

## **Module 6 Cost-effectiveness Analysis of Screening Program**

### **6.1 Framework of economic appraisal of intervention program of breast cancer**

In any economic appraisal for prevention of breast cancer death, several aspects should be delineated including setting, population of interest, disease natural history, referral and treatment, effectiveness, and cost (money). Settings under the context of cost and effectiveness in health care field may include community, ambulatory health care center, hospital, and institution. Different settings may imply different intervention point relating to disease natural process or prognosis. Intervention at community usually identified several types of subjects, including the refuser that are invited to intervention but never come. This group often follows the disease natural course with the progression from asymptomatic phase to clinical phase at very late stage due to clinical symptom and sign. Due to advanced stage, the treatment is useless and complication and disability may often call for institution care. They may die early. The second group from the general population is amenable to intervention if invited. The disease natural history of this group is often altered by the introduction of organized service screening program to interrupt the disease natural history at asymptomatic phase and administered by early treatment or therapy. The third group is called opportunistic screening participant in the arm of screening and also called self-selected for intervention in the field of primary prevention even in the absence of invited and organized intervention. They have high awareness to access to medical care by themselves. However, the proportion of this group in

general population is often related to economic level. The selection of comparator against the intervention program should be well clearly defined in this framework. In enhanced awareness program or screening program, the comparator may include subjects with opportunity to screening even in the absence of organized service screening.

The intervention programs within the context of primary prevention include health education program for changing life style or awareness program for enhancing the accessibility to early detection and possible prophylactic intervention such as the administration of hormone to high risk group or prophylactic mastectomy for high risk group carrying with susceptible gene. The aims of these intervention programs are to reduce the incidence of breast cancer. Although economic appraisal for these interventions can be modeled in a similar manner, the current study does not give a scenario for this part.

For the level of secondary prevention, the screening methods used may highly depend on different levels of economic development. In the context of state-of-the art breast cancer screening, breast self-examination, physical examination, mammographic examination and other emerging techniques may be applied with the order following the level of economic development. In highly economic developed country, economic evaluation of new emerging technique may be of great interest whereas simple and cheap screening like physical examination in conjunction with clinical awareness program may take precedence over other screening methods. For tertiary prevention, economic appraisal is tailored for evaluation of alternative treatment and novel therapy in the wake of a large proportion of early-detected breast cancer as a result of screening or

perhaps enhanced awareness program. Figure 6-1 shows other components, particularly related to screening program, involved in economic appraisal. The effectiveness is defined by a series of outcome including the proportion of screen-detected cancers among total breast cancers identified from the screening program (including screening-detected cases, interval cancer and refuser), reassurance, false alarm, advanced cancer, severe complication and disability, and mortality from breast cancer. These outcomes can be adjusted by utility usually defined by QAL or measured by another popular estimate of the maximum amount of willing (WTP). The final column describes the relevant direct and indirect costs.

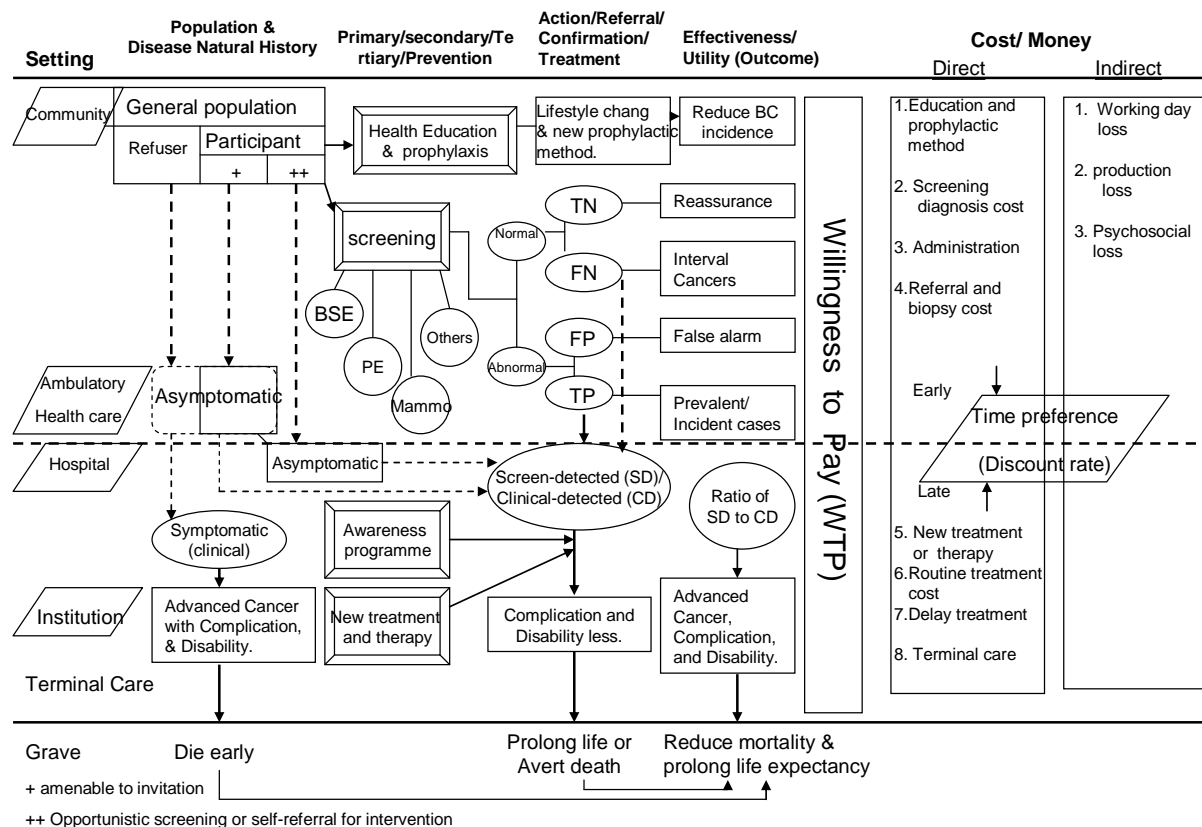


Figure 6-1. Framework of economic appraisal of intervention program of breast cancer

## **6.2 Decision Modelling of Economic Evaluation of Intervention Program of Breast Cancer**

### **6.2.1 The process of building an economic appraisal for the guidance of health policy-makers**

Figure 6-2 shows the process of building an economic appraisal for the guidance of health policy-makers. The first step is to set up different decisions to achieve the goal of the intervention program i.e. mortality reduction. The medical literature is searched for intervention studies by level of evidence-based medicine from well-designed randomized controlled trials to fragmental expert opinions. Meta-analysis will be required to integrate different empirical findings into a base-case estimate to be used in the decision modeling.

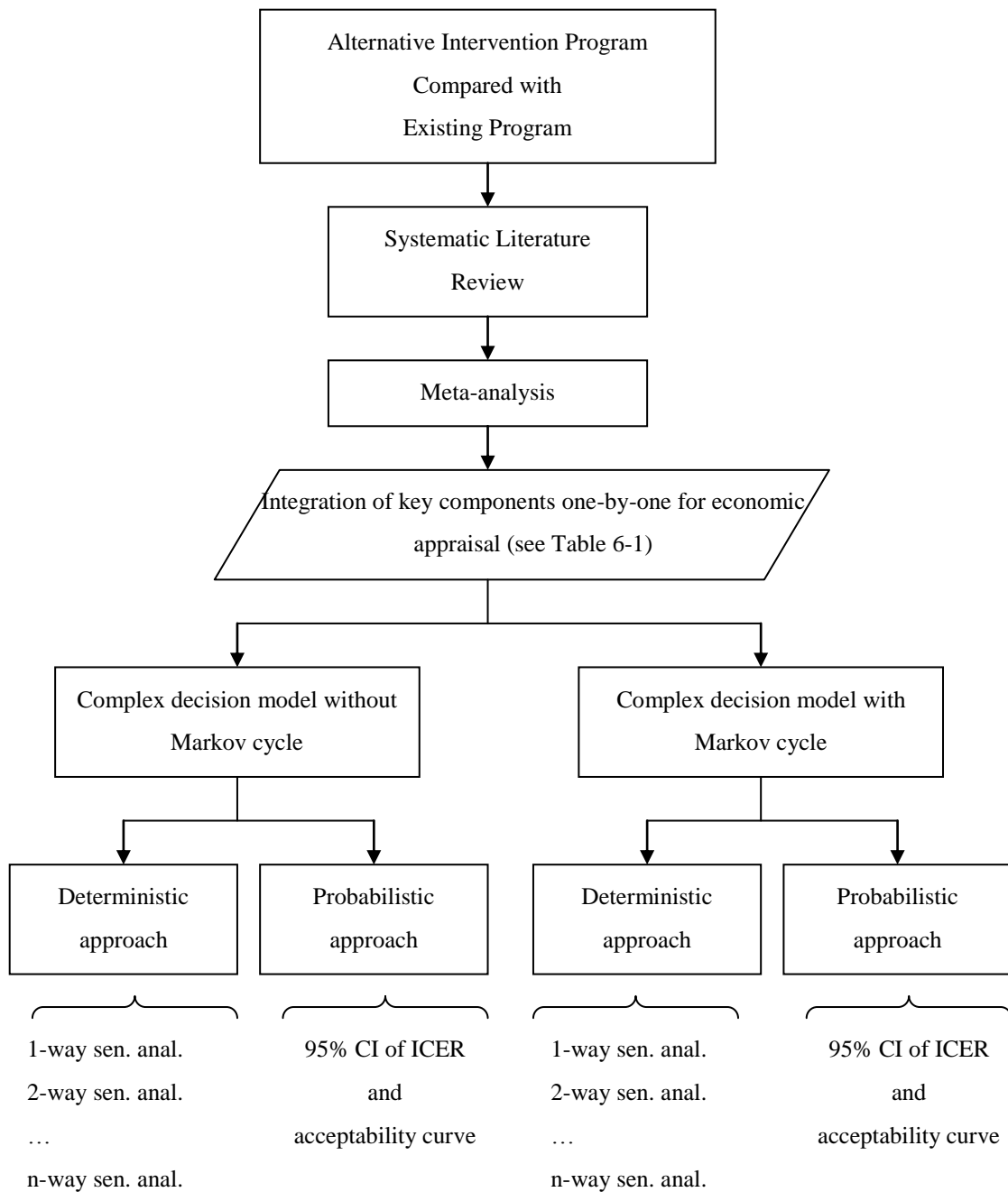


Figure 6-2 Formulation of complex decision model for the economic evaluation of the intervention program for breast cancer

### **6.2.1 Key components of a complex decision model**

The complex decision model from these empirical estimates is then built up by simulating the target population with the assignment of the key components listed in Table 6-1.

Table 6-1 Key components for decision modeling of economic evaluation of a primary or secondary prevention program for breast cancer

Component	Sub-component	Data Source	Meta-analysis	Variation of sources	Distribution
<u>I. Demographic features</u>	1. Age, gender, socioeconomic status and other attributes (Target population)	<u>1. Vital statistics</u>	No	Country/ geographic area difference	1. Multinomial distribution
		<u>2. Life-table</u>	No		2. Gamma or Beta distribution
	2. Competing causes of death				
<u>II. Disease natural history</u>	1. Onset of preclinical screen-detected phase (PCDP)	<u>1. Cancer registry</u>	No	Ethnic group difference	Gamma distribution
	2. Subsequent progression to clinical phase	<u>2. Medical literature</u>	Yes		
<u>III. Performance indicator of intervention program</u>	1. Participation rate	<u>Medical literature</u>	No	Countries with different level of economic development	Beta distribution
	2. Sensitivity and specificity	<u>on intervention</u>	Yes		
	3. Referral rate for confirmation procedure	<u>programs</u>	No		
	4. Compliance with follow-up		No		

Component	Sub-component	Data Source	Meta-analysis	Variation of sources	Distribution
<u>IV. Efficacy of intervention</u>	1. Incidence and mortality reduction	<u>Medical literature on randomized controlled trials</u>	Yes	Countries with different level of economic development	Gamma distribution
	2. Reduction of advanced breast cancer				
	3. Reduction of Relapse				
<u>V. Prognosis</u>	1. Survival rate of breast cancer by stage, tumor size, histological grade, and treatment or therapy	<u>Medical literature on clinical studies</u>	Yes	Countries with different level of economic development	Exponential or Gamma distribution
	2. Relapse or recurrence rate of breast cancer by stage, tumor size, histological grade, and treatment or therapy				
<u>VI. Cost</u>	1. Perspective (societal or single health care payer)	<u>Insurance claimed data and medical literature</u>	No	Countries with different level of economic development	Triangular or log-normal distribution
	2. Direct cost (1) Treatment				



Component	Sub-component	Data Source	Meta-analysis	Variation of sources	Distribution
	(2) Intervention (3) Administration 3. Indirect Cost (1) Production loss, i.e. hospitalization (2) Psychosocial cost				
<u>VII. Effectiveness</u>	1. Life-years gained 2. Quality-adjusted life years (QALY), adjusted by utility 3. Avoidance of advanced cancer 4. Enhancement of attendance rate 5. Others	<u>Selection of outcome is dependent on the available resources and economic level</u>	No		
<u>VIII. Discount rate</u>	3%			No	Beta distribution
<u>IX. Economic</u>	1. Cost-effectiveness	1. $ICER = \Delta C / \Delta E^*$	No	The criteria of	Scatterplot of C-E

Component	Sub-component	Data Source	Meta-analysis	Variation of sources	Distribution
<u>appraisal indicator</u>	analysis (CEA) or cost-utility analysis (CUA): Incremental cost-effectiveness (utility) ratio (ICER or ICUR) 2. Cost-benefit analysis * translation of benefit into monetary value (1) Human capital (2) Willingness-to-pay	2. benefit-cost ratio    (1) GNP (2) Primary survey		being cost-effective affected by the threshold of willingness-to-pay (WTP) level under different economic development	plane and acceptability curve

\*  $\Delta C$  and  $\Delta E$  are differences of cost and effectiveness between the alternative intervention program and existing program

### 6.2.3 Comparison of economic efficiency between interventions

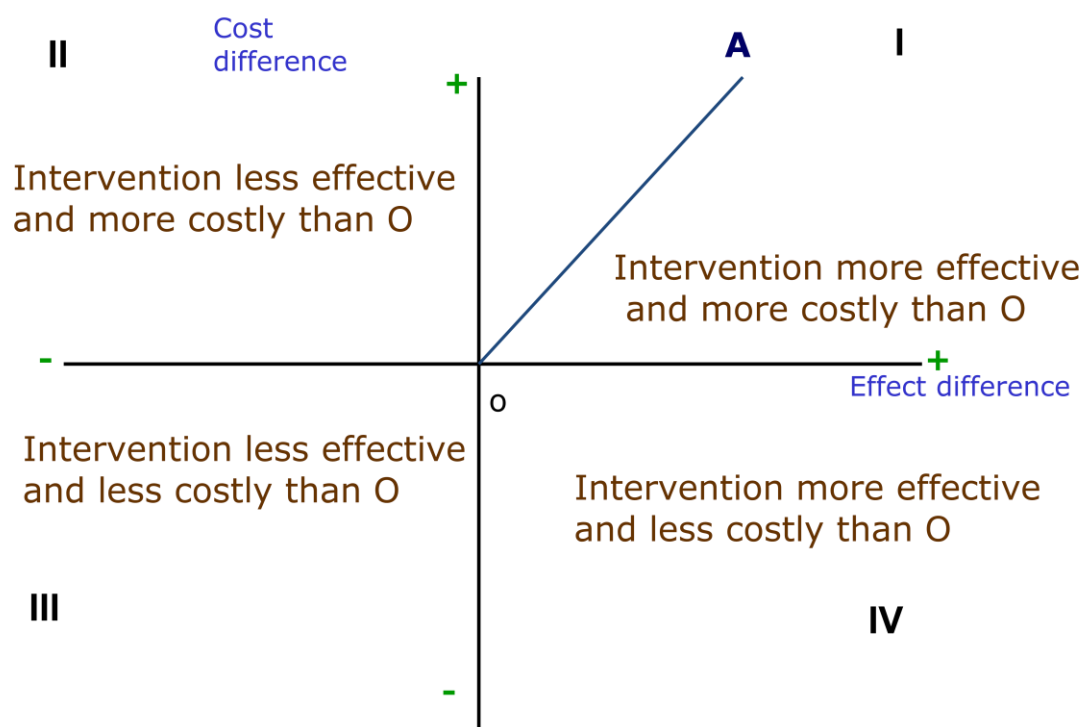
(A) Incremental Cost-Effectiveness Ratio, ICER

$$\text{ICER} = (C_1 - C_2) / (E_1 - E_2) = \Delta C / \Delta E$$

$\Delta E$ : Increment Effectiveness

$\Delta C$ : Incremental Cost

(B) The Cost-effectiveness Plane (C-E plane)



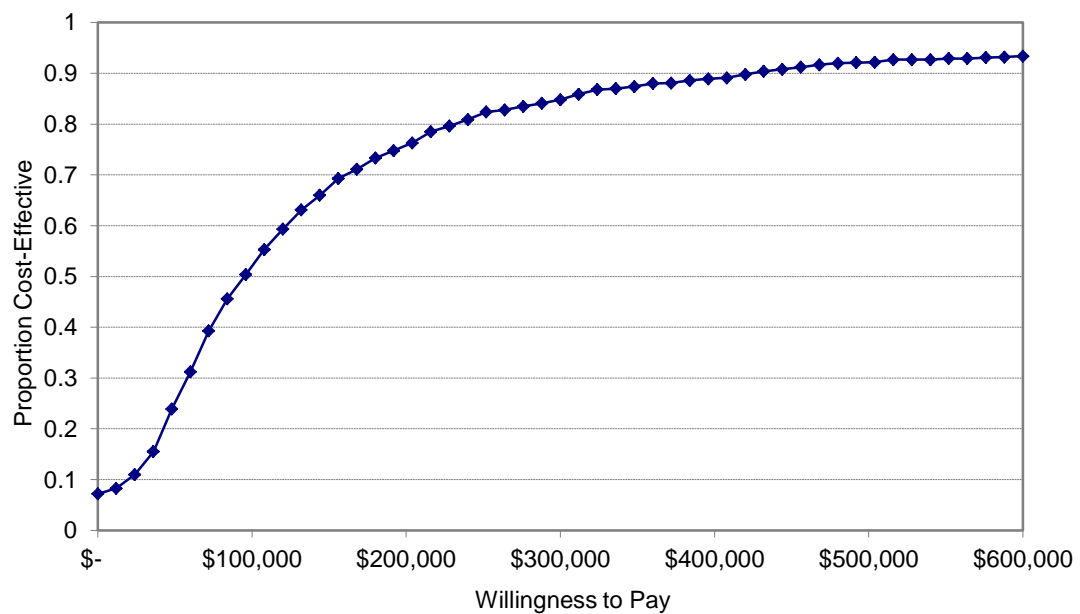
### (C) Net Benefit

$$\beta(K) = K * \Delta E - \Delta C$$

K: ceiling ratio/critical value, the maximum willingness to pay (WTP) per incremental effectiveness

The alternative strategy is cost- effectiveness compared to the reference strategy given on K if Net Benefit>0

### (D) Acceptability curve



#### **6.2.4 Criteria for the choice of intervention**

##### **(1) Incremental cost-effectiveness (utility) ratio; ICER**

The first indicator for assessing cost-effectiveness analysis is an incremental cost-effectiveness ratio (ICER), which gives an indication of additional costs that would be incurred for the intervention program of interest in order to save one additional unit of utility (one quality-adjusted life-year (QALY) is often used). The assessment of this indicator is highly dependent on how much a society is willing to pay (WTP), which is partly determined by the economic level attained by that society. Consequently, the threshold of WTP varies from country to country and indeed from individual to individual opinion. In a highly developed country like the USA, it has been set at USD 60,000 whereas it may be set at 20, 000 USD in a medium economically developed country and 10,000 USD or even lower in a low economically developed country. The ICER is therefore a relative rather than absolute value determined by relative cost and effectiveness in each setting in question. Also, due to variation in unit costs and health outcomes, for example from competing risks, the ICER obtained from one setting may not necessarily be applicable setting. It can, however, usually be interpreted in the light of the GNP of the country under consideration.

##### **(2) Acceptability of an intervention program by WTP**

The second indicator is a supplement to the first, providing an answer to the question: "What are the odds of being cost-effective for a new intervention or treatment compared with standard or existing method for different levels of WTP?" This indicator can help health policy-makers to make a decision in the face of a series of alternative choices in the light of the economic principle

“willingness to pay” and “ability to pay” because a spectrum of the chances of being cost-effective against different WTPs can be quantified, with an acceptability curve for decisions varying with different ceiling ratios.

### (3) Benefit-cost (B/C) ratio and difference

The third indicator is the ratio or the difference between benefit and cost when both are expressed in the same monetary scale. There are two approaches to translating effectiveness into monetary value by using the human capital approach which estimates the indirect costs of not providing the intervention, or the willingness to pay (WTP) method, both of which are well described in the classic textbooks of economic evaluation. The WTP can be estimated by asking the informant the following question “How much are you willing to pay for an x% mortality reduction in an area with y/100,000 incidence of breast cancer”. The scenario will be created by using a series of questions that are compared to basic intervention programs such as universal vaccination in order to enable the informant to make a reasonable estimate. A positive difference between net benefit and net cost or a Benefit/Cost (B/C) ratio larger than 1 indicates that early investment in intervention may have a return in later life which is considered worthwhile. In addition to its usefulness for the comparison between health intervention programs and other non-health programs, the B/C ratio and difference also provide a straightforward way of giving the individual user of resources a better understanding of the balance between early investment and later return for a specific intervention program.

#### **4. Probabilistic Economic Appraisal Model**

Information on each parameters listed in Table 6-2 is subject to uncertainty. The conventional deterministic method to deal with such uncertainty is to apply a series of one-way, two-way, and n-way sensitivity analyses to analyze influential parameters. A more recent approach is probabilistic, specifying each parameter's distribution. Table 6-2 lists the appropriate distributions for the corresponding parameters. The joint uncertainty of relevant parameters is displayed on a scatter plot of incremental cost against incremental effectiveness analysis, supplemented by an acceptability curve, plotting the probability of being cost-effective against a series of WTPs. A 3% discount rate was applied to give a reflection of different time horizons for early cost incurred but benefit gained later.

#### **5. An illustration with adjuvant therapy for early-detected breast cancer**

The intervention under consideration here is defined under the context of tertiary prevention. Suppose a new adjuvant therapy may be administered to early breast cancer (node negative) patients. We aim to address whether such a new therapy is cost-effective compared to conventional care. The scenario proposed in our manuscript is based on the meta-analysis of randomized trials of polychemotherapy (PolyCT). The target patient group for the comparison of PolyCT with no PolyCT is women with node negative breast cancer. Annual transition probabilities between states in each cycle were converted from the empirically observed cumulative risk of relapse and breast cancer death (BCD) during 15-year follow-up from the meta-analysis paper. The simulations were of a cohort of 30,000 patients free of relapse, which is close to the number of participants in the meta-analysis paper. Other cause death (OCD) rates were

estimated from US life table data. By using a Markov cycle tree (See figure 6-4), in the absence of therapy, after the first cycle, a patient free of disease has three possible further progressions, OCD, BCD and relapse. Thus there are four states in all (disease free, relapse, OCD, BCD). The two death states end the Markov cycle without any further progression. The initial state with relapse has two further transitions to OCD or BCD. The cycles following the four-state Markov model (See figure 6-3) were repeated until 15 complete cycles, BCD or OCD whichever occurred first.

For simulation of the outcomes with the intervention of PolyCT, the corresponding probabilities of relapse, metastases and BCD were multiplied by the estimated efficacy of PolyCT from the meta-analysis of randomized controlled trials.

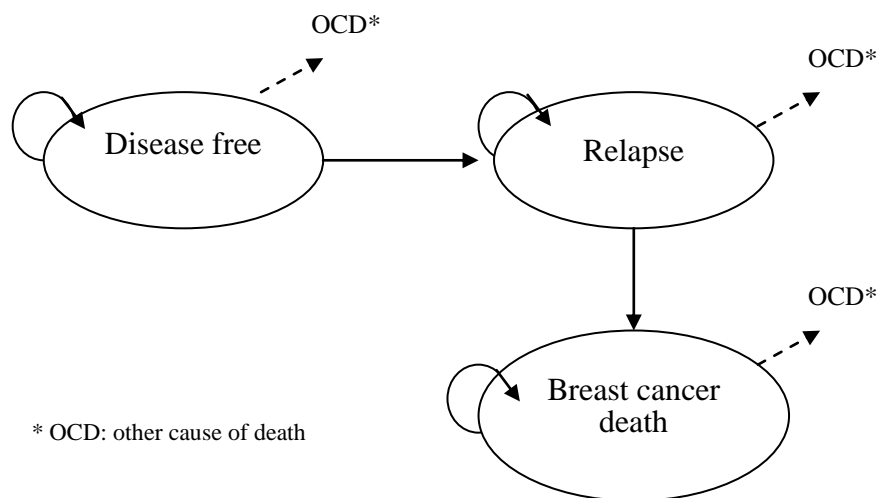
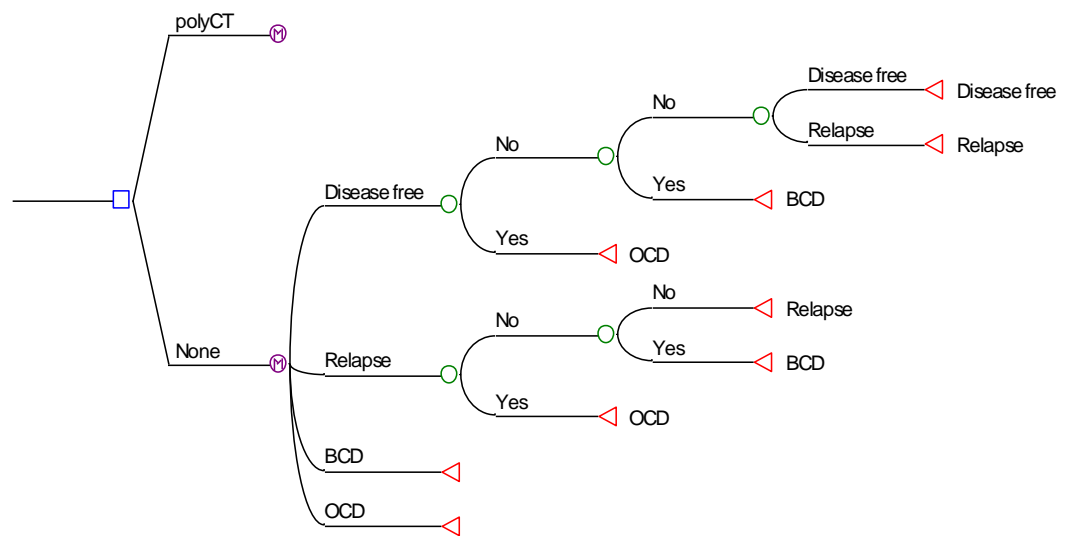


Figure 6-3 Four-state natural history of breast cancer treatment





BCD: Breast cancer death

OCD: Other causes death

Ⓜ: Represents a four-state Markov model (see right)

Figure 6-4 Markov cycle tree for the choice between adjuvant “PolyCT” vs. “None”

Table 6-2 Parameters used, values for base case and distributions for probabilistic approach, for the decision tree with comparison of PolyCT and no PolyCT

Variable	Base-case analysis	Distribution for probabilistic approach	Source
Relapse			
Hazard rate without adjuvant	0.038/year	Gamma(0.0481,1.2667)	13
Relative risk with PolyCT	0.77	Gamma(237.16,308)	13
Breast cancer death			13
Hazard rate without adjuvant	0.0123/year	Gamma(1.5129,123)	13
Relative risk with PolyCT	0.77	Gamma(237.16,308)	
Treatment Cost			
PolyCT	\$4676/yr	Triangular(3740.8,4676,5111.2)	19
Relapse	\$16200	Triangular(12960,16200,19440)	20
Follow up	\$700/yr	Triangular(560,700,840)	21
End stage before dying from breast	\$40000	Triangular(32000,40000,48000)	Assumption
Utility			
Disease free	0.97	Beta(97,3)	22
Disease free after relapse	0.92	Beta(92,8)	22
Relapse	0.82	Beta(82,18)	23
End stage in the year dying from BC	0.58	Beta(58,42)	23
Discount Rate	3%		

Table 6-3 shows base-case estimates, relevant distributions, and sources of estimates. In the light of uncertainty of parameters mentioned above, we sampled 1000 times based on distributions assigned to each parameter with Monte Carlo simulation. Costs were assigned with the triangular distribution with the most likely value from the literature and a 20% range for the likely maximum and minimum.

We therefore assumed that the transition rates following different Gamma distributions with shape and scale parameters converted from their means and SEs, estimated from the meta-analysis . Gamma distributions were similarly assigned to relative risks of relapse and breast cancer death. The treatment cost for PolyCT, relapse, and follow up followed triangular distributions with parameters from other studies. The utilities of the four states

were assigned by Beta distributions with parameters determined by previous studies. A 3% discount rate was applied.

Table 6-3 shows the simulated results based on base-case estimates for cost, effectiveness, and ICER. This suggests an additional 41,155 USD would be invested in order to gain an additional unit of QALY.

Table 6-3 Results of cost-utility analysis for the comparison between adjuvant PolyCT and no PolyCT based on a cohort of 30,000 patients

Strategy	Cost*	Effectiveness**	C/E	ICER
None	379.756	153,860	2,468.19	-
PolyCT	539.436	157,740	3,419.79	41,155

\* in Million US dollars

\*\* Quality adjusted person-year

Figure 6-5 displays the scatter plot of ICER, with lines of different WTP figures marked. The probability of being cost-effective decreased with the threshold of WTP from 32% for USD 60,000, 8% for USD 20,000 to 7% for USD 10,000.

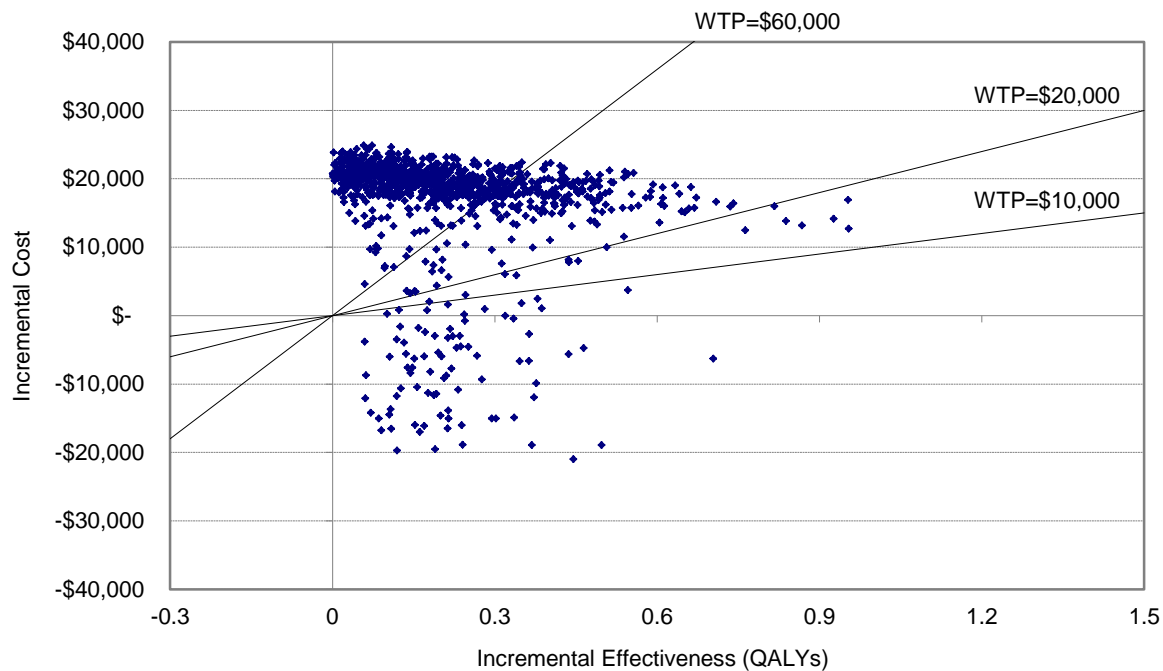


Figure 6-5 Incremental cost-utility scatter plot for PolyCT. The Probability of being cost-effective or domination for PolyCT with WTP as \$10,000, \$20,000, and \$60,000 were 8.2%, 9.7%, and 31.2%, respectively.

From the acceptability curve, it is clearly seen that the probability of being cost-effective increased from 32% for USD 60,000 to 48% for USD 100,000 and up to 90% for USD 420,000 (Figure 6-6).

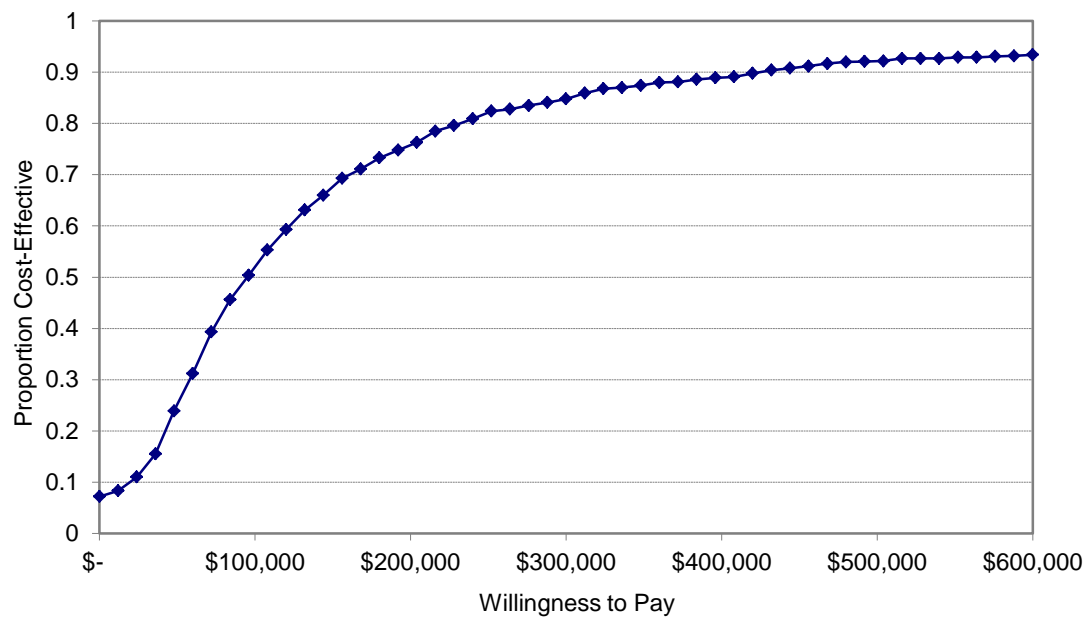


Figure 6-6 Acceptability curve of the cost-utility analysis for PolyCT vs none

