Menopause: The Journal of The North American Menopause Society
Vol. 15, No. 2, pp. 000-000
DOI: 10.1097/gme.0b013e31812e558f

Individualizing the risks and benefits of postmenopausal hormone therapy

Tjeerd P. van Staa, MD, PhD,[1,2] Cyrus Cooper, DM, FRCP, FMedSci, MA,[3] David Barlow, MD, FRCOG, MRCP, FMedSci, BSc,[4] and Hubert G.M. Leufkens, PhD[2]

Abstract

Objective: The objective was to develop an individualized risk-benefit model quantifying the impact of combined use of estrogen and progestogen on chronic diseases.

Design: The study population consisted of women, aged 40+, prescribed postmenopausal hormone therapy (HT) in the UK General Practice Research Database (N > 200,000). Individualized risks of fracture, colorectal cancer, diabetes mellitus, myocardial infarction, deep venous thrombosis/pulmonary embolism, breast cancer, and stroke were estimated using Cox regression. Relative rates from the Women's Health Initiative trial were used to estimate attributable risks (ie, excess risks) in a risk-benefit simulation model.

Results: Risks and benefits increased with age and length of HT use. HT use for 5 years initiated at age 45 increased the absolute risk of myocardial infarction by 0.04% and breast cancer by 0.3% and reduced the risk of hip fracture by 0.03%. Comparably, 5-year HT use started at age 75 led to increases in the risks of myocardial infarction and breast cancer (+0.4% and +0.2%, respectively) and reduced that of hip fracture (−0.9%). There was considerable heterogeneity in the risks and benefits of HT. In most of the younger HT users, the frequency of risks exceeded that of the benefits, although the absolute excess risks were small. In HT users aged 70+, 62.4% experienced more benefits than risks, whereas 37.6% experienced more risks than benefits.

Conclusions: The frequency of beneficial and adverse effects of HT on chronic diseases was low in younger women, whereas the ratio of these risks and benefits varied substantially among the older users. However, the study could not asses the effects of HT on menopausal symptoms and quality of life, benefits more likely to be observed among younger women.

Key Words: Hormone therapy – Epidemiology – Risks – Benefits.

The Women's Health Initiative (WHI) trial reported that combined use of an estrogen and progestogen regimen increased the risks of breast cancer and deep venous thrombosis and decreased the risks of fracture and colorectal cancer. Like many randomized clinical trials, this study estimated the relative risk (RR), the ratio of the proportions of the exposed and placebo groups with that outcome.[1] Although RRs are widely used, they do not provide information on the probability that a person has the outcome due to exposure.[2]

Attributable risks are the probability of a particular event occurring over a specific time period as a result of exposure. They can be estimated from clinical trials as the difference between the absolute risks in the exposed and placebo groups. However, women included in clinical trials often are not representative of the women using the drug in actual clinical practice. Conversely, epidemiologic studies, more likely to include women representative of actual clinical practice, are often limited with respect to interpreting the causality of any increases in the risk of disease (due to confounding).

The WHI is the largest clinical study of postmenopausal hormone therapy (HT) to date. It was designed to investigate the effects of HT on a range of health outcomes, particularly those relevant to older American women. The average age of women included in the WHI was 63 years.[1]

There has been extended controversy about how the principal findings can be taken to represent the effects of HT in women in other countries, who are predominantly younger than 60 years[3] and who may be using different types of HT. The number of women affected by the adverse effects of a drug may vary depending on the extent of use by high-risk women. It is therefore important to establish the potential impact of the WHI findings in a UK context. With only a minor impact and small attributable risks, the WHI should have little relevance to clinical practice. However, with

Received February 6, 2007; revised and accepted May 25, 2007.

From the [1]General Practice Research Database, Medicines and Healthcare Products Regulatory Agency, London, UK; [2]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [3]Medical Research Council Resource Center in Epidemiology, University of Southampton, Southampton, UK; and [4]Department of Reproductive Medicine, University of Glasgow, Glasgow, UK.

Financial disclosure: None reported.

Address correspondence to: Tjeerd P. van Staa, MD, PhD, General Practice Research Database, Medicines and Healthcare Products Regulatory Agency, 1 Nine Elms Lane, London SW8 5NQ, UK. E-mail: Tjeerd.vanstaa@GPRD.com

potentially large attributable risks, it would be important to formally test in randomized clinical trials the extent of generalizability of the WHI findings.

The objective of our study was to develop and apply an individualized risk-benefit model that quantified the impact of combined use of estrogen and progestogen on chronic diseases in a large population of UK users. The novel approach that we used combined RRs from clinical trials and absolute risks from epidemiologic studies to estimate the attributable risks of drug therapy in a representative population of drug users.

METHODS

Study population

The study population consisted of women aged 40 years or older who were included in the General Practice Research Database (GPRD) and prescribed both estrogen and progestogen. GPRD collates the computerized medical records of general practitioners (GPs). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semipermanently affiliated with a practice that centralizes the medical information from the GPs, specialist referrals, and hospitalizations. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes.[4]

Incidence of outcome events

The cumulative incidences of various outcomes (fracture, colorectal cancer, diabetes mellitus, myocardial infarction, deep venous thrombosis/pulmonary embolism, breast cancer, and stroke) were estimated in this population exposed to HT. The incidence of each of the outcomes was estimated using the survival function in Cox proportional hazards regression.[5] For each set of patient characteristics, the Cox model allows calculation of an individual's probability of an outcome (ie, survivor function). The study population was randomly divided into two groups. The first group was used to develop the statistical models for the risk estimation (one model for each outcome). We first fitted regression models with age, duration of HT, and all risk factors. Past use was considered the reference category. Forward regression was conducted using a significance level of 0.05 to select clinical risk factors. Strong interactions between age and the selected clinical risk factors were then also selected. The selected variables were then used to develop the final Cox regression models in the second group. For each set of patient characteristics, the Cox model allows calculation of an individual's probability of an outcome of interest (ie, survivor function). Various methods were used to test the fitting of the final Cox regression models (one model for each of the outcome events). The proportional hazards assumption was evaluated by visual examination of the Schoenfeld residuals. We also compared the observed 5-year probability of each outcome (based on the Kaplan-Meier estimate) with the probability predicted by the Cox model.

TABLE 1. *Number of prevented cases of fracture, CRC, and diabetes, and number of excess cases of MI, DVT/PE, breast cancer, and stroke per 10,000 HT users stratified by age and duration of HT use (scenario of WHI increases in risk due to HT)*

		Benefits: no. of cases prevented						Risks: excess no. of cases					Benefits − risks
Age at baseline, y	Duration of HT use, y	Hip Fracture	Vertebral fracture	Other osteoporotic fracture	CRC	Diabetes	Total[a]	MI	DVT/PE	Breast cancer	Stroke	Total[a]	Total[a] (95% CI)
40-49	1	1.0	3.3	8.1	2.2	4.6	3.0	2.2	8.7	−0.2	0.6	2.8	0.2 (−8.9 to 6.2)
	5	3.4	21.9	55.2	8.5	18.5	13.0	4.2	34.7	31.9	7.8	23.1	−10.1 (−24.0 to 6.5)
	10	5.0	35.1	127.6	13.5	41.9	22.2	15.9	73.5	52.1	17.4	45.9	−23.7 (−49.5 to 10.5)
50-59	1	0.5	2.6	13.2	1.8	5.3	3.0	1.5	9.6	−2.8	1.6	2.9	0.03 (−9.0 to 12.0)
	5	5.5	19.3	65.8	7.5	22.0	15.0	6.3	38.0	22.0	12.1	20.4	−5.4 (−24.6 to 21.9)
	10	17.8	47.0	139.1	19.9	60.8	39.0	17.8	76.6	53.3	32.7	47.4	−8.4 (−41.0 to 41.0)
60-69	1	4.4	9.0	22.3	5.1	10.3	11.1	4.4	13.4	−0.1	3.4	9.2	1.9 (−12.5 to 15.7)
	5	19.5	49.1	89.1	23.6	44.1	51.9	14.2	54.6	23.7	25.4	46.4	5.5 (−47.3 to 44.3)
	10	42.2	120.9	198.0	42.7	69.2	105.0	40.3	129.4	45.8	70.4	116.9	−11.9 (−50.0 to 67.1)
70+	1	25.0	24.7	27.8	9.5	12.9	39.4	9.5	17.5	0.4	12.1	31.1	8.3 (−38.4 to 58.9)
	5	85.8	149.7	131.5	36.4	58.4	170.1	44.5	75.2	18.3	65.1	155.4	14.6 (−73.9 to 126.9)
	10	194.1	286.8	256.9	65.6	62.2	327.6	94.6	146.4	27.6	134.3	313.7	13.8 (−163.1 to 222.5)

CRC, colorectal cancer; MI, myocardial infarction; DVT/PE, deep vein thrombosis/pulmonary embolism; HT, hormone therapy; WHI, Women's Health Initiative.
[a]Based on CRC equivalents; the risks included myocardial infarction, DVT/PE, breast cancer, or stroke; the benefits included fracture, colorectal cancer, or diabetes mellitus.

The cumulative incidences were individualized, ie, estimated specifically for age, clinical risk factors, and duration of current and past use of HT. The following clinical risk factors were considered in the analysis:

- •Smoking history, alcohol use, body mass index (BMI) where available
- •Number of GP visits in the year before the start of HT
- •Fractures: fracture or fall history, history of early or late menopause, history of a selected chronic disease (chronic obstructive pulmonary disease, cerebrovascular disease, heart failure, rheumatoid arthritis, inflammatory bowel disease), recent use (ie, prescription in the 6 mo before) of central nervous system medication or oral glucocorticoids
- •Colorectal cancer: history of inflammatory bowel disease or polyps in colon/rectum, recent use of oral glucocorticoids, total number of previous prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin
- •Diabetes mellitus: history of hypertension, recent use of oral glucocorticoids.
- •Myocardial infarction: history of diabetes mellitus, hypertension, angina, cerebrovascular disease, high cholesterol, systemic inflammation (rheumatoid arthritis or systemic lupus erythematosus), atrial fibrillation, renal failure, oophorectomy, recent use of cardiac glycosides, nitrates, statins, anticoagulants, aspirin, NSAIDs, or oral glucocorticoids
- •Deep venous thrombosis or pulmonary embolism: history of epilepsy, cerebrovascular disease, cancer, renal failure, diabetes, ischemic heart disease
- •Breast cancer: history of early or late menopause, dysplasia or benign neoplasm of breast, recent use of NSAIDs
- •Stroke: history of transient ischemic attacks, diabetes mellitus, hypertension, ischemic heart disease, high cholesterol, systemic inflammation (rheumatoid arthritis or systemic lupus erythematosus), atrial fibrillation, recent use of nitrates, cardiac glycosides, anticoagulants, aspirin, statins, or oral glucocorticoids

For risk factors with missing data (alcohol use, smoking, and BMI), indicator variables for missing values were included in the regression models.

Attributable risks of HT

The cumulative incidence of an event in women using a drug is a function of the underlying (unexposed) event probability and of the causal effects of exposure (the RR). If the RR of drug effect is known, the underlying (unexposed) event probability can be estimated by dividing the event probability in those exposed through the RR. The attributable risk is the difference between the exposed and unexposed rate (ie, the difference between the exposed and unexposed event probabilities). In epidemiologic research, RRs are determined by comparing users with nonusers. However, such comparisons may be confounded as a result of baseline differences. For example, HT users have been reported to be healthier than nonusers at the start of therapy.[6] To avoid such confounding in this study, we used the RRs from the WHI and applied these to the GPRD population of HT users. Our assumption was that the RRs observed in the WHI could be generalized to the UK population of HT users.

The WHI reported that the risk of hip fracture was reduced by 34% in women using estrogen plus progestogen compared with women taking placebo (RR = 0.66; 95% CI: 0.45-0.98). For clinically symptomatic vertebral fractures, the RR was

TABLE 2. *Number of hip fractures prevented and excess number of cases of myocardial infarction, breast cancer, and stroke per 10,000 HT users (treated for 5 years) stratified by baseline risk and age (scenario of WHI increases in risk due to HT)*

		Benefits: no. of cases prevented		Risks: excess no. of cases				Benefit − risks
Age	Baseline risk[a]	Hip fracture	Total[b]	MI	Breast cancer	Stroke	Total[b]	Total[b] (95% CI)
50-59								
Hip fracture	Low	2.9	20.6	8.9	20.9	9.3	20.6	0.04 (−30.7 to 37.8)
	High	14.5	22.0	5.4	22.5	17.7	21.6	0.3 (−24.0 to 28.5)
MI	Low	3.4	16.5	1.4	24.2	5.0	15.8	0.7 (−14.7 to 23.8)
	High	12.3	25.4	27.3	16.3	20.4	29.8	−4.4 (−26.6 to 12.3)
Breast cancer	Low	4.0	18.1	7.4	26.6	12.5	21.8	−3.7 (−28.5 to 42.4)
	High	7.6	16.7	7.2	30.1	13.2	22.2	−5.4 (−22.8 to 9.9)
Stroke	Low	2.1	13.7	2.6	24.3	6.4	16.6	−2.9 (−24.7 to 12.3)
	High	6.9	22.9	23.2	25.2	24.8	33.3	−10.3 (−43.7 to 14.6)
70+								
Hip fracture	Low	23.3	107.6	23.5	26.0	41.3	115.5	−7.8 (−59.2 to 35.5)
	High	311.0	365.5	54.0	27.3	78.5	180.4	185.1 (84.6 to 312.7)
MI	Low	47.2	116.2	17.7	20.9	28.4	94.1	22.1 (−44.9 to 117.6)
	High	196.0	264.0	123.9	21.5	98.4	282.6	−18.6 (−120.6 to 56.9)
Breast cancer	Low	57.2	135.1	28.9	27.3	49.9	119.3	15.9 (−73.3 to 65.6)
	High	152.1	221.3	48.6	25.0	65.3	161.3	60.0 (−35.5 to 220.3)
Stroke	Low	35.2	105.6	19.6	20.8	25.2	87.0	18.6 (−44.5 to 71.4)
	High	201.7	272.1	96.5	18.7	140.9	280.8	−8.7 (−87.0 to 147.9)

HT, hormone therapy; WHI, Women's Health Initiative; MI, myocardial infarction.
[a]The low risk-group comprises patients in the lowest decile of risk for the event; patients at high risk are in the 10th decile of risk.
[b]Based on colorectal cancer equivalents; the risks included myocardial infarction, deep venous thrombosis/pulmonary embolism; breast cancer, or stroke; the benefits included fracture, colorectal cancer, or diabetes mellitus.

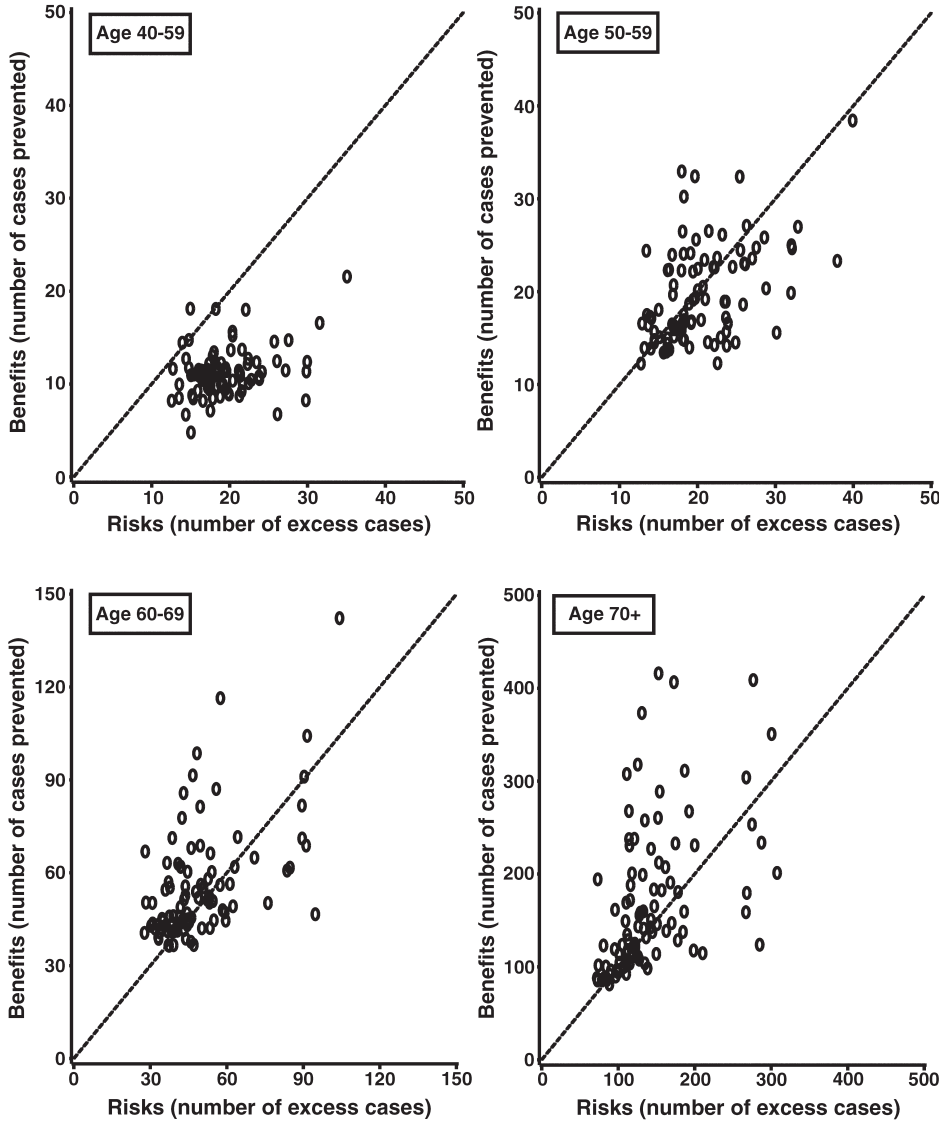

FIG. 1. Number of colorectal cancer (CRC) equivalent cases reduced by hormone therapy (HT) (*y* axis: benefits) and number of CRC-equivalent cases increased by HT (*x* axis: adverse events). Each circle corresponds to 10,000 women using HT for 5 years with different baseline probabilities for adverse events and benefits.

0.66 (95% CI: 0.44-0.98), other osteoporotic fractures RR = 0.77 (95% CI; 0.69-0.86), colorectal cancer RR = 0.63 (95% CI: 0.43-0.92), diabetes mellitus RR = 0.79 (95% CI: 0.67-0.93), myocardial infarction RR = 1.29 (95% CI: 1.02-1.63), deep venous thrombosis/pulmonary embolism RR = 2.11 (95% CI: 1.58-2.82), breast cancer RR = 1.26 (95% CI: 1.00-1.59), and stroke RR = 1.41 (95% CI: 1.07-1.85).[1] Subsequent age-specific reports on stroke and heart disease from WHI indicated that the effects of combined estrogen and progestogen were not statistically significantly increased.[7,8] However, we used the original estimates from the WHI in the main analyses for coronary heart disease and stroke for two reasons: (1) the results of reanalyses were not available for all outcomes, and (2) the point estimates for the RR and 95% CIs did not change substantially in the later WHI analyses.[7,8]

A sensitivity analysis was conducted using the WHI age-specific estimates where available (coronary heart disease, stroke, diabetes, and colorectal cancer).[7-10]

Simulation model

We used simulation methodology to estimate the outcomes with different scenarios of drug toxicity and benefit of HT compared with no HT use. Of the study population of HT users, 5,000 women were randomly sampled, and their characteristics at start of treatment were used to calculate the individual probabilities for each of the outcome events and death. The simulation model was used to estimate the outcomes in this cohort based on these event probabilities. The outcomes in this cohort of HT users were then compared with those of a no-use cohort by varying the event probabilities in the simulation model (ie, by dividing the

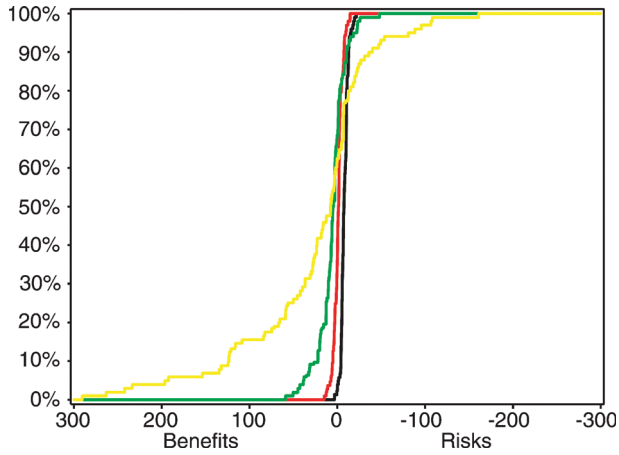

FIG. 2. Benefit-risk acceptability curve of the percentage of patients with different excess benefits over adverse events in 10,000 women stratified by age and gender (black line, ages 40-49; red line, ages 50-59; green line, ages 60-69; yellow line, ages 70+). For each subgroup the magnitude of changes in the frequency of adverse events and benefits was measured. The adverse events and benefits were then added, weighting by mortality (risks were positive and benefits were negative). The figure of −100 indicates that the reduction in benefits exceeded the increase in adverse events by 100 cases (per 10,000 women). The figure of 100 indicates that adverse events exceeded benefits by 100 cases. The curve gives the percentage of women with each total of benefits over adverse events, or better. For example, 5.5% of the women aged 70+ had benefits exceeding adverse events at a frequency of 1% or higher. Ninety-seven percent of the women had adverse events exceeding benefits at a frequency of 1% or lower or had more benefits than adverse events.

event probabilities through the RR of drug effect). Over the course of the model, the individual risks were adjusted at each 3-month period for increasing age and duration of HT use. For each cohort the outcomes over a period of follow-up were then assessed and the excess number of cases calculated by comparing the number of HT-using women with outcomes with that of nonusers. This analysis was repeated 20 times and conducted separately for each 10-year age group (40-49, 50-59, 60-69, and 70+ at start of drug use). The random variability of the excess number of cases was determined as follows. The outcome and mortality risks were randomly selected from a normal distribution based on the mean and SD of the parameter in the final Cox regression models. The RRs for each of the outcomes were randomly selected from a normal distribution based on the point estimates for the RR and the nominal 95% CIs, as reported by WHI.[1] Nonparametric bootstrapping techniques were then used to estimate the 95% CIs, repeating the analysis 5,000 times using data from 20 cohorts. The 95% CI was based on the 2.5% and 97.5% percentiles of the distribution of the bootstrapping results.[11]

To explore the heterogeneity of the risks and benefits of HT, an analysis was done stratifying the study population into subgroups based on the baseline probability of risks and benefits. Each 10-year age group was divided into 10 deciles based on the baseline probability of the risk. Each decile was then again subdivided into 10 deciles based on the baseline probabilities of the benefit.

Weighting of risks and benefits

To establish an overall estimate of the total risks and benefits of HT, each of the different outcomes was weighted by the 5-year mortality after the outcome. Life expectancy has previously been used to standardize outcomes of different medical interventions.[12] Patients with colorectal cancer had the lowest 5-year survival, so colorectal cancer was considered the reference disease. For another disease with, as an example, a survival twice as high as that of colorectal cancer, two events of this disease would be considered equivalent. Given mortality differences across age, the weights were specific for each 10-year age group. The following weights were used: hip fracture: 0.124 at age 40 to 49, 0.281 at age 50 to 59, 0.216 at age 60 to 69, 0.54 at age 70+; vertebral fracture: 0.077, 0.123, 0.267, 0.32; other fractures: 0.03, 0.034, 0.063, 0.20; diabetes mellitus: 0.038, 0.059, 0.122, 0.225; myocardial infarction: 0.245, 0.267, 0.545, 1.008; deep venous thrombosis: 0.24, 0.256, 0.375, 0.638; breast cancer: 0.324, 0.195, 0.20, 0.412; stroke: 0.431, 0.387, 0.529, 0.846. In a sensitivity analysis we also

TABLE 3. *Comparison of outcomes in WHI and the GPRD risk-benefit model (for women using estrogen and progestogen)*

	HT users		Controls		Excess no. of cases in HT group	
	WHI, no. of cases	Model,[a] no. of cases	WHI, no. of cases	Model,[a] no. of cases	WHI	Model[a]
Death	231	231	218	218	+13	+13
Hip fracture	44	46	62	67	−18	−21
Vertebral fracture	41	96	60	140	−19	−45
Other osteoporotic fracture	579	266	701	327	−122	−61
Colorectal cancer	45	31	67	47	−22	−15
Diabetes mellitus	277	106	324	133	−15	−27
MI	164	77	122	59	+42	+18
DVT/PE	151	86	67	38	+84	+47
Breast cancer	166	101	124	79	+42	+23
Stroke	127	86	85	58	+42	+28

WHI, Women's Health Initiative; GPRD, General Practice Research Database; HT, hormone therapy; MI, myocardial infarction; DVT/PE, deep venous thrombosis/pulmonary embolism.
[a]Standardized to size and age distribution of the WHI study population.

TABLE 4. *Sensitivity analyses of the number of risks and benefits per 10,000 HT users (treated for 5 years) stratified by age*

	Total benefits: no. of cases prevented[a]				Risks: excess no. of cases[a]			
Analysis	Age 40-49	Age 50-59	Age 60-69	Age 70+	Age 40-49	Age 50-59	Age 60-69	Age 70+
Use of overall WHI RRs (main analysis)	13.0	15.0	51.9	170.1	23.1	20.4	46.4	155.4
Use of age-specific WHI RRs	NA	12.1	71.4	127.4	NA	23.8	47.1	130.4
Weighting by mortality (main analysis)	13.0	15.0	51.9	170.1	23.1	20.4	46.4	155.4
Equal weighting of outcomes	107.5	120.1	225.4	461.8	78.6	78.4	117.9	203.1
Weighting by quality of life weight[b]	11.5	12.3	40.6	111.0	71.7	71.8	108.3	187.6

HT, hormone therapy; WHI, Women's Health Initiative; RR, relative risk; CRC, colorectal cancer; DVT/PE, deep venous thrombosis/pulmonary embolism
[a]Based on CRC equivalents; the risks included myocardial infarction, DVT/PE, breast cancer, or stroke; the benefits included fracture, colorectal cancer, or diabetes mellitus.
[b]Using quality-of-life weights (relative to CRC) based on published data[13]: hip fracture weight of 0.92; colorectal cancer, 0.80; myocardial infarction, 0.86; DVT/PE, 0.87; breast cancer, 0.89; stroke, 0.86. Vertebral and other osteoporotic fractures and diabetes were not considered because similar quality of weights were not available.

used weights based on published estimates for the quality of life for each outcome.[13]

A benefit-risk acceptability curve was estimated using the weighted total of the risks and benefits in each of the 100 subgroups.[14] The cumulative percentage of women at each level of a benefit-risk threshold, or higher, was then estimated. This benefit-risk acceptability curve allows a graphic representation of the distribution of the risks and benefits and of the percentage of users who are below the threshold of risk.[14]

RESULTS

The study population included 205,289 women prescribed estrogen and progestogen. The mean duration of follow-up (from first HT use until date of censoring) was 5 years. Table 1 provides the risks and benefits of HT for ages and for different durations. For the average HT user who started treatment at age 45, HT use for 5 years increased the absolute risk of myocardial infarction by 0.04% (or 4.2 excess cases per 10,000), deep vein thrombosis/pulmonary embolism by 0.3%, and breast cancer by 0.3%. It reduced the absolute risk of hip fracture by 0.03%. For those who started at age 75, 5 years of HT use increased the absolute risk of myocardial infarction by 0.4%, deep vein thrombosis/pulmonary embolism by 0.8%, and breast cancer by 0.2% and decreased the risk of hip fracture by 0.9%. Weighting the events by survival, the risks exceeded the benefits of HT use in the average younger woman, whereas benefits exceeded risks in the average elderly user.

It was found that there was considerable heterogeneity in the risks and benefits of HT (due to the presence or absence of clinical risk factors). Table 2 shows the risks and benefits stratified by age and baseline risk. An excess of 1.4 myocardial infarction cases was found in 10,000 women aged 50 to 59 with the lowest baseline risk for myocardial infarction, whereas those with the highest baseline risk experienced an excess of 27.3 cases (using HT for 5 years).

Figure 1 shows the extent of heterogeneity in risks and benefits (number of colorectal cancer equivalent cases) in women using HT for 5 years. Generally women with higher frequencies of adverse outcomes also experienced higher frequencies of beneficial outcomes.

Figure 2 shows the benefit-risk acceptability curve. It was found that most younger HT users had a nearly similar frequency of risks and benefits because the curve increased steeply. In most of the younger HT users, the frequency of risks exceeded that of benefits (when weighting these different events by mortality), although the absolute excess risks were small. In HT users aged 70+, there was considerable variability in the benefits over risks. About 15.5% had excess benefits over risks of 1% or higher; 62.4% experienced more benefits than risks, whereas the remaining 37.6% experienced more risks than benefits. In 3.0% of the older women, the risks exceeded the benefits by 1% or more.

Table 3 shows the outcomes observed in the WHI and the GPRD risk-benefit model. Although this table shows that there were some differences in outcomes between the WHI and GPRD risk-benefit model, it is important to note that the WHI population and the GPRD population of users of estrogen and progestogen were very different. The mean age of the WHI population was 63 years, whereas the average age in the GPRD population was 51 years. When standardizing by age, the BMI of HT users in the WHI population was considerably higher than that of the GPRD population (30% of the WHI population had a BMI <25 compared with 60% in the GPRD population; 34% of the WHI population had a BMI ≥30 compared with 12% in the GPRD population). More women in the WHI population smoked (50%) compared with the GPRD population (37%). History of hypertension was recorded in 36% of the WHI women, whereas this was 14% in the GPRD population.

A sensitivity analysis was conducted by using the age-specific RRs of the WHI population. As shown in Table 4, the use of age-specific RRs of WHI did not change the results. However, the results were related to the choice of the weighting of outcomes.

DISCUSSION

This study quantified the individualized impact of combined use of estrogen and progestogen on chronic diseases. The frequency of beneficial and adverse effects of HT on chronic diseases varied substantially with age and with the presence of clinical risk factors. It was also found

that frequencies of beneficial and adverse effects of HT on chronic diseases were correlated. Patients with higher risks of breast cancer, coronary heart disease, stroke, and deep venous thrombosis also had greater reductions in the risks of fracture and colorectal cancer.

The main assumption in this study was that the RRs observed in the WHI population were generalizable to the UK population of HT users. Use of drugs in actual clinical practice is generally contingent on demonstrating efficacy in randomized clinical trials, and the results of these studies serve as a guide to the use of these drugs in daily clinical practice. Thus, our approach of applying clinical trial results to a population in actual clinical practice seems reasonable. A recent review found that the estimates of the WHI were broadly similar to those of a meta-analysis for hip and vertebral fractures, colon and breast cancer, and thromboembolic events. Smaller detrimental effects of HT were found in the meta-analysis for coronary heart disease and stroke.[15] Another assumption in this study was that the effects (RRs) of HT were similar across women. The WHI found that there were few noteworthy interactions between various patient characteristics and the RRs.[1] However, the statistical power of the WHI to detect interactions may have been limited. A recent reanalysis of the WHI concluded that women who initiated HT close to menopause tended to have a reduced risk of cardiovascular disease compared with an increase in risk among women more distant from menopause, but this trend did not meet statistical significance.[16] Given the low incidence of major clinical outcomes, very large trials would be required to investigate the effects of HT in younger women, who comprise most of the HT users in actual clinical practice.

Our risk-benefit model can be easily applied to other drugs. The basic idea is to quantify the impact of various possible effects of a drug in actual clinical practice. With only a small impact, it would be less important to establish whether these effects are indeed causal. Conversely, a potentially large impact would suggest that high-quality evidence on causality would be needed before the evidence is rejected. As an example, our results suggest that young HT users would suffer only small risks if the WHI findings are indeed correct and generalizable. Conversely, HT should not be prescribed broadly to elderly women, unless there is high-quality evidence (such as large trials) that rejects the generalizability of the WHI findings to this group of users. In the absence of such evidence, the precautionary principle[17] suggests that some groups of older women (eg, those with high cardiovascular baseline risk) should not be prescribed HT, given the substantial risk of negative outcomes. A small proportion of the elderly women had considerably more benefits than risks associated with HT due to the underlying frequency of fractures in these subgroups.

The main limitation of our study is that we did not consider any beneficial effects of the combined estrogen and progestogen on the patient's quality of life and relief of menopausal symptoms due to effects such as reductions in night sweating and hot flushes. Other studies have evaluated the trade-off between symptom relief and risk of inducing disease.[13,18] These studies evaluated only women aged 50 and used general population incidence data rather than data specific for HT users and for patient risk factors. Because we did not have individual data on quality of life, we considered only the major clinical outcomes of HT in this study. Our study included the main clinical effects as reported by the WHI.[1] The data for this study were from the GPRD, a well-validated and widely used database.[4] Significant medical outcomes, such as fracture, breast cancer, and myocardial infarction, are well recorded in the GPRD,[4] but the database has limited or no information on some risk factors for the outcomes in this study. For example, age at menarche or genetic characteristics as risk factors for breast cancer were not available in the GPRD. Unlike the other outcomes, the clinical risk factors for breast cancer included in this study did not differentiate between women with a high and low risk of breast cancer, and there was little heterogeneity in excess risk. Individual prediction of breast cancer based on clinical risk factors is often imprecise.[19]

CONCLUSION

In conclusion, the frequency of beneficial and adverse effects of HT on chronic diseases was low in younger women, whereas the ratio of these risks-benefits varied substantially among the older users. However, the study could not assess the effects of HT on menopausal symptoms and quality of life, benefits more likely to be observed among younger women. Therapy decisions can only be made by women and physicians using individualized estimates for the frequencies of risks and benefits.

REFERENCES

1. Anderson GL, Prentice RL, LaCroix AZ, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
2. Relative or attributable risk? *Lancet* 1981;2:1211-1212.
3. Bromley SE, de Vries CS, Farmer RD. Utilisation of hormone replacement therapy in the United Kingdom. A descriptive study using the General Practice Research Database. *Br J Obstet Gynaecol* 2004;111:369-376.
4. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097-1099.
5. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. *Q J Med* 2005;98:191-198.
6. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 1996;143:971-978.
7. Manson JE, Hsia J, Johnson KC, et al. Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.
8. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of oestrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289: 2673-2684.
9. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004;47:1175-1187.

10. Schurmann R, Cronin M, Meyer JU. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;350: 2417-2419.
11. Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. *Expert Rev Pharmacoecon Outcomes Res* 2001;1:25-36.
12. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions—standardizing data on outcomes. *N Engl J Med* 1998;339: 380-386.
13. Minelli C, Abrams KR, Sutton AJ, Cooper NJ. Benefits and harms associated with hormone replacement therapy: clinical decision analysis. *BMJ* 2004;328:371-376.
14. Lynd LD, O'Brien BJ. Advances in risk-benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis. *J Clin Epidemiol* 2004;57:795-803.
15. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;288:872-881.
16. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477.
17. United Nations Environment Programme: Rio Declaration on Environment and Development. Available at: http://www.unep.org/Documents.multilingual/Default.asp?DocumentID=78&ArticleID=1163. Accessed September 13, 2006.
18. Col NF, Weber G, Stiggelhout A, Chuo J, D'Agostino R, Corso P. Short-term menopausal hormone therapy for symptom relief: an updated decision model. *Arch Intern Med* 2004;164:1634-1640.
19. McTiernan A. Assessing individual risk for breast cancer: risky business. *J Clin Epidemiol* 1997;50:547-556.