International Journal of Technology Assessment in Health Care, 15:2 (1999), 352–365.

A COMPUTER MODEL TO ANALYZE THE COST-EFFECTIVENESS OF HORMONE REPLACEMENT THERAPY

Niklas Zethraeus
Magnus Johannesson
Bengt Jönsson
Stockholm School of Economics

Abstract

This paper gives a detailed presentation of a computer model for evaluating the cost-effectiveness (CE) of hormone replacement therapy (HRT), describing the model's design, structure, and data requirements. The model needs data specified for costs, quality of life, risks, and mortality rates. As an illustration, the CE of HRT in Sweden is calculated. Two treatment strategies are evaluated for asymptomatic women: estrogen-only therapy and estrogen combined with a progestin. The model produces similar results compared with earlier studies. The CE ratios improve with the size of the risk reduction and generally with age. Further, estrogen-only therapy is associated with a lower cost per gained effectiveness unit compared with combined therapy. Uncertainty surrounding the long-term effects of HRT means that the CE estimates should be interpreted carefully. The model permits the inclusion of indirect costs and costs in added life-years, allowing the analysis to be made from a societal perspective, which is an improvement relative to previous studies.

Keywords: Cost-Effectiveness, Evaluation, HRT, Computer Model

At menopause, which occurs on the average at age 50, a majority of women (about 75%) experience menopausal symptoms such as hot flashes, night sweats, and atrophy-related symptoms of the urogenital tract. Menopausal symptoms may substantially decrease a woman's quality of life (4;31). Hormone replacement therapy[1] (HRT) mitigates or eliminates these symptoms and increases quality of life. HRT may also have a cardioprotective effect and offers protection against osteoporosis and related fractures (26). Evidence of the effect HRT has on breast cancer is inconclusive, although the risk is assumed to increase after a long period of treatment (2;3;19;20;23;26). For women with an intact uterus, there appears to be an increased

Comments from participants at the Health Economics Workshop at the Stockholm School of Economics and two anonymous referees are highly appreciated. We are also grateful to Anja Launila for helping us develop the computer model.

risk of endometrial cancer from estrogen-only therapy (26). The increased risk of endometrial cancer is decreased or eliminated by the addition of a progestin (21;26). Combining estrogen with a progestin may induce uterine bleeding; however, such bleedings may decrease or vanish if a combined HRT is continuously applied, although breakthrough bleeding often occurs in the first few months (1;26).

HRT has been used to treat menopausal symptoms for many years. In the last few years, HRT also has been recommended for women at a high risk of osteoporosis-related fractures. Whether HRT can be recommended for asymptomatic women as a preventive treatment has also been discussed (26). From a health economic perspective, these and other issues may be considered by using cost-effectiveness analysis (CEA).

CEA is based on maximizing health effects, subject to a cost constraint (29). In a CEA, costs are measured in monetary units and effects in nonmonetary units such as life-years gained (LYG) or quality-adjusted life-years (QALYs). The CEA is usually referred to as cost-utility analysis (CUA) if the health effects take into account changes in quantity and quality of life. The most frequently used health outcome measures in CUA are QALYs, although healthy years equivalents (HYEs) have also been proposed (6). CEA must be provided with a useful decision rule such that the price per effectiveness unit must be determined (e.g., the willingness to pay [WTP] for a QALY or a life-year gained). Without information about the price per effectiveness unit, a CEA gives no information about whether a program should be implemented unless the intervention is a dominated alternative such that the program has higher costs and lower effects. Furthermore, if a fixed price is used as a decision rule, the CEA approach can be seen as a special case of cost–benefit analysis where the price per QALY is constant (at all levels of change) and the same for everyone (10).

The cost-effectiveness of HRT is often modeled due to uncertainty surrounding the long-term effects of HRT. One model frequently used in the cost-effectiveness literature is the Markov model (16). The Markov model is useful when a decision problem involves risk that is ongoing over time, when the timing of events is important, and when important events may happen more than once (22). This model is defined using a finite number of (health) states in which an individual may be found at any given time. The states are mutually exclusive and collectively exhaustive, meaning that an individual must be in exactly one of the states at any time. The model assumes that all individuals in a specific state are identical and that each individual obtains the same cost or benefit irrespective of which transitions led to the health state, i.e., the model has no memory of prior states (22). Markov models occur in a discrete time frame and time progresses in units of arbitrary but fixed length (e.g., 1 year), called cycles. A transition occurs when an individual moves from one state to the next. Transitions among states occur instantaneously at the beginning or the end of a cycle, but often a half-cycle correction is included. The transition probability (p_{ij}) is the probability of going from state i to state j; the transition probabilities for exiting a specific state at a particular stage must always sum to one: i.e., $\sum_j p_{ij} = 1$. Three basic methods exist to evaluate a Markov model. The first method is a Monte Carlo simulation in which an individual passes through the process many times. The second way is to use a cohort simulation whereby a large group of individuals (e.g., 1,000 individuals) are filtered through the model at the same time, choosing their transitions according to decided distributions. The third method involves matrix algebra and produces an analytical solution (22). The

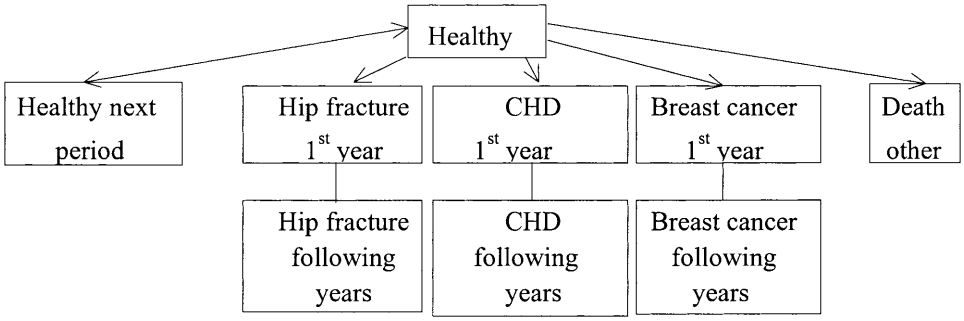

Figure 1. The basic model structure for evaluating the cost-effectiveness of hormone replacement therapy.

advantage of using a cohort or Monte Carlo simulation is that transition probabilities, benefits, and costs may be viewed as a function of not only the health state but also other population characteristics such as age.

Previous studies analyzing the cost-effectiveness of HRT suffer from several shortcomings. First, the underlying model upon which the analyses are based is seldom explicitly presented or is only briefly explained. Second, the analyses never include indirect costs or costs in added life-years, which means that the analyses are not based on a societal perspective. Third, the analyses are often based on assumptions and not on empirical investigations. This paper gives a detailed presentation of a computer model that also allows for the inclusion of indirect costs and costs in added life-years. In the empirical application of the model, intervention costs, morbidity costs for hip fracture, and coronary heart disease (CHD) are based on empirical studies.

THE COMPUTER MODEL

The computer model is programmed in C++ and built as a Markov model around menus in a Microsoft® Windows environment.[2] It is developed to analyze the cost-effectiveness of HRT and is evaluated using a cohort simulation. The model integrates two previously described computer models: one used for prevention of cardiovascular disease and one for fracture prevention (11;13;14). The model also includes a risk function for breast cancer.

Design and Structure of the Model

The model's overall structure, showing the included health states, is illustrated in Figure 1. These basic health states are: a) healthy; b) hip fracture first year; c) hip fracture following years; d) breast cancer first year; e) breast cancer following years; f) CHD first year; g) CHD following years; and h) death. CHD is subdivided into five health states: 1) recognized acute myocardial infarction; 2) unrecognized acute myocardial infarction; 3) angina pectoris; 4) coronary insufficiency[3]; and 5) sudden death. The health states a–g are also considered disease states, and are included because the medical literature shows that HRT may affect these disease risks (26). Each disease state is characterized by age-dependent mortality rates, costs, and quality-of-life weights. Hip fractures, breast cancer, and CHD are divided into "first" and "second and following years" after a disease event, since mortality rates,

costs, and quality of life differ between these time periods. When a disease event occurs, the patient will stay in that state or transition until death. At present, there are no transitions between health states after an event such as hip fracture to CHD or CHD to breast cancer. Solving this problem can be done in two ways. One way is to introduce new states, such as a hip fracture after CHD. The problem is that the model becomes very complicated and difficulties with data arise. An alternative is to include the risks and costs of the other two diseases in the sequel after an event. The latter approach has been taken in this model.

The basic model structure assumes a healthy cohort of individuals in its initial population group (the cohort size can vary between 1–100,000), in which "healthy" means free from CHD, breast cancer, and hip fractures. At each cycle of the process, the cohort is reallocated to health states according to specified transition probabilities. All transitions are assumed to occur instantaneously halfway through each cycle. In the first cycle, the cohort is exposed to disease risks of CHD, breast cancer, and hip fractures as well as the risk of dying from other causes. A patient experiencing a disease event can only transit to death or "postdisease states." Patients in postdisease states can only remain in that state or transit to death. The cohort is followed until age 110. The disease risk function is specified as a logistic distribution function including different risk factors (9). The disease risk function can be expressed as:

$$p_i = \frac{1}{1 + e^{-z_i}} \tag{1}$$

$$\text{where } Z_i = \alpha_0 X_1 + \alpha_1 X_{1i} + \alpha_2 X_{2i} + \ldots + \alpha_n X_{ni}, \tag{2}$$

where p_i is the risk of the disease during a cycle, $X_i \ldots X_n$ are risk factors, and $\alpha_0 \ldots \alpha_n$ are parameters to be estimated. The model can also tabulate the risks instead of using the risk functions.

The cost-effectiveness formula used in the computer model can be expressed as:

$$\frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta INT + \Delta MORB + \Delta MORT}{\Delta QLE} = \frac{\Delta INT + \Delta MORB + \Delta MORT}{\Delta LE + \Delta LEQ}, \tag{3}$$

where a subscript 0 (1), referring to C_i and E_i denotes no intervention (with intervention), where $i = 0.1$. ΔINT = intervention costs, direct and indirect; $\Delta MORB$ = changes in morbidity costs, direct and indirect, due to the intervention; $\Delta MORT$ = changes in mortality costs, direct and indirect, due to the intervention; ΔLE = changes in life expectancy due to the intervention; ΔLEQ = changes in quality of life measured in years due to the intervention (where "quality of life" refers to changes in morbidity and side effects); and $\Delta QLE = \Delta LE + \Delta LEQ$.

The numerator in the above formula represents the change in costs resulting from an intervention. The denominator is the change in effectiveness generated by the intervention. The change in costs and effectiveness resulting from the intervention is compared to a baseline alternative, i.e., no intervention. The change in cost is based on the sum of changes in intervention, morbidity, and mortality costs generated through the intervention, whereas the change in effectiveness is based on the sum of changes in life expectancy and quality of life due to the intervention. The model permits the cost-effectiveness (CE) ratio to be expressed either as costs

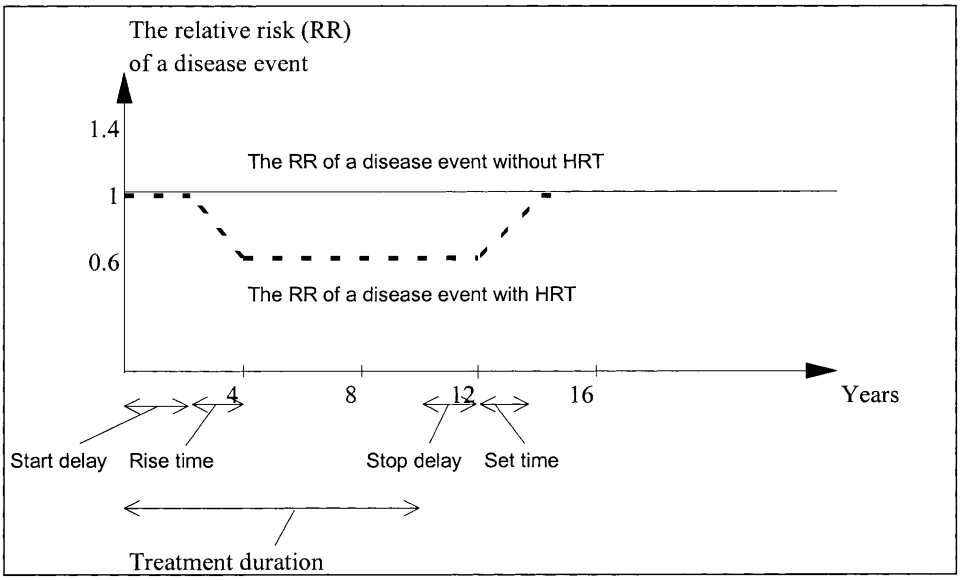

Figure 2. Modeling an intervention.

per life-year gained (if ΔLEQ is set to zero) or costs per QALYs gained. As the model incorporates consequences for different diseases, effectiveness measures, such as number of events avoided from an intervention, do not provide meaningful information. Instead, a composed outcome measure is needed that incorporates the interventions effectiveness for different risks.

Intervention costs (ΔINT) are divided into yearly and initial costs. Yearly costs consist of direct and indirect costs. Direct costs for an intervention include cost of drugs, costs for services in hospitals (physician visits), primary health care, and traveling costs. Indirect costs reflect resources foregone due to the treatment (e.g., production losses). These costs are particularly relevant for primary prevention when healthy time is used for the interventions (e.g., physician visits). Initial costs consist of direct and indirect costs and may, for example, be costs for screening patients to be treated.

Changes in morbidity costs ($\Delta MORB$) consist of costs saved because of reduced morbidity from CHD and hip fractures and costs added because of increased morbidity from breast cancer. The change in morbidity costs are divided into changes in direct and indirect costs. The model also permits the inclusion of changes in mortality costs ($\Delta MORT$). Changes in mortality costs are equal to changes in total consumption minus changes in the total production due to a change in mortality from the intervention (17). The estimation of consumption and production should in principle be based on a healthy population, which are free from hip fractures, breast cancer, and CHD.

Modeling an Intervention

An intervention is modeled by its impact on the disease risks (Figure 2). The example illustrated in Figure 2 assumes that treatment duration lasts 10 years. Without treatment, the relative risk (RR) is equal to 1. With treatment, the RR follows the dotted line. The risk reduction in entered as a percentage change in

the base-case risk. For example, if the risk of CHD is assumed to be reduced by 40% during HRT, this is equal to multiplying Equation 1 for CHD above by 0.6. According to the CHD risk equation, the risk without treatment of CHD for a woman of age 60 years is 6.2 per 1,000. The intervention reduces the risk by 40%, and the resulting risk of CHD for this woman with treatment is then equal to:

$$0.6 \times \frac{6.2}{1{,}000} = \frac{3.72}{1{,}000}.$$

Different options are available for the user when modeling disease risks affected by the intervention. Start delay is defined as the time prior to when the intervention affects the risk (2 years in Figure 2). Rise time is defined as the time it takes from the end of the start delay until the risk reduction has reached its maximum value (2 years in the Figure 2). The rise time is specified as a linear function of time. Stop delay and set time are defined analogously to start delay and rise time. The model also permits a remaining effect lasting from the end of set time until the rest of the lifetime. Thus, the model allows the user to make several different assumptions about how the intervention affects the disease risks.

Data for the Model

The model demands data about risks, mortality rates, quality-of-life weights, and costs.

Risks. First, the base-case risk of CHD, breast cancer, and hip fractures without treatment need to be known. Within the model, it is possible to use risks specified as risk functions, risks manually incorporated into tables, or a combination of both. The base-case risk of hip fractures can also be elevated in the model. This option makes it easier to analyze cohorts subject to an increased base-case risk of hip fractures where only the relative risk is available (e.g., women with osteoporosis).

Values must be identified for the risk factors involved in the CHD risk function, including cholesterol, diastolic blood pressure, smoking status (fraction between 0 and 1), glucose intolerance (fraction between 0 and 1), and left ventricular hypertrophy (fraction between 0 and 1). These may represent mean values (an average woman) in the population that are subject to analysis. By changing the risk factors, it also becomes possible to analyze cohorts subject to an increased risk of CHD. Conditional on sustaining CHD, a table determines the distribution among the CHD disease states. The age-dependent probability of different CHD disease states must therefore also be identified.

When modeling the intervention, the user must identify how the intervention affects the disease risks and specify the different options associated with the intervention as described above (% risk change, start delay, rise time, stop delay, set time, and remaining).

Mortality Rates. Age-specific annual mortality rates have to be specified for CHD, breast cancer, and hip fractures for the first year, as well as the second and following years after the disease event. Mortality rates need to be stated for all ages between the initial age of the cohort and 110 years. CHD mortality rates are divided into four categories: recognized acute myocardial infarction, unrecognized acute myocardial infarction, angina pectoris, and coronary insufficiency. Sudden death is defined as death within 1 hour from the onset of the disease.

Age-specific annual mortality rates also must be identified for death from other causes ("death other"). To calculate the mortality rate for "death other," the risk

of dying from CHD, breast cancer, or hip fractures is subtracted from the normal mortality rate. In the model, mortality rates for "death other" are obtained by multiplying values extracted from normal mortality tables with one minus the fraction of death that breast cancer and CHD constitutes.

Quality-of-life Weights. Age-dependent quality-of-life weights must be specified for CHD, breast cancer, and hip fractures for the first and following years after an event. The quality-of-life weight is a number between 0 (dead) and 1 (full health) that reflects health state preference. Quality-of-life weights also need to be identified for healthy individuals (the quality-of-life weight may be lower than 1 due to other diseases not included in the model). The model also permits the inclusion of quality-of-life weights during treatment, which takes into account potential side effects associated with the intervention.

Costs. Costs necessary for the model can be divided into intervention, morbidity, and mortality costs. Their inclusion is based on a societal perspective, meaning that all costs are incorporated into the analysis, no matter who pays the costs (see also the CE formula in Equation 3 above). The model permits other perspectives as well, such as a health care budget perspective.

Age-specific annual morbidity costs must be specified for the first year, as well as the second and following years after a disease event. Morbidity costs are those associated with the treatment of CHD, breast cancer, and hip fractures and are also divided into direct and indirect costs as follows: direct costs are those related to the patients' treatment and rehabilitation, whereas indirect costs are equivalent to a decrease in the value of production caused by the disease. The morbidity costs are interpreted as the extra costs related to morbidity (i.e., the increase in costs due to the disease compared with being "healthy").

Finally, age-specific costs in added life-years may be included. Costs in added life-years, or mortality costs, are equal to total consumption minus total production in these years (17).

Output from the Model

Cost per Gained Life-year and QALY. At the top of the intervention result menu, the change in life-years resulting from the intervention is shown. This change is calculated as the change in expected survival for the cohort generated by the intervention (all results are presented per individual). Subsequently, the change in quality of life due to morbidity and side effects, is shown. Adding the change in life expectancy with the change in quality of life gives the change in QALYs resulting from the treatment.

The change in total costs is presented as changes in intervention, morbidity, and mortality costs. The costs are also presented as direct and indirect costs. At the bottom of the intervention menu, the model presents CE ratios expressed as costs per change in life-years and costs per change in QALYs.

Diseases, Lifetime Risk, and Life Expectancy. The model shows the distribution of individuals with or without intervention in the different health states (death other, healthy, CHD, hip fracture, and breast cancer) for a given cycle after treatment onset (0–60 years if the cohort is followed from 50 years). It is also possible to calculate the *lifetime risk* of different diseases for an individual at a certain age. For example, the lifetime risk of hip fracture for an individual at a certain age is the number of individuals who sustained a hip fracture during the remaining lifetime divided by the number of individuals at risk (the initial cohort).

These figures may be compared with estimates on lifetime risks in the general population to check the model's credibility.

Life expectancy is defined as the average future lifetime of the cohort. The total number of cycles (years) for each health state is divided by the size of the original cohort. The total life expectancy is the sum of cycles for the included health states. The life expectancy, conditional on a certain disease state, is calculated as the number of cycles in the disease state divided by the number of women who end up in the disease state, assuming that the cohort starts in the healthy state.

Treatments. There is an option that enables the cohort of individuals to be followed through the model by varying the time horizon for the analysis. It is possible to view the number of individuals in different disease states and number of cycles the individuals have been in the disease state. In addition to following the cohort at any time horizon, this option can be used as an aid for controlling the model's calculations.

EMPIRICAL APPLICATION: ESTIMATIONS BASED ON SWEDISH DATA

A sample simulation was applied to a hypothetical cohort of average asymptomatic women at the age of 50, 60, and 70 years with an assumed treatment duration of 10 years. For each age group two indications were analyzed: women with an intact uterus and women who had had a hysterectomy. Women who had had a hysterectomy were given estrogen-only therapy, whereas women with an intact uterus were given estrogen combined with a progestin. For each indication and age, the treatment strategy was compared with no treatment. Thus, six independent patient groups were considered, two for each age group. The stated question was whether there is good value for money to treat asymptomatic women with an intact uterus or posthysterectomy with HRT compared with no treatment.

The costs were collected using a societal perspective, including intervention costs, morbidity costs, and costs in added life-years (17). The intervention cost includes costs for the drug, travel/time, and physician visits. Morbidity costs include both direct and indirect costs. Reduced morbidity costs occur when the risk of hip fractures and CHD decrease from using HRT. Increased morbidity costs occur due to increases in the risk of breast cancer from using HRT. Costs in added life-years were calculated as the difference between total consumption (i.e., private and public) and total production (12;17). The base-case risk of hip fracture and breast cancer were estimated using Swedish incidence data in different age groups (18;25), whereas the base-case risk of CHD was extracted from the Framingham Heart Study, in which the results are based on a U.S. population (15). The hip fracture risk reduction was assumed, during treatment, to be 40 or 50% (19;20;26). The risk of hip fractures was assumed to gradually adjust to the base-case risk at 10 years after HRT cessation (26). The CHD risk reduction was assumed, during treatment, to be 20 or 50% (19;20;26). The decrease in the risk of CHD was assumed to be the same for estrogen-only therapy and estrogen combined with a progestin (7). The increase in the risk of breast cancer was assumed to be 0 or 35%, respectively (19;20). The increased risk of breast cancer was assumed to start intanstaneously after 5 years of HRT and remain elevated during the rest of treatment (19;20;26). Costs (given in 1995 prices) and effects were discounted at the rate of 3% (8). A detailed presentation of the assumptions made and the included data is presented in a working paper (32).

Table 1 demonstrates the cost per life-year gained and QALY for different risk reductions and ages. Treating women who had had a hysterectomy with estrogen-only therapy was associated with lower CE ratios compared with treating intact women with combined therapy for all ages and risk reductions (5;28). This is explained by a higher intervention cost associated with the combined therapy.

Assuming a 20% reduction in the risk of CHD, the CE ratios improve with age at treatment onset. The improved CE ratios are mainly explained by an increased absolute risk of CHD as age increases and, therefore, a larger decrease in the number of CHD events and related mortality compared with HRT at younger ages. There is also an increased age-related absolute risk of breast cancer and hip fractures, but not as large as CHD.

Assuming a 50% reduction in the risk of CHD, the CE ratios increase with age in some cases. With low CE ratios at the age of 50 years, increases in the effectiveness of starting treatment in older ages result in higher CE ratios due to costs in added life-years. Thus, the increase in the CE ratio is due to increases in the costs in added life-years, which are large in the ages above 65 years (i.e., increases in life expectancy are outweighed by increases in costs in added life-years).

By adding the risk of breast cancer, the CE ratio generally increases (i.e., worsens). This is due to a lower life expectancy and that savings in morbidity costs are decreased. However, due to the lower life expectancy, costs in added life-years decrease, which implies a decrease in total costs and that the CE ratio is unaffected. In some cases a slight decrease in the CE ratio is observed.

The CE ratio is sensitive to changes in the assumptions about the relative-risk reduction in CHD. This sensitivity is confirmed in Table 1, which shows a substantial decrease in the cost per gained effectiveness unit at 50 years of age when the risk reduction is 50% instead of 20%. Also note that the CE ratio is sensitive to the inclusion of breast cancer risk for 50-year-old women with a 20% reduction in the risk of CHD. This is explained by the fact that such women have a rather small increase in life expectancy (when breast cancer is excluded) compared with other groups. The inclusion of breast cancer then has a large influence on life expectancy and CE ratios for these subgroups.

If a 5% discount rate for costs and effects are used, the CE ratios increase. This is due to the fact that benefits of the treatment in terms of increased life expectancy and avoided morbidity occur in the distant future, whereas the costs mainly arise in the near future (intervention costs), implying that benefits are given lesser weight (more heavily discounted) compared with the costs. The cost-effectiveness of HRT is very sensitive to the presence of side effects. Assuming any side effects during the entire treatment period implies that HRT is dominated by the no-intervention alternative in all patient groups. On the other hand, if it is assumed that HRT increases quality of life during the treatment period, the CE ratios improve substantially. The CE ratios also improve if the women are assumed to be subject to an increased risk (a doubled risk compared with an average woman) of hip fractures, i.e., if the women have osteoporosis. This is explained by an increased number of avoided fractures due to the increased base risk of hip fractures.

As mentioned above, a CEA gives no information about whether a program should be implemented unless the intervention is a dominated alternative, e.g., when side effects are prevalent, as discussed above. Under some restrictive conditions, it is possible to conclude that if the willingness to pay (WTP) exceeds the costs per gained QALY, the treatment program should be carried out. Recently the WTP per gained QALY was estimated at about SEK 160,000, which may be interpreted

Table 1. Cost (SEK thousand) per gained life-year and QALY (QALY in parentheses), assuming different risk reductions for CHD, hip fracture, and breast cancer[a]

	Estrogen (posthysterectomy)			Estrogen + Progestin (intact uterus)		
Risk change	50 yr	60 yr	70 yr	50 yr	60 yr	70 yr
Hip, −40%; CHD, −20%	400 (310)	240 (230)	170 (190)	580 (450)	300 (300)	200 (230)
Hip, −40%; CHD, −50%	160 (140)	170 (190)	160 (200)	230 (200)	200 (220)	180 (220)
Hip, −50%; CHD, −20%	360 (280)	210 (200)	150 (170)	540 (410)	280 (260)	180 (200)
Hip, −50%; CHD, −50%	150 (120)	160 (170)	150 (180)	220 (190)	190 (200)	170 (200)
Hip, −40%; CHD, −20%; Cancer, +35%	D (640)	270 (240)	170 (190)	D (1060	370 (320)	210 (230)
Hip, −40%; CHD, −50%; Cancer, +35%	190 (130)	180 (180)	160 (200)	320 (230)	210 (220)	180 (220)
Hip, −50%; CHD, −20%; Cancer, +35%	D (500)	240 (200)	150 (160)	D (860)	330 (280)	180 (200)
Hip, −50%; CHD, −50%; Cancer, +35%	170 (120)	170 (170)	150 (180)	300 (210)	200 (200)	170 (200)

Abbreviations: Hip = hip fracture; CHD = coronary heart disease; cancer = breast cancer; D = HRT is dominated by the no-intervention alternative.
[a] The treatment duration is 10 years for women aged 50, 60, and 70 years.

as a lower bound for the WTP per gained QALY (30). Using this lower bound and comparing it with the costs per gained QALY as estimated in TAble 1, one conclusion is that estrogen-only therapy is cost-effective for women at the age of 50 years if the assumed risk reduction of CHD amounts to 50%.

The life expectancy calculated from the model is 31.9 years for a woman at the age of 50 years, which is near the expected survival of 32.3 years extracted from Swedish populations (24). The model predicts a lifetime risk of having CHD of 25.6%. The predicted lifetime risks of hip fractures and breast cancer are 16.4 and 7.3%, respectively (27).

CONCLUSION

The model, constructed to be as general and flexible as possible theoretically may be used for any population. However, the default data used for the model in empirical applications are assumed to be valid only for Swedish populations. To make accurate conclusions using the model in other countries, the data must be valid for the specific setting to which the model is applied. Below, opportunities and data needs for extending the model to other countries are discussed.

Direct and indirect costs must be determined for each country subject to analysis. Using Swedish cost data, multiplied with an appropriate exchange rate, implicitly assumes that the absolute and relative price level is the same as in Sweden. It also assumes that medical and social care patterns are equivalent. These are very strong assumptions and can only be recommended as a preliminary analysis. Ideally, country-specific costs should be collected. Yearly direct intervention costs, including the costs of pharmaceuticals and physician visits as well as time and traveling costs, can be estimated empirically by following patients during a year of treatment.

Direct and indirect disease costs must be collected for the first 12 months following an event and for the second and following years. Direct morbidity costs are interpreted as the extra costs of the disease compared with no disease occurrence and can be estimated by, for example, subtracting the costs during 1 year before a disease event from the costs during 1 year after the disease event (33). Another alternative is to estimate the costs without the disease by using a matched cohort. The direct costs include all costs associated with the treatment during the initial hospital stay, as well as rehabilitation in aftercare. Indirect morbidity costs can be estimated by subtracting the production value the year after disease onset from its value the year prior to disease.

Quality-of-life weights may differ between countries, and the data should be based on empirical studies. Different methods exist for estimating the quality-of-life weights (6). For example, the rating scale, time trade-off, and standard gamble methods are commonly used to estimate weights to construct QALYs.

The risk of disease may differ between countries and should be based on country-specific data. The model permits the default values to be changed for the estimated parameters in the risk equations. With these changes, it is then possible to estimate country-specific risk equations for the same risk factors and use these parameter estimates in the model. The risk of breast cancer and hip fractures may be estimated using country-specific incidence data. In the absence of such epidemiological data in Sweden at the moment, the risk equation of CHD is extracted from the Framingham Study; whether the results of this study can be extrapolated to other populations is uncertain. One alternative to verify whether the results are applicable is to compare them with incidence data. Instead of using the risk

equations, tabulations may be used. Data on mortality after disease events should be based on country-specific empirical studies. Mortality data is referring to the first year and subsequent years after an event. General mortality may be estimated from national registers involving statistics of mortality rates from the general population.

The model in its original setting evaluates a treatment compared with a baseline alternative (i.e., no treatment). However, the model also permits comparisons between two or more treatments for a given population. The incremental CE ratios between these alternatives must then be calculated. This is made by first calculating the change in costs and effects for the treatments separately; (for example, the case of two treatments (1 and 2), calculate (C_1 - C_0) and $E_1 - E_0$) for treatment 1 compared with the baseline alternative (0) and then calculate ($C_2 - C_0$) for treatment 2 compared with the baseline alternative).

The marginal CE ratio for treatments 1 and 2 is calculated as:

$$\frac{(C_2 - C_0) - (C_1 - C_0)}{(E_2 - E_0) - (E_1 - E_0)} = \frac{C_2 - C_1}{E_2 - E_1} \quad \textbf{(4)}$$

Adherence is the extent to which the patient follows a physician's treatment recommendations. Nonadherence is present if the patient does not follow these recommendations and may be one of two types. First, the patient may not buy the drug the physician has prescribed such that no costs or effects associated with the treatment are present. Second, the patient may buy the drug, but diverge from the physician's recommendations, in which case costs for the drug are incurred and only a fraction of the full effect (or no effect) from using the drug is incurred. The second definition of nonadherence necessitates information about how the drug's effect is altered by nonadherence. Note that this type of adherence should be reflected in the estimates of the costs and effects used such that estimates of costs and effects in a clinical trial are based on actual adherence within the trial. To analyze the effect of adherence, which differs from adherence within the trial, this necessitates information on how to adjust the effects.

To illustrate the model, the cost-effectiveness of HRT in Sweden was calculated for a hypothetical cohort of asymptomatic women. The analysis was mainly based on Swedish data for risks, mortality, quality of life, and costs. It is shown that the model produces similar results compared with earlier studies. However, uncertainty surrounding the long-term effects of HRT means that the CE estimates should be interpreted carefully. Further, the risk and mortality of CHD is based upon a U.S. population, which may not be representative of a Swedish setting. The model can be improved by including newer and better data as they become available. A matter for future research is to investigate the possibility of improving the data quality and whether the results based on the Framingham study are applicable to Swedish settings.

NOTES

[1]Unless otherwise indicated, HRT refers both to estrogen-only therapy and estrogen combined with a progestin.

[2]For a more thorough presentation of the model and the menus, see Zethraeus et al. (32).

[3]Coronary insufficiency or unstable angina pectoris can be used interchangeably.

REFERENCES

1. Andersson, K., Mattsson, L.-Å., Rybo, G., & Stadberg, E. Intrauterine release of levonorgestrel, a new way of adding progestogen in hormone replacement therapy. *Obstetrics and Gynecology*, 1992, 79, 963–67.

2. Colditz, G. A., Hankinson, S. E., Hunter, D. J., et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine*, 1995, 332, 1589–93.
3. Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*, 1997, 350, 1047–59.
4. Daly, E., Gray, A., Barlow, D., et al. Measuring the impact of menopausal symptoms on quality of life. *British Medical Journal*, 1993, 307, 836–40.
5. Daly, E., Roches, M., Barlow, D., et al. HRT: An analysis of benefits, risks and costs. *British Medical Bulletin*, 1992, 48, 368–400.
6. Drummond, M. F., O'Brien, B., Stoddart, G. L., Torrance, G. W. *Methods for the economic evaluation of health care programmes*; 2nd ed. New York: Oxford University Press, 1997.
7. Falkeborn, M., Persson, I., Adami, H.-O., et al. The risk of acute myocardial infarction after estrogen and estrogen-progestogen replacement. *British Journal of Obstetrics and Gynaecology*, 1992, 99, 821–28.
8. Gold, M. R., Siegel, J. E., Russell, L. B., & Weinstein, M. C. *Cost-effectiveness in health and medicine.* New York: Oxford University Press, 1996.
9. Gujarati, D. N. *Basic Econometrics.* Singapore: McGraw-Hill International Editions, 1988.
10. Johannesson, M. *Theory and methods of economic evaluation in health care*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1996.
11. Johannesson, M., Hedbrant, J., & Jönsson, B. A computer simulation model for cost-effectiveness analysis of cardiovascular disease prevention. *Medical Informatics*, 1991, 16, 355–62.
12. Johannesson, M., Meltzer, D., & O'Conor, R. M. Incorporating future costs in medical cost-effectiveness analysis: Implications for the cost-effectiveness of the treatment of hypertension. *Medical Decision Making*, 1997, 17, 382–89.
13. Jönsson, B., Christiansen, C., Johnell, O., & Hedbrant, J. Cost-effectiveness of fracture prevention in established osteoporosis. *Osteoporosis International*, 1995, 5, 136–42.
14. Jönsson, B., Hedbrant, J., & Johnell, O. *A computer simulation model to analyze the cost-effectiveness of fracture prevention of osteoporosis.* EFI Research Paper No. 6525, 1993.
15. Kannel, W. B., Wolf, P. A., & Garrison, R. J. *The Framingham study: An epidemiological investigation of cardiovascular disease, Section 37: The probability of developing certain cardiovascular diseases in eight years at specified values of some characteristics.* Springfield, MA: U.S. Department of Commerce National Technical Information Service, 1987.
16. Keller, E. Decision trees and Markov models in cost-effectiveness research. In F. A. Sloan (ed.), *Valuing health care*. New York: Cambridge University Press, 1995.
17. Meltzer, D. Accounting for future costs in medical cost-effectiveness analysis. *Journal of Health Economics*, 1997, 16, 33–64.
18. National Board of Health and Welfare (Socialstyrelsen), Sweden, 1993.
19. Office of Technology Assessment, Congress of the United States. Effectiveness and costs of osteoporosis screening and hormone replacement therapy. Background paper. In: *Cost-effectiveness analysis*, vol. 1. Washington, DC: U.S. Government Printing Office, 1995.
20. Office of Technology Assessment, Congress of the United States. Effectiveness and costs of osteoporosis screening and hormone replacement therapy. Background paper. In *Evidence on benefits, risks, and costs*, vol. 2. Washington, DC: U.S. Government Printing Office, 1995.
21. Persson, I., Adami, H.-O., Bergkvist, L., et al. Risk of endometrial cancer after treatment with estrogens alone or in conjunction with progestogens: Results of a prospective study. *British Medical Journal*, 1989, 298, 147–51.
22. Sonnenberg, F. A., & Beck, J. R. Markov models in medical decision making. *Medical Decision Making*, 1993, 13, 322–38.

23. Stanford, J. L., Weiss, N. S., Voigt, L. F., et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *Journal of the American Medical Association*, 1995, 274, 137–42.
24. Statistics Sweden. *Statistical yearbook of Sweden.* Stockholm: Norstedts tryckeri AB, 1995.
25. Stockholm Country Council. Stockholm inpatient register. Stockholm, 1990.
26. The Swedish Council on Technology Assessment in Health Care. SBU report no. 131. Stockholm: SBU, 1996.
27. Torgerson, D. J., & Reid, D. M. The economics of osteoporosis and its prevention. A review. *PharmacoEconomics*, 1997, 11, 126–38.
28. Tosteson, A., Weinstein, M. C. Cost-effectiveness of hormone replacement therapy after the menopause. *Baillière's Clinical Obstetrics and Gynaecology*, 1991, 5, 943–59.
29. Weinstein, M. C., & Zeckhauser, R. Critical ratios and efficient allocation. *Journal of Public Economics*, 1973, 2, 147–57.
30. Zethraeus, N. Willingness to pay for hormone replacement therapy. *Health Economics*, 1998, 7, 31–38.
31. Zethraeus, N., Johannesson, M., Henriksson, P., & Strand, R. The impact of hormone replacement therapy on quality of life and willingness to pay. *British Journal of Obstetrics and Gynaecology*, 1997, 104, 1191–95.
32. Zethraeus, N., Johannesson, M., & Jönsson, B. *A computer model to analyze the cost-effectiveness of hormone replacement therapy.* EFI Research Paper No. 6578, January 1998.
33. Zethraeus, N., Strömberg, L., Jönsson, B., Svensson, O., & Öhlén, G. The cost of a hip fracture. Estimates for 1,709 patients in Sweden. *Acta Orthopaedica Scandinavica*, 1997, 68, 13–17.