associated with an elevated risk of cardiovascular disease.[8]

Despite current recommendations to limit HT initiation to women under 60, a significant number of older women continue to use it. In the United States in 2015, over a third of HT prescriptions were written for women over 60.[9] Furthermore, ~4% of menopausal women continue HT use after age 65.[10] This may involve using low-dose formulations, non-oral routes like patches or gels, and different combinations of estrogens and progestogens. However, data on the specific effects of these various HT regimens in older women are limited.[11] A recent study found that the prevalence of HT use declined significantly over the last two decades, with the greatest declines observed among women aged 52-65 years.[12]

A 2024 study in *Menopause* examined HT use beyond age 65 among women with Medicare. The research found that estrogen monotherapy was associated with significant risk reductions in mortality, breast cancer, and other health conditions.[13] However, the study emphasized that the implications of HT use vary significantly depending on the specific type, route, and strength of hormones used.

Current guidelines often recommend limiting HT initiation to women within 10 years of menopause or before the age of 60. However, some experts suggest that these recommendations may need to be revisited.[14] This highlights the evolving understanding of HT and the importance of individualized risk-benefit assessments for each woman.[1] The Menopause Society (formerly The North American Menopause Society) recognizes that there is no universal age limit for discontinuing HT. For healthy women with persistent bothersome symptoms, continuing HT beyond 65 may be a reasonable option, provided it's undertaken with careful risk-benefit assessment, judicious selection of HT regimens, and ongoing counseling.[2]

This study aimed to investigate the long-term health outcomes of HT use in women over the age of 65 compared with younger initiators and never-users, using a large, real-world dataset from Clalit Health Services in Israel. We analyzed a 22-year span of data to examine cardiovascular, cerebrovascular, oncologic, and other health outcomes, with stratification by age at initiation and duration of use.

METHODS

We conducted a retrospective cohort study of 83,147 women aged 50 years and older to investigate the long-term outcomes of HT use in women aged 50 years and older, specifically those over 65 years old. The study population comprised female members of Clalit Health Services, Israel's largest integrated health care provider, in the Southern District of Israel, with data collected between January 1, 2000, and December 31, 2022.

Women entered follow-up at the age when they first met all eligibility criteria: 50 years and older, continuous active membership in Clalit at entry, and no documented diagnosis of the outcome of interest before analytic entry. Only incident events recorded after baseline were included in outcome analyses. Validated medical records before 2000 were unavailable due to the national transition from paper to digital records; therefore, undetected pre-existing conditions or prior HT exposure cannot be fully excluded. However, transitions between Israeli health plans in this age group are uncommon, reducing the likelihood of major misclassification.

HT exposure was defined by the first recorded dispensing of an HT prescription during the study period. Women were categorized into mutually exclusive groups according to age at initiation and continuation: never-users; initiators at 50-65 years; initiators at 65 years and above; and initiators after age 50 who continued treatment beyond 65. Exposure classification was fixed at initiation to maintain a clear temporal relationship between first documented HT use and subsequent outcomes; time-varying exposure modeling was not applied.

Duration of HT exposure was calculated cumulatively from the first to the last dispensing record. Participants were considered continuous users if their cumulative dispensed supply covered $\geq 50\%$ of the interval between first and last dispensing; a gap of ≥ 12 months was considered discontinuation. Duration-stratified analyses were performed to examine potential dose-response effects, grouped as 1-4, 5-9, 10-14, and 15 years and above.

Time-to-event analyses used Cox proportional hazards regression with age as the underlying time scale. Each woman entered the risk set at her attained age at baseline and exited at age at event, death, disenrollment, or end of follow-up (December 31, 2022). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for major outcomes, including overall malignancies, cerebrovascular accident (CVA), ischemic heart disease (IHD)/myocardial infarction (MI), and other cardiovascular events. Analyses included both overall and age-restricted comparisons (50-65 years and 65 years and older separately). χ^2 tests were used to compare crude incidence differences across exposure groups. All analyses were performed using SPSS software, version 29 (IBM Corp., Armonk, NY).

RESULTS

Our study included 83,147 women aged 50 years and above, investigating the implications of HT use on subsequent morbidities according to both age at initiation and duration of therapy. Among the participants, 6.6% initiated HT at ages 50-65, and 1.0% initiated HT at 65 and above (Fig. 1). After applying eligibility and exclusion criteria, total follow-up encompassed 1,359,167 person-years (PY) for never-users, 19,323 PY for women initiating HT at 50-65, 12,075 PY for women initiating after 50, and

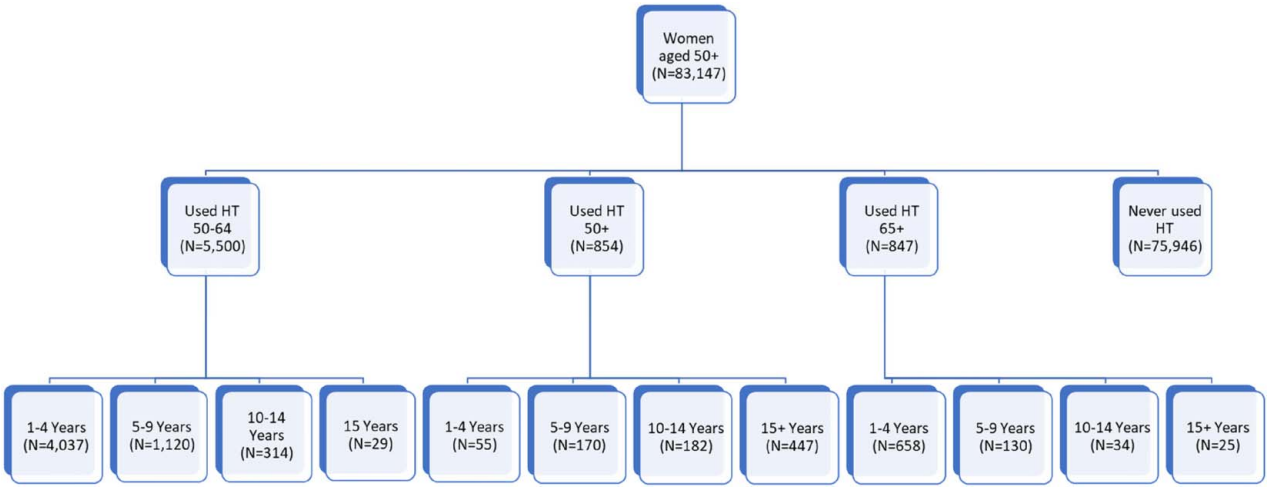

FIG. 1. Study design and flow of participants included in the cohort. The diagram shows the total number of women aged 50 years and above in Clalit Health Services between 2000 and 2022, and the final number of participants classified into groups: never-users, HT initiators at ages 50-65, HT initiators at 65 and above, and HT initiators after 50. HT, hormone therapy.

2,955 PY for women initiating at 65 and above. Baseline characteristics and crude outcome frequencies are presented in Table 1.

Overall, HT use was significantly associated with an increased risk of both hormone-sensitive and non–hormone-sensitive malignancies, as well as overall cancer (Table 1). For example, breast cancer incidence nearly doubled among women aged 50-65 (6.7% vs. 3.5%, $P < 0.001$). Elevated risks were also observed for thyroid and lung cancer, non-Hodgkin lymphoma, and melanoma, contributing to a higher overall cancer risk (19.2% vs. 13.4%, $P < 0.001$). Conversely, HT use at ages 50-65 was associated with a significantly lower crude incidence of IHD compared with nonusers (3.6% vs. 9.7%, $P < 0.001$). In contrast, among women initiating therapy at 65 and above, HT use was correlated with an increased risk of IHD compared with nonusers (12.9% vs. 9.7%, $P < 0.001$), venous thromboembolism (VTE), stroke, and carotid artery disease. The incidence of hypertension (HTN) showed an opposite pattern between age groups—higher among HT users aged 50-65 (11.0% vs. 8.2%, $P < 0.001$), yet lower among those 65 and above (4.3% vs. 8.2%, $P < 0.001$).

During follow-up, age-stratified crude incidences diverged by initiation age (Tables 2–4). Among women aged 50-65, HT users had lower crude rates of IHD/MI (3.6% vs. 9.2%, $P < 0.001$) but higher rates of HTN (11.0% vs. 6.2%, $P < 0.001$). Overall cancer incidence was significantly lower among HT users aged 50-65 (19.2% vs. 31.9%, $P < 0.001$). Among women aged 65 and above, HT use was associated with higher crude stroke incidence (22.2% vs. 19.9%, $P = 0.093$), although this difference was not statistically significant, and higher overall cancer (26.1% vs. 15.8%, $P < 0.001$). In addition, breast cancer was higher (5.8% vs. 3.4%, $P < 0.001$) compared with never-users of the same age group. In the overall 50+ cohort, patterns appeared mixed, with lower crude IHD among HT users but consistently higher rates of HTN and cancer.

Duration analyses (Tables 5–7) indicated that longer exposure was generally associated with higher morbidity, although statistical significance was not consistent across outcomes. In women initiating HT at ages 50-65, HTN increased with duration, and cancers such as breast cancer ($P < 0.001$) and melanoma ($P = 0.011$) rose proportionally with exposure, representing the clearest duration-dependent associations. In contrast, outcomes such as IHD, osteoporosis, HTN, and dementia demonstrated nonlinear patterns that were not statistically robust. Among women initiating HT at 65 and above, longer duration was associated with higher rates of CVA and peripheral vascular disease, while cancer incidence (breast, thyroid, melanoma) also increased with longer use, though without consistent statistical significance. Importantly, the distribution of HT duration differed markedly between age strata: nearly 40% of women aged 50-65 continued therapy for ≥ 10 years, compared with fewer than 15% of those initiating at 65 and above, most of whom discontinued within 1-4 years. This uneven exposure distribution likely reduced statistical power in the older group and may partly explain the lack of consistent significance across many endpoints in the duration-stratified analyses.

Multivariable-adjusted results from Cox regression models with age as the underlying time scale (Table 8) further clarified these associations. In adjusted models, among women initiating HT at 50-65 years, CVA risk was markedly increased (HR: 16.692, 95% CI: 15.571-17.893, $P < 0.001$), cancer risk was substantially elevated (HR: 8.490, 95% CI: 7.281-9.900, $P < 0.001$), and IHD/MI risk was also higher (HR: 9.169, 95% CI: 8.321-10.102, $P < 0.001$), consistent with the overall trend toward increased vascular and oncologic risks in this group. In women initiating HT at 65 and above, HRs were substantially increased for both cancer (HR: 2.216, 95% CI: 1.833-2.677, $P < 0.001$) and stroke (HR:

TABLE 1. All morbidities investigated among the four different groups by age

	N (%)						
	Never used HT (N = 75,946)	**Used HT 50-65 (N = 5,500)**	**Used HT 50+ (N = 854)**	**Used HT 65+ (N = 847)**	***P*1**	***P*2**	***P*3**
IHD MI	8,313 (9.7)	198 (3.6)	42 (4.9)	109 (12.9)	< 0.001	0.06	< 0.001
IHD other	12,336 (14.4)	532 (9.7%)	111 (13.0)	186 (22.0)	< 0.001	0.003	< 0.001
CHF systolic	1,185 (1.4)	85 (1.5)	21 (2.5)	32 (3.8)	< 0.001	0.052	< 0.001
CHF nonsystolic	3,845 (4.5)	102 (1.9)	21 (2.5)	58 (6.8)	< 0.001	0.233	< 0.001
CHF combined	117 (0.1)	8 (0.1)	2 (0.2)	4 (0.5%)	0.124	0.633	0.065
CHF NOS	4,490 (5.2)	86 (1.6)	19 (2.2)	64 (7.6)	< 0.001	0.159	< 0.001
HTN diet	2,011 (2.3)	150 (2.7)	33 (3.9)	17 (2.0)	0.097	0.065	0.223
HTN drug	25,099 (29.2)	1,326 (24.1)	296 (34.7)	310 (36.6)	< 0.001	< 0.001	< 0.001
HTN	7,022 (8.2)	607 (11.0)	127 (14.9)	36 (4.3)	< 0.001	0.001	< 0.001
CVA	11,233 (13.1)	473 (8.6)	84 (9.8)	188 (22.2)	< 0.001	0.235	< 0.001
Carotid artery disease	3,406 (4.0)	322 (5.9)	85 (10.0)	103 (12.2)	< 0.001	< 0.001	< 0.001
Diabetes PVD	2,411 (2.8)	104 (1.9)	15 (1.8)	37 (4.4)	< 0.001	0.787	< 0.001
PVD	1,701 (2.0)	92 (1.7)	26 (3.0)	38 (4.5)	< 0.001	0.006	< 0.001
Pulmonary embolism	1,151 (1.3)	66 (1.2)	16 (1.9)	27 (3.2)	< 0.001	0.105	< 0.001
Osteoporosis	16,744 (19.5)	1,465 (26.6)	239 (28.0)	293 (34.6)	< 0.001	0.408	< 0.001
Breast cancer	3,007 (3.5)	369 (6.7)	85 (10.0)	49 (5.8)	< 0.001	< 0.001	0.313
Malignancy of colon or rectum	2,006 (2.3)	127 (2.3)	23 (2.7)	33 (3.9)	0.056	0.492	0.006
Malignancy of lung	806 (0.9)	85 (1.5)	16 (1.9)	20 (2.4)	< 0.001	0.476	0.083
Malignancy of bladder	349 (0.4)	23 (0.4)	10 (1.2)	9 (1.1)	0.001	0.004	0.014
Malignancy of ovary	401 (0.5)	45 (0.8)	9 (1.1)	10 (1.2)	< 0.001	0.485	0.289
Malignancy of uterus	801 (0.9)	89 (1.6)	14 (1.6)	10 (1.2)	< 0.001	0.964	0.339
Malignancy of pancreas	494 (0.6)	41 (0.7)	6 (0.7)	12 (1.4)	0.045	0.892	0.046
Malignancy of brain CNS	209 (0.2)	27 (0.5)	5 (0.6)	3 (0.4)	0.013	0.61	0.79
Stomach cancer	394 (0.5)	20 (0.4)	8 (0.9)	3 (0.4)	0.117	0.019	1
Melanoma	451 (0.5%)	62 (1.1)	19 (2.2)	16 (1.9)	< 0.001	0.008	0.061
Hodgkins lymphoma	152 (0.2)	19 (0.3)	4 (0.5)	3 (0.4)	0.037	0.539	1
Non-Hodgkin lymphoma mycosis fungoides	627 (0.7)	78 (1.4)	17 (2.0)	18 (2.1)	< 0.001	0.2	0.117
Acute leukemia	214 (0.2)	14 (0.3)	2 (0.2)	8 (0.9)	0.004	1	0.001
Chronic leukemia	282 (0.3)	27 (0.5)	1 (0.1)	7 (0.8)	0.048	0.166	0.213
Malignancy of kidney	387 (0.5)	30 (0.5)	1 (0.1)	8 (0.9)	0.119	0.114	0.161
Malignancy of larynx	75 (0.1)	5 (0.1)	1 (0.1)	1 (0.1)	0.992	0.58	0.577
Malignancy of cervix uteri	219 (0.3)	31 (0.6)	4 (0.5)	2 (0.2)	0.004	1	0.306
Malignancy of pharynx	205 (0.2)	15 (0.3)	2 (0.2)	4 (0.5)	0.727	1	0.307
Malignancy of esophagus	115 (0.1)	3 (0.1)	0 (0.0)	1 (0.1)	0.2	1	0.436
Malignancy of liver bile ducts	401 (0.5)	24 (0.4)	4 (0.5)	7 (0.8)	0.499	0.784	0.177
Malignancy of thyroid	246 (0.3)	41 (0.7)	4 (0.5)	2 (0.2)	< 0.001	0.51	0.114
Malignancy of bone	79 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0.524	1	1
Malignancy of connective tissue sarcoma	211 (0.2)	20 (0.4)	0 (0.0)	4 (0.5)	0.184	0.098	0.552
Malignancy of other male female genital organs	180 (0.2)	16 (0.3)	4 (0.5)	3 (0.4)	0.417	0.333	0.733
Multiple myeloma	258 (0.3)	19 (0.3)	7 (0.8)	9 (1.1)	< 0.001	0.043	0.003
Polycytemia vera	153 (0.2)	9 (0.2)	2 (0.2)	3 (0.4)	0.7	0.651	0.209
Myelodysplastic syndrome	148 (0.2)	6 (0.1)	0 (0.0)	2 (0.2)	0.291	1	0.29
Myelo lymphoproliferative syndrome	36 (0.0)	6 (0.1)	1 (0.1)	0 (0.0)	0.178	1	1
Malignancy of other sites	849 (1.0)	52 (0.9)	11 (1.3)	12 (1.4)	0.499	0.347	0.201
Malignancy of Unknown Site	791 (0.9)	19 (0.3)	4 (0.5)	13 (1.5)	< 0.001	0.539	< 0.001
Dementia Alzheimer's OMS	12,378 (14.4)	252 (4.6%)	87 (10.2)	265 (31.3)	< 0.001	< 0.001	< 0.001
Cancer	11,553 (13.4)	1,057 (19.2)	220 (25.8)	221 (26.1)	< 0.001	< 0.001	< 0.001
Time of use							
Mean ± SD	17.9 ± 7.1	3.51 ± 2.99	14.14 ± 5.81	3.49 ± 3.67	< 0.001	< 0.001	1
Median	23	3	15	2			
Range	1-23	1-16	3-21	1-21			

CHF, congestive heart failure; CNS, central nervous system; CVA, cerebrovascular accident; HT, hormone therapy; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

*P*1 relates to the comparison across all four groups.

*P*2 relates to the comparison between HT 50-65 and HT 50+.

*P*3 relates to the comparison between HT 50-65 and HT 65+.

TABLE 2. All morbidities investigated among the four different groups by age

	N (%)		
	Never used HT 50-65 (N=1,754)	**Used HT 50-65 (N=5,500)**	***P*-value**
IHD MI	162 (9.2%)	198 (3.6%)	< 0.001
IHD Other	253 (14.4%)	532 (9.7%)	< 0.001
CHF systolic	4 (0.2%)	85 (1.5%)	< 0.001
CHF nonsystolic	69 (3.9%)	102 (1.9%)	< 0.001
CHF combined	2 (0.1%)	8 (0.1%)	0.757
CHF NOS	124 (7.1%)	86 (1.6%)	< 0.001
HTN diet	44 (2.5%)	150 (2.7%)	0.621
HTN drug	473 (27.0%)	1,326 (24.1%)	0.016
HTN	108 (6.2%)	607 (11.0%)	< 0.001
CVA	210 (12.0%)	473 (8.6%)	< 0.001
Carotid Artery Disease	18 (1.0%)	322 (5.9%)	< 0.001
Diabetes PVD	84 (4.8%)	104 (1.9%)	< 0.001
PVD	28 (1.6%)	92 (1.7%)	0.827
Pulmonary Embolism	41 (2.3%)	66 (1.2%)	< 0.001
Osteoporosis	138 (7.9%)	1,465 (26.6%)	< 0.001
Breast Cancer	126 (7.2%)	369 (6.7%)	0.493
Malignancy of Colonor Rectum	86 (4.9%)	127 (2.3%)	< 0.001
Malignancy of Lung	71 (4.0%)	85 (1.5%)	< 0.001
Malignancy of Bladder	13 (0.7%)	23 (0.4%)	0.094
Malignancy of Ovary	34 (1.9%)	45 (0.8%)	< 0.001
Malignancy of Uterus	43 (2.5%)	89 (1.6%)	0.023
Malignancy of Pancreas	40 (2.3%)	41 (0.7%)	< 0.001
Malignancy of Brain CNS	27 (1.5%)	27 (0.5%)	< 0.001
Stomach Cancer	19 (1.1%)	20 (0.4%)	< 0.001
Melanoma	7 (0.4%)	62 (1.1%)	0.006
Hodgkins Lymphoma	7 (0.4%)	19 (0.3%)	0.743
Non Hodgkin Lymphoma Mycosis Fungoides	30 (1.7%)	78 (1.4%)	0.379
Acute Leukemia	13 (0.7%)	14 (0.3%)	0.004
Chronic Leukemia	11 (0.6%)	27 (0.5%)	0.491
Malignancy of Kidney	17 (1.0%)	30 (0.5%)	0.054
Malignancy of Larynx	1 (0.1%)	5 (0.1%)	0.667
Malignancy of Cervix Uteri	18 (1.0%)	31 (0.6%)	0.039
Malignancy of Pharynx	7 (0.4%)	15 (0.3%)	0.402
Malignancy of Esophagus	4 (0.2%)	3 (0.1%)	0.042
Malignancy of Liver Bile Ducts	26 (1.5%)	24 (0.4%)	< 0.001
Malignancy of Thyroid	10 (0.6%)	41 (0.7%)	0.444
Malignancy of Bone	5 (0.3%)	4 (0.1%)	0.028
Malignancy of Connective Tissue Sarcoma	10 (0.6%)	20 (0.4%)	0.241
Malignancy of Other Male Female Genital Organs	6 (0.3%)	16 (0.3%)	0.734
Multiple Myeloma	10 (0.6%)	19 (0.3%)	0.194
Polycytemia Vera	3 (0.2%)	9 (0.2%)	0.947
Myelodysplastic Syndrome	5 (0.3%)	6 (0.1%)	0.099
Myelo Lymphoproliferative Syndrome	1 (0.1%)	6 (0.1%)	0.541
Malignancy of Other Sites	96 (5.5%)	52 (0.9%)	< 0.001
Malignancy of Unknown Site	15 (0.9%)	19 (0.3%)	0.006
Dementia Alzheimers OMS	66 (3.8%)	252 (4.6%)	0.145
Cancer	559 (31.9%)	1,057 (19.2%)	< 0.001

CHF, congestive heart failure; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; HT, hormone therapy; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

2.695, 95% CI: 2.358-3.079, $P < 0.001$). Among women in the 50+ group, CVA risk was also elevated (HR: 4.151, 95% CI: 3.629-4.747, $P < 0.001$), along with higher risks of cancer and IHD/MI. Duration-stratified models confirmed that longer use was consistently linked to greater hazards across multiple outcomes ($P < 0.01$ for trend). Notably, while crude analyses suggested lower IHD incidence among women initiating HT at ages 50-65, this association did not persist after adjustment, indicating residual confounding in unadjusted comparisons.

Taken together, HT initiation at ages 50-65 was associated with a mixed pattern of lower crude IHD but higher HTN and malignancies, whereas initiation at 65 and above was consistently associated with lower HTN, but increased risks of stroke and cancer. Increasing duration of therapy was accompanied by higher morbidity, reinforcing the cumulative burden associated with advancing age and prolonged HT exposure.

DISCUSSION

This large-scale retrospective cohort study provides valuable insights into the long-term implications of HT use, considering both the age at initiation and duration of

TABLE 3. All morbidities investigated among the four different groups by age

	N (%)		
	Never used HT 50+ (N=37,650)	**Used HT 50+ (N=854)**	***P*-value**
IHD MI	2,263 (6.0%)	42 (4.9%)	0.183
IHD Other	4,356 (11.6%)	111 (13.0%)	0.198
CHF systolic	628 (1.7%)	21 (2.5%)	0.076
CHF non systolic	1,223 (3.2%)	21 (2.5%)	0.197
CHF combined	55 (0.1%)	2 (0.2%)	0.508
CHF NOS	971 (2.6%)	19 (2.2%)	0.518
HTN diet	1,058 (2.8%)	33 (3.9%)	0.066
HTN drug	9,744 (25.9%)	296 (34.7%)	<0.001
HTN	4,573 (12.1%)	127 (14.9%)	0.016
CVA	3,764 (10.0%)	84 (9.8%)	0.877
Carotid Artery Disease	1,534 (4.1%)	85 (10.0%)	<0.001
Diabetes PVD	1,013 (2.7%)	15 (1.8%)	0.094
PVD	501 (1.3%)	26 (3.0%)	<0.001
Pulmonary Embolism	476 (1.3%)	16 (1.9%)	0.117
Osteoporosis	7,826 (20.8%)	239 (28.0%)	<0.001
Breast Cancer	1,623 (4.3%)	85 (10.0%)	<0.001
Malignancy of Colon Rectum	834 (2.2%)	23 (2.7%)	0.349
Malignancy of Lung	378 (1.0%)	16 (1.9%)	0.013
Malignancy of Bladder	143 (0.4%)	10 (1.2%)	<0.001
Malignancy of Ovary	170 (0.5%)	9 (1.1%)	0.011
Malignancy of Uterus	471 (1.3%)	14 (1.6%)	0.314
Malignancy of Pancreas	196 (0.5%)	6 (0.7%)	0.467
Malignancy of Brain CNS	105 (0.3%)	5 (0.6%)	0.097
Stomach Cancer	150 (0.4%)	8 (0.9%)	0.015
Melanoma	219 (0.6%)	19 (2.2%)	<0.001
Hodgkins Lymphoma	78 (0.2%)	4 (0.5%)	0.102
Non-Hodgkin Lymphoma Mycosis Fungoides	300 (0.8%)	17 (2.0%)	<0.001
Acute Leukemia	74 (0.2%)	2 (0.2%)	0.806
Chronic Leukemia	109 (0.3%)	1 (0.1%)	0.351
Malignancy of Kidney	174 (0.5%)	1 (0.1%)	0.138
Malignancy of Larynx	34 (0.1%)	1 (0.1%)	0.797
Malignancy of Cervix Uteri	120 (0.3%)	4 (0.5%)	0.445
Malignancy of Pharynx	90 (0.2%)	2 (0.2%)	0.997
Malignancy of Esophagus	48 (0.1%)	0 (0.0%)	0.296
Malignancy of Liver Bile Ducts	164 (0.4%)	4 (0.5%)	0.886
Malignancy of Thyroid	152 (0.4%)	4 (0.5%)	0.769
Malignancy of Bone	37 (0.1%)	0 (0.0%)	0.359
Malignancy of Connective Tissue Sarcoma	92 (0.2%)	0 (0.0%)	0.148
Malignancy of Other Male Female Genital Organs	89 (0.2%)	4 (0.5%)	0.172
Multiple Myeloma	123 (0.3%)	7 (0.8%)	0.014
Polycytemia Vera	71 (0.2%)	2 (0.2%)	0.762
Myelodysplastic Syndrome	43 (0.1%)	0 (0.0%)	0.323
Myelo Lymphoproliferative Syndrome	21 (0.1%)	1 (0.1%)	0.458
Malignancy of Other Sites	268 (0.7%)	11 (1.3%)	0.05
Malignancy of Unknown Site	244 (0.6%)	4 (0.5%)	0.516
Dementia Alzheimer's OMS	2,721 (7.2%)	87 (10.2%)	0.001
Cancer	5,209 (13.8%)	220 (25.8%)	<0.001

CHF, congestive heart failure; CVA, cerebrovascular accident; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

treatment among women aged 50 and older. Our findings demonstrate a nuanced and age-dependent pattern of risks across cardiovascular and oncologic outcomes, contributing to the ongoing debate regarding HT safety in older populations.[1]

Consistent with previous research,[6] our study demonstrated a significantly increased risk of hormone-sensitive cancers, notably breast cancer, among women aged 50-65 using HT. This heightened risk, which appeared to be duration-dependent for breast cancer and melanoma in this age group, underscores the importance of careful risk-benefit assessments, particularly for prolonged use in younger postmenopausal women.[15] We also observed an elevated risk of several non–hormone-sensitive malignancies, including thyroid cancer, non-Hodgkin lymphoma, lung cancer, and melanoma, contributing to the increased overall cancer incidence seen in this group.[16]

Conversely, HT use among women aged 50-65 was associated with a significantly lower crude incidence of IHD, which may support the "timing hypothesis."[19,22] However, this crude association was not preserved after multivariable adjustment in Cox regression models, where HT users exhibited higher IHD/MI HRs. Therefore, a true protective cardiovascular effect cannot be inferred, and

TABLE 4. All morbidities investigated among the four different groups by age

	N (%)		
	Never used HT 65+ (N=36,542)	**Used HT 65+ (N=847)**	***P*-value**
IHD MI	5,888 (16.1%)	109 (12.9%)	0.011
IHD Other	7,727 (21.1%)	186 (22.0%)	0.566
CHF systolic	553 (1.5%)	32 (3.8%)	< 0.001
CHF nonsystolic	2,553 (7.0%)	58 (6.8%)	0.876
CHF combined	60 (0.2%)	4 (0.5%)	0.032
CHF NOS	3,395 (9.3%)	64 (7.6%)	0.085
HTN diet	909 (2.5%)	17 (2.0%)	0.374
HTN drug	14,882 (40.7%)	310 (36.6%)	0.016
HTN	2,341 (6.4%)	36 (4.3%)	0.011
CVA	7,259 (19.9%)	188 (22.2%)	0.093
Carotid Artery Disease	1,854 (5.1%)	103 (12.2%)	< 0.001
Diabetes PVD	1,314 (3.6%)	37 (4.4%)	0.234
PVD	1,172 (3.2%)	38 (4.5%)	0.038
Pulmonary Embolism	634 (1.7%)	27 (3.2%)	0.002
Osteoporosis	8,780 (24.0%)	293 (34.6%)	< 0.001
Breast Cancer	1,258 (3.4%)	49 (5.8%)	< 0.001
Malignancy of Colonor Rectum	1,086 (3.0%)	33 (3.9%)	0.119
Malignancy of Lung	357 (1.0%)	20 (2.4%)	< 0.001
Malignancy of Bladder	193 (0.5%)	9 (1.1%)	0.036
Malignancy of Ovary	197 (0.5%)	10 (1.2%)	0.013
Malignancy of Uterus	287 (0.8%)	10 (1.2%)	0.2
Malignancy of Pancreas	258 (0.7%)	12 (1.4%)	0.016
Malignancy of Brain CNS	77 (0.2%)	3 (0.4%)	0.372
Stomach Cancer	225 (0.6%)	3 (0.4%)	0.334
Melanoma	225 (0.6%)	16 (1.9%)	< 0.001
Hodgkins Lymphoma	67 (0.2%)	3 (0.4%)	0.256
Non Hodgkin Lymphoma Mycosis Fungoides	297 (0.8%)	18 (2.1%)	< 0.001
Acute Leukemia	127 (0.3%)	8 (0.9%)	0.004
Chronic Leukemia	162 (0.4%)	7 (0.8%)	0.1
Malignancy of Kidney	196 (0.5%)	8 (0.9%)	0.111
Malignancy of Larynx	40 (0.1%)	1 (0.1%)	0.94
Malignancy of CervixUteri	81 (0.2%)	2 (0.2%)	0.93
Malignancy of Pharynx	108 (0.3%)	4 (0.5%)	0.352
Malignancy of Esophagus	63 (0.2%)	1 (0.1%)	0.705
Malignancy of Liver Bile Ducts	211 (0.6%)	7 (0.8%)	0.347
Malignancy of Thyroid	84 (0.2%)	2 (0.2%)	0.97
Malignancy of Bone	37 (0.1%)	0 (0.0%)	0.354
Malignancy of Connective Tissue Sarcoma	109 (0.3%)	4 (0.5%)	0.362
Malignancy of Other Male Female Genital Organs	85 (0.2%)	3 (0.4%)	0.47
Multiple Myeloma	125 (0.3%)	9 (1.1%)	< 0.001
Polycytemia Vera	79 (0.2%)	3 (0.4%)	0.396
Myelodysplastic Syndrome	100 (0.3%)	2 (0.2%)	0.836
Myelo Lymphoproliferative Syndrome	14 (0.0%)	0 (0.0%)	0.569
Malignancy of Other Sites	485 (1.3%)	12 (1.4%)	0.822
Malignancy of Unknown Site	472 (1.3%)	13 (1.5%)	0.536
Dementia Alzheimers OMS	9,591 (26.2%)	265 (31.3%)	< 0.001
Cancer	5,785 (15.8%)	221 (26.1%)	< 0.001

CHF, congestive heart failure; CVA, cerebrovascular accident; HTN, hypertension; IHD, Ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

the potential benefit of delaying early menopause must be interpreted cautiously.[20,21] HTN was more common in users aged 50-65, a discrepancy that challenges cardioprotective assumptions and reinforces the need for blood pressure monitoring.[11,23] The notably high CVA HR in this group likely reflects prothrombotic effects of estrogen, baseline risk factors, and preferential continuation among women experiencing benefit.

Among women initiating HT after age 65, risks were consistently and substantially elevated. Both cancer and CVA hazards were significantly higher compared with never-users (HR: 2.216 and 2.695, respectively), consistent with guideline recommendations discouraging late HT initiation.[3,8] These findings align with biological mechanisms suggesting increased vulnerability of aging vasculature to estrogen-related thrombotic effects and potential stimulation of subclinical malignancies.[22-24] Notably, HTN behaved in the opposite direction in this group, being lower among HT users, which may reflect differences in baseline characteristics, medication use, or survivorship effects. This warrants further investigation. The inverse HTN association in the 65 and above group likely reflects baseline differences, selective prescribing, or survivorship bias, and should not be interpreted as a protective effect of HT.

TABLE 5. All morbidities investigated among the four different groups by time of use periods

	Used HT 50-65 (N=5,500)				
	N (%)				
	1-4 y (n=4,037)	5-9 y (n=1,120)	10-14 y (n=314)	15 y (n=29)	*P*-value
IHD MI	137 (3.4%)	49 (4.4%)	12 (3.8%)	0 (0.0%)	0.313
IHD Other	364 (9.0%)	133 (11.9%)	32 (10.2%)	3 (10.3%)	0.04
CHF systolic	68 (1.7%)	16 (1.4%)	1 (0.3%)	0 (0.0%)	0.243
CHF non systolic	75 (1.9%)	25 (2.2%)	2 (0.6%)	0 (0.0%)	0.263
CHF combined	7 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0.811
CHF NOS	67 (1.7%)	16 (1.4%)	3 (1.0%)	0 (0.0%)	0.662
HTN diet	106 (2.6%)	32 (2.9%)	12 (3.8%)	0 (0.0%)	0.483
HTN drug	920 (22.8%)	325 (29.0%)	75 (23.9%)	6 (20.7%)	< 0.001
HTN	446 (11.0%)	129 (11.5%)	29 (9.2%)	3 (10.3%)	0.725
CVA	339 (8.4%)	106 (9.5%)	23 (7.3%)	5 (17.2%)	0.197
Carotid Artery Disease	234 (5.8%)	66 (5.9%)	20 (6.4%)	2 (6.9%)	0.972
Diabetes PVD	75 (1.9%)	23 (2.1%)	6 (1.9%)	0 (0.0%)	0.863
PVD	66 (1.6%)	20 (1.8%)	5 (1.6%)	1 (3.4%)	0.875
Pulmonary Embolism	51 (1.3%)	14 (1.3%)	1 (0.3%)	0 (0.0%)	0.463
Osteoporosis	1,038 (25.7%)	342 (30.5%)	80 (25.5%)	5 (17.2%)	0.007
Breast Cancer	231 (5.7%)	104 (9.3%)	32 (10.2%)	2 (6.9%)	< 0.001
Malignancy of Colon or Rectum	99 (2.5%)	20 (1.8%)	7 (2.2%)	1 (3.4%)	0.593
Malignancy of Lung	57 (1.4%)	20 (1.8%)	8 (2.5%)	0 (0.0%)	0.33
Malignancy of Bladder	17 (0.4%)	5 (0.4%)	1 (0.3%)	0 (0.0%)	0.974
Malignancy of Ovary	31 (0.8%)	11 (1.0%)	3 (1.0%)	0 (0.0%)	0.847
Malignancy of Uterus	69 (1.7%)	16 (1.4%)	4 (1.3%)	0 (0.0%)	0.759
Malignancy of Pancreas	29 (0.7%)	11 (1.0%)	1 (0.3%)	0 (0.0%)	0.598
Malignancy of Brain CNS	23 (0.6%)	4 (0.4%)	0 (0.0%)	0 (0.0%)	0.455
Stomach Cancer	14 (0.3%)	6 (0.5%)	0 (0.0%)	0 (0.0%)	0.532
Melanoma	39 (1.0%)	16 (1.4%)	5 (1.6%)	2 (6.9%)	0.011
Hodgkins Lymphoma	12 (0.3%)	7 (0.6%)	0 (0.0%)	0 (0.0%)	0.261
Non Hodgkin Lymphoma Mycosis Fungoides	54 (1.3%)	21 (1.9%)	3 (1.0%)	0 (0.0%)	0.431
Acute Leukemia	8 (0.2%)	4 (0.4%)	2 (0.6%)	0 (0.0%)	0.415
Chronic Leukemia	17 (0.4%)	9 (0.8%)	1 (0.3%)	0 (0.0%)	0.395
Malignancy of Kidney	25 (0.6%)	4 (0.4%)	1 (0.3%)	0 (0.0%)	0.661
Malignancy of Larynx	3 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0.71
Malignancy of Cervix Uteri	23 (0.6%)	7 (0.6%)	1 (0.3%)	0 (0.0%)	0.901
Malignancy of Pharynx	9 (0.2%)	6 (0.5%)	0 (0.0%)	0 (0.0%)	0.245
Malignancy of Esophagus	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.78
Malignancy of Liver Bile Ducts	17 (0.4%)	6 (0.5%)	1 (0.3%)	0 (0.0%)	0.918
Malignancy of Thyroid	30 (0.7%)	8 (0.7%)	2 (0.6%)	1 (3.4%)	0.403
Malignancy of Bone	3 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0.961
Malignancy of Connective Tissue Sarcoma	14 (0.3%)	3 (0.3%)	3 (1.0%)	0 (0.0%)	0.327
Malignancy of Other Male Female Genital Organs	9 (0.2%)	5 (0.4%)	2 (0.6%)	0 (0.0%)	0.938
Multiple Myeloma	17 (0.4%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0.429
Polycytemia Vera	5 (0.1%)	3 (0.3%)	1 (0.3%)	0 (0.0%)	0.649
Myelodysplastic Syndrome	5 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0.92
Myelo Lymphoproliferative Syndrome	5 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0.92
Malignancy of Other Sites	37 (0.9%)	12 (1.1%)	3 (1.0%)	0 (0.0%)	0.918
Malignancy of Unknown Site	14 (0.3%)	4 (0.4%)	1 (0.3%)	0 (0.0%)	0.99
Dementia Alzheimer's OMS	185 (4.6%)	60 (5.4%)	5 (1.6%)	2 (6.9%)	0.04
Cancer	734 (18.2%)	246 (22.0%)	72 (22.9%)	5 (17.2%)	0.011

CHF, congestive heart failure; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; HT, hormone therapy; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

The duration analyses demonstrated a general pattern of higher morbidity with longer exposure, especially for cancers in women initiating at 50-65. Although some nonlinear patterns were noted for other conditions (IHD, osteoporosis, dementia), these lacked statistical robustness. Importantly, duration distribution differed markedly between age groups, limiting power to detect associations in women initiating 65 and above, most of whom discontinued within 1-4 years.

These findings emphasize the complexity of HT risk stratification and support recommendations advocating individualized management and cautious continuation in older age groups. It is also important to note that some women continue HT for prolonged periods due to recurrence or emergence of VMS after discontinuation,[17,18] contributing to real-world patterns that diverge from guideline intentions.

Despite its strengths, including the large sample size and extended follow-up, our study is subject to several limitations inherent in its retrospective cohort design. First, HT exposure was determined based on pharmacy dispensing records, which identify prescription fills but

TABLE 6. All morbidities investigated among the four different groups by time of use periods

	Used HT 50+ (N=854)				
	N (%)				
	1-4 y (n=55)	5-9 y (n=170)	10-14 y (n=182)	15+ years (n=447)	*P*-value
IHD MI	6 (10.9%)	12 (7.1%)	8 (4.4%)	16 (3.6%)	0.052
IHD Other	12 (21.8%)	33 (19.4%)	24 (13.2%)	42 (9.4%)	0.002
CHF systolic	2 (3.6%)	5 (2.9%)	4 (2.2%)	10 (2.2%)	0.89
CHF non systolic	1 (1.8%)	11 (6.5%)	3 (1.6%)	6 (1.3%)	0.002
CHF combined	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)	0.689
CHF NOS	3 (5.5%)	5 (2.9%)	4 (2.2%)	7 (1.6%)	0.269
HTN diet	2 (3.6%)	6 (3.5%)	8 (4.4%)	17 (3.8%)	0.977
HTN drug	26 (47.3%)	83 (48.8%)	55 (30.2%)	132 (29.5%)	< 0.001
HTN	4 (7.3%)	29 (17.1%)	29 (15.9%)	65 (14.5%)	0.34
CVA	9 (16.4%)	25 (14.7%)	17 (9.3%)	33 (7.4%)	0.016
Carotid Artery Disease	9 (16.4%)	20 (11.8%)	19 (10.4%)	37 (8.3%)	0.204
Diabetes PVD	4 (7.3%)	4 (2.4%)	4 (2.2%)	3 (0.7%)	0.004
PVD	2 (3.6%)	6 (3.5%)	7 (3.8%)	11 (2.5%)	0.774
Pulmonary Embolism	0 (0.0%)	6 (3.5%)	3 (1.6%)	7 (1.6%)	0.276
Osteoporosis	25 (45.5%)	64 (37.6%)	43 (23.6%)	107 (23.9%)	< 0.001
Breast Cancer	4 (7.3%)	16 (9.4%)	26 (14.3%)	39 (8.7%)	0.167
Malignancy of Colon or Rectum	3 (5.5%)	3 (1.8%)	6 (3.3%)	11 (2.5%)	0.474
Malignancy of Lung	0 (0.0%)	3 (1.8%)	3 (1.6%)	10 (2.2%)	0.698
Malignancy of Bladder	2 (3.6%)	0 (0.0%)	4 (2.2%)	4 (0.9%)	0.077
Malignancy of Ovary	1 (1.8%)	3 (1.8%)	2 (1.1%)	3 (0.7%)	0.623
Malignancy of Uterus	2 (3.6%)	5 (2.9%)	3 (1.6%)	4 (0.9%)	0.196
Malignancy of Pancreas	1 (1.8%)	1 (0.6%)	0 (0.0%)	4 (0.9%)	0.469
Malignancy of Brain CNS	0 (0.0%)	3 (1.8%)	1 (0.5%)	1 (0.2%)	0.145
Stomach Cancer	1 (1.8%)	4 (2.4%)	1 (0.5%)	2 (0.4%)	0.134
Melanoma	0 (0.0%)	6 (3.5%)	4 (2.2%)	9 (2.0%)	0.445
Hodgkins Lymphoma	0 (0.0%)	1 (0.6%)	0 (0.0%)	3 (0.7%)	0.668
Non Hodgkin Lymphoma Mycosis Fungoides	1 (1.8%)	6 (3.5%)	3 (1.6%)	7 (1.6%)	0.459
Acute Leukemia	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0.045
Chronic Leukemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0.823
Malignancy of Kidney	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0.296
Malignancy of Larynx	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0.823
Malignancy of Cervix Uteri	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)	0.301
Malignancy of Pharynx	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0.081
Malignancy of Esophagus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Malignancy of Liver Bile Ducts	1 (1.8%)	1 (0.6%)	0 (0.0%)	2 (0.4%)	0.382
Malignancy of Thyroid	1 (1.8%)	0 (0.0%)	1 (0.5%)	2 (0.4%)	0.395
Malignancy of Bone	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Malignancy of Connective Tissue Sarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Malignancy of Other Male Female Genital Organs	0 (0.0%)	1 (0.6%)	1 (0.5%)	2 (0.4%)	0.952
Multiple Myeloma	0 (0.0%)	2 (1.2%)	4 (2.2%)	1 (0.2%)	0.074
Polycytemia Vera	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)	0.728
Myelodysplastic Syndrome	(0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Myelo Lymphoproliferative Syndrome	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.002
Malignancy of Other Sites	0 (0.0%)	4 (2.4%)	3 (1.6%)	4 (0.9%)	0.397
Malignancy of Unknown Site	1 (1.8%)	2 (1.2%)	0 (0.0%)	1 (0.2%)	0.144
Dementia Alzheimer's OMS	12 (21.8%)	29 (17.1%)	18 (9.9%)	28 (6.3%)	< 0.001
Cancer	17 (30.9%)	48 (28.2%)	54 (29.7%)	101 (22.6%)	0.164

CHF, congestive heart failure; CVA, cerebrovascular accident; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

cannot confirm actual medication adherence or the precise quantity consumed. Variations in compliance, such as missed doses or discontinuation between refills, may have introduced misclassification bias, potentially underestimating or overestimating the true effects of HT. Second, although women with prevalent disease at baseline for a given outcome were excluded from the corresponding analysis, residual misclassification of pre-existing conditions cannot be entirely ruled out. Third, while follow-up ended at the earliest of outcome, death, disenrollment, or study termination, loss-to-follow-up, though uncommon, could not be fully quantified and may have varied slightly across groups. Fourth, although age was employed as the underlying time scale in Cox models, HT exposure was modeled as fixed at initiation and not updated over time; thus, time-varying changes in exposure or covariates were not captured. Fifth, we were unable to account for specific HT formulations (eg, estrogen monotherapy vs. combined therapy), varying doses, or routes of administration (eg, oral, transdermal). As highlighted in the literature, these factors can substantially influence outcomes, and the lack of such granular data may obscure

TABLE 7. All morbidities investigated among the four different groups by time of use periods

	Used HT 65+ (N=847)				
	N (%)				
	1-4 y (n=658)	5-9 y (n=130)	10-14 y (n=34)	15+ years (n=25)	*P*-value
IHD MI	86 (13.1%)	15 (11.5%)	5 (14.7%)	3 (12.0%)	0.951
IHD Other	143 (21.7%)	29 (22.3%)	10 (29.4%)	4 (16.0%)	0.648
CHF systolic	28 (4.3%)	2 (1.5%)	2 (5.9%)	0 (0.0%)	0.308
CHF non systolic	48 (7.3%)	8 (6.2%)	1 (2.9%)	1 (4.0)	0.697
CHF combined	4 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.764
CHF NOS	54 (8.2%)	8 (6.2%)	1 (2.9%)	1 (4.0%)	0.521
HTN diet	14 (2.1%)	2 (1.5%)	1 (2.9%)	0 (0.0%)	0.836
HTN drug	213 (32.4%)	62 (47.7%)	19 (55.9%)	16 (64.0%)	< 0.001
HTN	29 (4.4%)	4 (3.1%)	3 (8.8%)	0 (0.0%)	0.343
CVA	137 (20.8%)	33 (25.4%)	14 (41.2%)	4 (16.0%)	0.028
Carotid Artery Disease	81 (12.3%)	11 (8.5%)	4 (11.8%)	7 (28.0%)	0.056
Diabetes PVD	27 (4.1%)	8 (6.2%)	1 (2.9%)	1 (4.0%)	0.735
PVD	24 (3.6%)	13 (10.0%)	0 (0.0%)	1 (4.0%)	0.008
Pulmonary Embolism	24 (3.6%)	2 (1.5%)	0 (0.0%)	1 (4.0%)	0.429
Osteoporosis	216 (32.8%)	50 (38.5%)	17 (50.0%)	10 (40.0%)	0.13
Breast Cancer	33 (5.0%)	11 (8.5%)	5 (14.7%)	0 (0.0%)	0.03
Malignancy of Colon or Rectum	28 (4.3%)	2 (1.5%)	2 (5.9%)	1 (4.0%)	0.472
Malignancy of Lung	15 (2.3%)	3 (2.3%)	0 (0.0%)	2 (8.0%)	0.23
Malignancy of Bladder	6 (0.9%)	2 (1.5%)	1 (2.9%)	0 (0.0%)	0.608
Malignancy of Ovary	8 (1.2%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0.836
Malignancy of Uterus	9 (1.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.779
Malignancy of Pancreas	8 (1.2%)	2 (1.5%)	2 (5.9%)	0 (0.0%)	0.144
Malignancy of Brain CNS	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.834
Stomach Cancer	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.834
Melanoma	13 (2.0%)	1 (0.8%)	0 (0.0%)	2 (8.0%)	0.086
Hodgkins Lymphoma	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.834
Non Hodgkin Lymphoma Mycosis Fungoides	12 (1.8%)	4 (3.1%)	1 (2.9%)	1 (4.0%)	0.709
Acute Leukemia	5 (0.8%)	1 (0.8%)	0 (0.0%)	2 (8.0%)	0.003
Chronic Leukemia	5 (0.8%)	1 (0.8%)	0 (0.0%)	1 (4.0%)	0.334
Malignancy of Kidney	6 (0.9%)	1 (0.8%)	1 (2.9%)	0 (0.0%)	0.629
Malignancy of Larynx	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.962
Malignancy of Cervix Uteri	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.902
Malignancy of Pharynx	4 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.764
Malignancy of Esophagus	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.78
Malignancy of Liver Bile Ducts	6 (0.9%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0.213
Malignancy of Thyroid	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0.001
Malignancy of Bone	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Malignancy of Connective Tissue Sarcoma	3 (0.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.913
Malignancy of Other Male Female Genital Organs	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.834
Multiple Myeloma	5 (0.8%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	0.101
Polycytemia Vera	2 (0.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.828
Myelodysplastic Syndrome	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.902
Myelo Lymphoproliferative Syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Malignancy of Other Sites	11 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.672
Malignancy of Unknown Site	10 (1.5%)	2 (1.5%)	1 (2.9%)	0 (0.0%)	0.841
Dementia Alzheimer's OMS	205 (31.2%)	43 (33.1%)	11 (32.4%)	6 (24.0%)	0.841
Cancer	165 (25.1%)	35 (26.9%)	11 (32.4%)	10 (40.0%)	0.308

CHF, congestive heart failure; CVA, cerebrovascular accident; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NOS, not otherwise specified; OMS, Organic Mental Syndrome; PVD, peripheral vascular disease.

the nuanced effects of different regimens. Sixth, our analysis did not incorporate comprehensive sociodemographic characteristics beyond age, such as ethnicity or SES. These factors can significantly shape health outcomes and health care access and may confound associations. For instance, differences in lifestyle, dietary habits, hysterectomy or mastectomy rates, or other baseline conditions linked to SES or ethnic background could have influenced the incidence of comorbidities and cancer, and our study could not fully adjust for such confounders. Seventh, confounding by indication remains possible, particularly among women initiating HT at older ages, as underlying health conditions or health care utilization may drive both the decision to prescribe HT and the subsequent risk of adverse outcomes. Eighth, although crude tables presented percentages for descriptive purposes, interpretation was based on person-years of follow-up and multivariable-adjusted HRs; nonetheless, the large number of outcomes analyzed raises the possibility of chance findings due to multiple comparisons. Finally, although outcomes preceding analytic entry were excluded whenever documented, validated medical information before

TABLE 8. Cox regression analysis for CVA, cancer, and IHD/MI

	95% CI											
	Cox regression for CVA				Cox regression for Cancer				Cox regression for IHD MI			
	HR	Low	High	*P*	HR	Low	High	*P*	HR	Low	High	*P*
HT group												
Never used	Reference				Reference				Reference			
Used HT 50-65	16.692	15.571	17.893	<0.001	8.49	7.281	9.9	<0.001	9.169	8.321	10.102	<0.001
Used HT 50+	4.151	3.629	4.747	<0.001	1.359	1.003	1.842	0.048	2.089	1.684	2.592	<0.001
Used HT 65+	2.695	2.358	3.079	<0.001	2.216	1.833	2.677	<0.001	2.342	2.028	2.706	<0.001

CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; HT, hormone therapy; IHD, ischemic heart disease; MI, myocardial infarction.

Multivariable-adjusted HR and 95% CIs are shown for cancer, CVA, and IHD/MI. Age was used as the underlying time scale, with entry at age at baseline and exit at age of event or censoring. Reference group: never-users.

Time: age as the underlying time scale.

2000 was unavailable. Therefore, residual misclassification of both pre-existing conditions and prior HT exposure is possible, particularly among women whose treatment history began earlier in life. These factors reinforce the exploratory nature of this study and the need for cautious interpretation. Future research employing prospective designs and leveraging detailed individual-level data, including adherence measures, regimen-specific exposures, and comprehensive sociodemographic and lifestyle information, would strengthen causal inference.

CONCLUSION

Although exploratory and observational in nature, our findings reinforce the importance of individualized risk-benefit assessment for HT use, particularly in older women. Despite guideline recommendations to limit HT initiation before age 60 or within 10 years of menopause, a notable subset continues or begins therapy beyond age 65. Our results indicate that late initiation (65 and above) is associated with significantly increased risks of both cancer and cerebrovascular events, whereas earlier initiation (50-65) demonstrated lower crude IHD prevalence but higher HTN and increased hazards of stroke and cancer in adjusted analyses. Clinical decisions in older women should therefore be made with caution, favoring regular reassessment, consideration of nonhormone alternatives, and vigilant surveillance for malignancy and vascular complications. Continued prospective research is required to clarify regimen-specific risks and optimize treatment selection.

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