# EFFICACY OF BREAST-CANCER SCREENING FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES: TAIWAN MULTICENTRE CANCER SCREENING (TAMCAS)

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Although the efficacy of mass screening for breast cancer has been established in Western countries, this strategy may be too costly for other countries with low incidence rates of breast cancer. We propose an alternative approach to screen female relatives of breast-cancer-index cases from hospitals, as part of the Taiwan multicentre cancer screening (TAMCAS) project. In order to assess the efficacy of this programme, and to estimate how often this high-risk group should be screened, we firstly elucidated the disease natural history from the pre-clinical screen-detectable phase (PCDP) by estimating the relevant parameters based on Markov chain models. We further predicted the proportion of interval cancers, advanced breast tumours and deaths from breast cancers by different screening frequencies. Results showed that the estimate of mean sojourn time (MST) for this high-risk group (1.9 years; 95% CI.1.18-4.86) is shorter than that for females from the general population. Analysis of a surrogate endpoint based on regional lymph-node spread and tumour size shows that annual screening for this high-risk group is likely to confer a significant 33% reduction in breast-cancer mortality compared with a non-significant 25 and 20% reduction for 2 yearly and 3-yearly screening regimes respectively. The above results suggest that a 1-year interval might be appropriate for this high-risk group. A simple cost-effectiveness analysis indicates a cost per year of life saved for mass screening (\$72,480) 15 times that for the high-risk group (\$4,851). Int. J. Cancer 78:21-26, 1998.

While mass screening for breast cancer using mammography has demonstrated a 30% reduction in breast-cancer mortality in West-ern countries (Shapiro *et al.*, 1971, 1982; Tabar *et al.*, 1985; Nystrom *et al.*, 1993), one concern is whether such mass breast-cancer screening can be applied to other countries with intermediate or low incidence rates of breast cancer. The application of mass breast screening to these areas might be costly, due to low disease frequency. To overcome this problem, screening of high-risk groups, *e.g.*, women with family history of breast cancer, might be considered as an alternative approach, in order to achieve the benefit of breast screening in an efficient way.

The efficacy of breast-cancer screening in a high-risk group in intermediate- or low-incidence areas has, to our knowledge, been rarely reported. The main reason might be that it is difficult to define or identify such a high-risk group, also, to offer screening to the group. In this study, we defined a high-risk group for breast cancer by recruiting female relatives of breast-cancer-index cases from hospitals. Screening for this high-risk group might be cost-effective, since the incidence rate for this group will be higher than that for females from the general population. Research has shown that women whose mother and sisters suffered from breast cancers are more likely to get breast cancers than those whose mother and sisters did not (Adami et al., 1980; Bain et al., 1980; Lubin et al., 1982; Brinton et al., 1982; Roseman et al., 1990). This is true particularly for young women. For example, there was a 3- to 8-fold risk of suffering from breast cancer for women aged 30 to 40 years who had a family history of breast cancer, compared with women without a family history. The corresponding risk for

women aged over 50 and older was only double (Bain et al., 1980; Lubin et al., 1982; Brinton et al., 1982; Ottman et al., 1986; Negri et al., 1988; Roseman et al., 1990; Calle et al., 1993).

Once the target population is selected, the next question is how often they should be screened. It is well known that the efficacy of breast-cancer screening is affected by the inter-screening interval, and the determination of this interval should be dependent on the natural history of breast cancer in the target population. For example, a smaller benefit from screening women aged under 50 years than for those aged over 50 was found to be due to a shorter sojourn time (duration of pre-clinical screen-detectable phase, PCDP) in the younger age group (Duffy et al., 1996). Accordingly, Tabar et al. (1995) suggested that women aged 40 to 49 years might be screened at annual intervals, whereas a 2- or 3-yearly screening regime might be sufficient for women aged 50 years or older. It is postulated that the natural history for a high-risk group might be different from that for females from the general population. To set up an optimal breast-cancer-screening policy, it is important to elucidate the natural history of breast cancer in this high-risk group.

Estimating the natural history of the progression of breast tumours from disease-free, to the PCDP, clinical phase and finally to potential death is by no means straightforward in that the transition from no disease to the PCDP is unobservable and if a disease in the PCDP by screening further progression is interrupted due to treatment. To tackle this issue, Markov chain models have been applied to estimate transition rates based on prevalent cases (cancers diagnosed at first screen), incident screen-detected cases (cancers diagnosed at later screens) and interval cancers (cancers diagnosed between screens) (Duffy et al., 1995). It has been shown that the occurrence of interval cancers was an important index for early assessment of the efficacy of breast-cancer screening (Tabar et al., 1987). A high ratio of interval cancers as a percentage of the unscreened incidence rate represents either rapid progression of breast tumours or poor sensitivity of the screening method. Although the majority of interval cancers from randomized trials or non-randomized programmes in Western Europe are comprehensively collected, the ascertainment of interval cancers might be difficult for developing countries, where the cancer registry systems are incomplete or suffer from under-reporting. It is necessary to adapt previous Markov chain models to estimate predicted interval cancers whereby the interim analysis for the efficacy of breast-cancer screening for female relatives of breast-cancer-index cases can be performed. The proposed left-censored and intervalcensored Markov chain models allow one to estimate the mean

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sojourn time (MST), albeit with low precision, without relying on interval cancer data (data not shown).

Another obstacle to assessing the efficacy of breast-cancer screening for this high-risk group is that if the primary endpoint for evaluation is mortality, the required long-term follow-up will not only incur high costs and take a considerable time, but will also have attrition problems. An alternative is to use appropriate surrogate endpoints to evaluate the efficacy of breast-cancer screening. The advantages of using surrogate endpoints are as follows: (1) the required sample size or the duration of follow-up is reduced; (2) evaluation based on surrogate endpoints is not confounded by treatment, which will affect the survival of breast-cancer cases; (3) the problem of attrition for long-term follow-up will be avoided.

However, a major caveat of using a surrogate endpoint is the question of whether it is a valid proxy for the primary endpoint, as determined by the criteria of Prentice (1990) and Freedman *et al.* (1992). It should be noted that regional lymph-node spread and tumour size have been demonstrated as valid surrogate endpoints by Tabar *et al.* (1995). We therefore consider using these surrogate endpoints to evaluate the efficacy of screening female relatives of breast-cancer-index cases.

The aims of this study were to (1) estimate the pre-clinical incidence rate and mean sojourn time (MST) for female relatives of breast-cancer-index cases; (2) estimate progression rates from the PCDP to the clinical phase taking regional lymph-node spread and tumour size into consideration; (3) estimate number of predicted interval cancer cases by different screening frequencies based on (1); (4) estimate number of predicted breast tumours with poor prognosis from tumour attributes by different screening frequencies based on (2); (5) predict mortality reductions by different screening frequencies based on known survival information and (1) to (4); (6) assess whether screening for female relatives of breast-cancerindex cases is more cost-effective than that for females from the general population; (7) suggest an optimal screening interval for this high-risk group.

### MATERIAL AND METHODS

Data used in this study are from a programme entitled the Taiwan Multicentre Cancer Screening (TAMCAS) for hepatocellular, colorectal and breast cancers launched by the Department of Health (DOH) in Taiwan in 1992. This is a hospital-based "high-risk" approach to identifying early cancers via different screening methods for hepatocellular, colorectal and breast cancers. There are 17 hospitals involved in this study, including medical centres and regional hospitals. Subjects who met the criteria of the high-risk group for each cancer were invited to screening between 1992 and 1997. For administrative reasons, dates for the commencement of screening for the 3 cancers are different.

The breast-cancer screening programme is aimed at female relatives (including mothers, daughter, sisters, grandmothers) of breast-cancer cases. Since 1994, relatives aged over 35 years have been invited to annual screening by a combination of physical examination, mammography and ultrasound. Those with positive results for all 3 screening methods were further confirmed by histological biopsy. Up to December 31, 1996, a total of 2,629 women with a family history of breast cancer have been recruited and received their first screening. Among the 2,629, only 575 attended the second screening. Information on tumour attributes such as regional lymph-node spread and tumour size (verified by mammography and ultrasound) were also ascertained. There were 31 and 3 breast cancers confirmed at first and second screening respectively. Table I shows number of breast-cancer cases and transition history at first screen and second screen.

A 3-state Markov chain model adapted to left-censored cases (first screen) and interval-censored cases (second screen) was applied to estimate the mean sojourn time (MST) and to predict the

**TABLE I** – NUMBER OF BREAST-CANCER CASES AND TRANSITION HISTORY BY FIRST AND SECOND SCREEN, TAMCAS PROGRAMME

	Number	Transition history
Prevalent screen		
Negative cases	2,598	(no disease → no disease, age at
D	21	first screen)
Breast-cancer cases	31	(no disease → pre-clinical, age at first screen)
Second screen		mst sereen)
Negative cases	572	(no disease → no disease, 1-year
		screening interval)
Breast-cancer cases	3	(no disease → pre-clinical, 1-year
		screening interval)

RLN, regional lymph-node spread; TS, tumour size.

FIGURE 1 – A progressive model of breast cancer for regional lymph-node spread or tumour size ( $\geq 2$  cm, < 2 cm).

proportion of interval cancers among total cancers (screen-detected + interval cancers) by different screening frequencies. In order to predict the proportion of breast tumours with regional lymph-node spread by different screening frequencies, a 5-state Markov chain model in conjunction with a known proportion of clinical cases without lymph-node spread or tumour size smaller than 2 cm in diameter was proposed to estimate transition rates within pre-clinical phase or from pre-clinical to clinical phase (Fig. 1). The 5-state Makov chain model used in this study was similar to that of Chen *et al.* (1997). Estimation of parameters was based on a non-linear-regression procedure, which means that our estimates were from a series of generalized estimating equations (Duffy *et al.*, 1995). The 95% confidence intervals (CI) were calculated according to an asymptotic method (Gallant, 1987).

In order to examine whether the pre-clinical incidence rate for this high-risk group was higher than that for females from the general population, we compared the former estimate with the latter, reported in 1994 from the Taiwan cancer registry, which was set up in 1979.

Prediction of deaths from breast cancer by different screening frequencies can be calculated by applying death rates from the study by Tabar *et al.* (1995) to breast tumours by regional lymph-node status or tumour size predicted by the 5-state Markov chain models. Variance for surrogate endpoints is calculated by the method of Day and Duffy (1996).

## RESULTS

# Parameter estimation

Table II shows the estimate of the pre-clinical incidence rate for female relatives of breast-cancer index cases to be 0.0057 (95% CI, 0.0026–0.0088), which is 34 times the breast-cancer incidence rate for the general female population (18.42 per 100,000) reported from the cancer registry in 1994. Reasons for this will be discussed below. The estimate of MST is 1.90 (95% CI, 1.18–4.86) years. Compared with 3.3 years estimated from the Swedish Two-County trial (Tabar *et al.*, 1995) the present estimate suggests that MST for this high-risk group is shorter than that for females from the general population.

Frequency of regional lymph-node spread and tumour size for those screen-detected cases are shown in Table III. The proportion of breast tumours without regional lymph-node spread was 67.9%,

TABLE II – ESTIMATED PARAMETERS FOR PRE-CLINICAL INCIDENCE RATE AND MEAN SOJOURN TIME (MST) BASED ON BREAST-CANCER SCREENING FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES,

TAMCAS PROGRAMME

Parameters	Estimates	95% CI <sup>1</sup>
Pre-clinical incidence	0.0057	$0.0026 \sim 0.0088$
MST	1.9048	$1.1844 \sim 4.8614$

<sup>&</sup>lt;sup>1</sup>According to asymptotic method (Gallant, 1987).

TABLE III – FREQUENCY OF SCREEN-DETECTED BREAST CANCERS FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES BY REGIONAL LYMPH-NODE SPREAD AND TUMOUR SIZE, TAMCAS PROGRAMME

Tumour attributes	Numbers <sup>1</sup>	%
Regional lymph-node spread		
+	9	32.1
_	19	67.9
Tumour size		
≥2 cm	11	40.7
<2 cm	16	59.3

<sup>1</sup>There are 6 and 7 missing cases for regional lymph-node spread and tumour size respectively.

**TABLE IV** – ESTIMATES OF MST FOR REGIONAL LYMPH-NODE SPREAD AND TUMOUR SIZE FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES. TAMCAS PROGRAMME

Tumour attributes and estimated parameters	Estimates	95% CI
Regional lymph-node spread MST for transition from pre- clinical N(−) → clinical N(−)	2.96 years	2.30–4.58 years
MST for transition from pre- clinical N(+) $\rightarrow$ clinical N(+)	0.90 years	0.64–1.14 years
Tumour size		
MST for transition from pre- clinical < 2 cm → clinical < 2 cm	2.73 years	2.12–4.27 years
MST for transition from pre- clinical $\geq 2 \text{ cm} \rightarrow$ clinical $\geq 2 \text{ cm}$	1.11 years	0.64–4.07 years

while 59.3% of breast tumours diagnosed by mammography were smaller than 2 cm in diameter. The corresponding figures on regional lymph-node spread and tumour size for screen-detected cases from the Swedish Two-County Trial are 70.1% and 66.7% respectively. A slightly smaller proportion of small or node negative tumours observed in this study might suggest that progression of breast tumours from the PCDP to the clinical phase for this high-risk group is more rapid than that for the general population. These findings are consistent with the above estimates of MST.

Table IV shows estimates of MST making allowance for regional lymph-node spread and tumour size. The estimate of MST for breast tumours without regional lymph-node spread is 2.96 (95% CI, 2.30–4.58) years. The corresponding figure for breast tumours with regional lymph-node spread is 0.90 (95% CI, 0.64–1.14) years. A similar result is found for tumour size.

Prediction of interval cancers, advanced breast cancers (including regional lymph-node spread and tumour size larger than 2 cm) and deaths from breast cancer by different screening frequencies

A simulated result on predicted interval cancers by different screening regimes. Based on the estimated parameters from Table II, a simulation was performed to calculate predicted interval cancers by annual, 2-yearly and 3-yearly screening regimes.

TABLE V – PREDICTED PREVALENT CASES, INCIDENT SCREEN-DETECTED CASES AND INTERVAL CANCERS BY ANNUAL, 2-YEARLY AND 3-YEARLY SCREENING REGIMES FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES, TAMCAS PROGRAMME

Screening regime	Year	Prevalent cases	Incident screen- detected cases (A)	Interval cancers (B)	$\frac{\text{(B)}}{\text{(A)} + \text{(B)}} \times 100\%$
Annual	0	28.5			22.8
	1		11.5	3.3	
	2		11.4	3.3	
	3		11.3	3.2	
			11.2	3.2	
	4 5		11.2	3.2	
	6		11.1	3.3	
Total	_	28.5	67.7	19.5	
Two-yearly	0	28.5			38.3
	2		18.2	11.2	
	4		17.9	11.1	
	6		17.6	10.9	
Total		28.5	53.7	33.2	
Three-yearly	0	28.5			50.0
, ,	3		22.0	21.9	
	6		21.4	21.4	
Total		28.5	43.4	43.3	
Control		27.6	_	88.4	

Assuming a total of 2,629 female relatives of breast-cancers-index cases were invited to screening for 6 years, the predicted interval cancers by 3 screening regimes were calculated as shown in Table V. The bottom panel lists predicted cancers for an equal number of a comparable female population not invited to screening. This hypothetical control group was assumed to receive one-shot screening at the end of the study, *i.e.*, at the end of 6 years of screening of the screened group. There are 2 types of breast cancer in this control group, those surfacing to clinical phase, and breast cancers detected at the first screen at the end of the 6 years. The proportion of interval cancers among all cancers increases from 23% for annual screening to 50% for a 3-yearly screening regime. This suggests that if the screening interval is longer than 3 years the majority of cases will come to clinical phase, and there is therefore small benefit from screening.

A simulated result for the effect of screening interval on the proportion of regional lymph-node spread or tumour size larger than 2 cm in diameter. To assess the proportion of advanced breast cancers by different screening frequencies, a similar simulation was performed to calculate predicted numbers of breast cancers by regional lymph-node spread or tumour size. Results from Tables VI and VII show that a long screening interval will lead to an increase in the proportion of breast tumours with regional lymph-node spread as well as tumour size larger than 2 cm in diameter. It should be noted that the proportion with regional lymph-node spread for the control group is 48%, which is slightly higher than that for the control group from the Swedish Two-County Trial (40%) (Tabar et al., 1995). The prevented fraction of regional lymph-node spread due to screening was 62% (95% CI, 36–77), 46% (95% CI, 16–66) and 36% (95% CI, 2–58) for annual vs. control group, 2-yearly vs. control, and 3-yearly vs. control. The corresponding figures for tumour size larger than 2 cm are 56% (95% CI, 31–72), 40% (95% CI, 9-60) and 30% (95% CI, 0-53). It should be noted that changing the screening interval from 3 years to 1 year leads to 40% (95% CI, 0-65) and 38% (95% CI, 0-77) reductions of nodal involvement and tumour size larger than 2 cm respectively.

Predicted mortality by different screening frequencies based on surrogate endpoints such as regional lymph-node spread and tumour size. Assuming that 10-year death rates for breast tumour with and without regional lymph-node spread are 50% and 14% respectively from the Two-County Trial, and applying these death rates to predicted numbers of breast tumours, as shown in Table VIII, gives predicted deaths from breast cancers by different

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TABLE VI – PREDICTED PREVALENT CASES, INCIDENT SCREEN-DETECTED CASES AND INTERVAL CANCERS BY REGIONAL LYMPH-NODE STATUS FOR ANNUAL, 2-YEARLY AND 3-YEARLY SCREENING REGIMES, IN FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES, TAMCAS PROGRAMME

Screening regime	Year	Preva			een-	or clir	cancers nically 1 cases	Regional (%) Positive
		LN-	LN+	LN-	$LN^+$	LN-	LN+	rositive
Annual	0	20.4	7.2					18.25
	ĩ			10.5	1.6	2.0	0.7	
	2			10.4	1.6	2.0	0.7	
	3			10.3	1.6	2.0	0.7	
	4			10.3	1.6	2.0	0.7	
	5			10.2	1.6	1.9	0.7	
	6			10.2	1.6	1.9	0.7	
Total		20.4	7.2	61.9	9.6	11.8	4.2	
Two-yearly	0	20.4	7.2					25.65
	2			15.4	3.8	6.4	3.7	
	4			15.3	3.7	6.3	3.7	
	6			15.1	3.7	6.3	3.6	
Total		20.4	7.2	45.8	11.2	19.0	11.0	
Three-yearly	0	20.4	7.2					30.63
	3			17.8	5.3	12.0	8.8	
	6			17.5	5.2	11.8	8.6	
Total		20.4	7.2	35.3	10.5	23.8	17.4	
Control		19.7	7.0	_	_	40.6	47.6	47.52

TABLE VII – PREDICTED PREVALENT CASES, INCIDENT SCREEN-DETECTED CASES AND INTERVAL CANCERS BY TUMOUR SIZE FOR ANNUAL, 2-YEARLY, AND 3-YEARLY SCREENING REGIMES IN FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES. TAMCAS PROGRAMME

Screening Yes		Prevalence cases		Screening- detected cases		Interval cancers		≥2 cm
regime		<2 cm	≥2 cm	<2 cm	≥2 cm	<2 cm	≥2 cm	(%)
Annual	0	16.8	9.8					23.39
	1			9.8	2.2	2.0	0.7	
	2			9.7	2.2	2.0	0.7	
	2			9.7	2.1	2.0	0.7	
	4 5			9.6	2.1	2.0	0.7	
	5			9.6	2.1	2.0	0.7	
	6			9.5	2.1	2.0	0.7	
Total		16.8	9.8	57.9	12.8	12.0	4.2	
Two-yearly	0	16.8	9.8					32.51
	2			13.8	5.1	6.4	4.0	
	4			13.6	5.1	6.4	4.0	
	6			13.5	5.0	6.3	4.0	
Total		16.8	9.8	40.9	15.2	19.1	12.0	
Three-yearly	0	16.8	9.8					37.83
	3			15.3	7.1	11.7	9.6	
	6			15.1	7.0	11.6	9.4	
Total		16.8	9.8	30.4	14.1	23.3	19.0	
Control		16.2	9.4	_	_	36.3	51.9	53.87

screening frequencies. Table VIII also shows predicted relative mortality and 95% CI by different screening regimes *vs.* control group. Based on regional lymph-node spread, annual, 2-yearly and 3-yearly screening regimes are expected to reduce the number of deaths from breast cancer by 33%, 25% and 20% respectively. Based on death rates by tumour size, the corresponding figures for the prevention of deaths from breast cancer are 33%, 24% and 18%.

### DISCUSSION

There are 3 major findings in this study. First, from analysis of surrogate endpoints, 33% reduction in breast-cancer mortality is predicted for an annual screening regime for female relatives of breast-cancer-index cases. Moreover, the annual screening regime is expected to prevent 62% and 56% of breast tumours with regional lymph-node spread or tumor size larger than 2 cm respectively. Such a benefit is in agreement with the efficacy of

TABLE VIII – PREDICTED DEATHS FROM BREAST CANCERS BASED ON SURROGATE ENDPOINT ANALYSIS FOR ANNUAL, 2-YEARLY AND 3-YEARLY SCREENING REGIMES, FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES, TAMCAS PROGRAMME

Tumour attributes and screening regime	Predicted deaths	Predicted relative mortality	95% CI
Regional lymph-node involvement			
Control	36.17	1.00	
Annual	24.11	0.67	0.49 - 0.90
Two-yearly	27.06	0.75	0.55 - 1.01
Three-yearly	29.11	0.80	0.59 - 1.09
Tumour size			
Control	33.58	1.00	
Annual	22.33	0.67	0.49 - 0.90
Two-yearly	25.68	0.76	0.56 - 1.04
Three-yearly	27.55	0.82	0.61-1.11

breast-cancer screening demonstrated by population-based randomized trials for women aged over 50 years (Shapiro *et al.*, 1971; Tabar *et al.*, 1985). It should be noted, however, that the screening interval for this high-risk group in this study is shorter than that for females from the general population. This suggests that, to achieve a benefit of breast-cancer screening similar to that observed in the general population, more frequent screening is required for this high-risk group, which appears to be subject to more rapid progression of breast tumours, as also indicated by the shorter MST found in this study.

Second, from the theoretical aspect of breast cancer screening, the present study assists in understanding the natural history of breast cancer in female relatives of breast-cancer-index cases, rather than in the general female population. The progression rate from the PCDP to the clinical phase for this high-risk group is more rapid than that for females from the general population, since a 1.9-year estimate of MST in our study is shorter than the 3.3 years for women aged 40 to 74 years in the Two-County study. It should be noted that estimated MST for women in this study is close to that for women aged 40 to 49 years, who have a shorter MST than women aged 50 to 74 years (Tabar et al., 1995). The proportions of regional lymph-node spread and large tumours for the high-risk group in this study are also similar to those for women aged 40 to 49 years but slightly larger than for women aged 50 to 74 years. Since a 1-year screening interval for women aged 40 to 49 was suggested in the Two-County Trial, due to rapid progression from PCDP to clinical phase and a larger proportion of breast tumours with regional lymph-node spread or more than 2 cm in diameter, a 1-year screening regime might be justified on the same grounds for the high-risk group in our study.

Since the efficacy of breast-cancer screening is highly dependent on the screening interval, it is important to propose a suitable interval for this high-risk group. To do this, we examined 2 early indicators developed by Day et al. (1989) for the evaluation of breast-cancer screening: (i) at least 25% reduction of mortality 10 years after starting the programme; and (ii) a rate of interval cancers no more than 25% of the expected incidence in the absence of screening in the first 2 years after a negative test. Table VIII shows that only annual screening can predict more than a 25% reduction in mortality, and results are significant. Approximately 25% and 20% mortality reduction is expected from 2-yearly and 3-yearly screening regimes respectively; however, neither reached statistical significance. To examine the criteria for the rate of interval cancers, we calculate the predicted incidence rate of interval cancers as a percentage of expected incidence rate in the absence of screening in the first 2 years after a negative test. Here we assume the expected incidence to be 0.0057 per year, which is equal to the pre-clinical incidence estimated from a 3-state Markov chain model (Table II). The predicted incidence rates of interval cancers as a percentage of the expected incidence for annual, 2-yearly and 3-yearly screening regimes are 22.3%, 37.9% and 98.8% respectively. In the light of both criteria, a 1-year screening interval is recommended for this high-risk group.

Third, the present study demonstrates evaluation of the effect of breast-cancer screening in a high-risk group (second-degree female relatives of breast-cancers-index cases from hospitals). From the practical point of view, the implication for such results is of paramount importance in intermediate- or low-incidence-rate areas, since such a high-risk approach may be considerably more cost-effective than mass screening. This postulate is supported by the fact that the pre-clinical incidence rate estimated in this study for the high-risk group is approximately 34 times the incidence rate of breast cancer, albeit probably under-estimated, reported from the cancer registry for females from the general population. A high incidence rate for this high-risk group is explained partly because women with a family history of breast cancer are at increased risk of breast cancer, and partly because selective factors inherited from a hospital-based design prompt those who feel themselves to be at potentially high risk of breast cancer to seek screening or examination in some special hospitals. It is also likely, for the same reasons, that interval cancer ascertainment cannot be relied on, since the underlying population incidence is an under-estimate. Also, those at high risk tend to be relatively young, since relatives also presented with breast cancer at an early age (73.5% of cases in this study presented below the age of 50 years). For such cases, the relative incidence might be expected to be 3 to 8 times the

TABLE IX – PROBABILITIES AND UNIT COSTS OF PRIMARY TREATMENT AND ADJUVANT THERAPY FOR BREAST CANCER

Surgical treatment	Adjuvant	\$	Probabilities
Mastectomy	None	4,000	46.66%
,	+Chemotherapy	5,651	0.86%
	+Radiotherapy	5,532	30.38%
Breast-conserving surgery	None	2,000	15.02%
	+Chemotherapy	4,804	0.10%
	+Radiotherapy	3,568	5.70%
None	Chemotherapy	2,000	0.30%
	None		1.01%

total-population incidence. Even so, there may still be an unexpected excess in this group, probably due to a sub-group of the screen-detected tumours already being symptomatic. If we perform the MST estimation using the node-negative tumours only (*i.e.*, assuming that all the node-positive were in the clinical phase), we obtain an MST estimate of 2.96 years, which is less than 3.3 years. This nevertheless suggests that a shorter screening interval should be required for this high-risk group.

To demonstrate whether this high-risk-group approach is costeffective, we performed a simple cost-effectiveness analysis, comparing costs per year of life saved of a high-risk-group approach and a mass screening programme. We assumed only 2 rounds of screening with a 1-year interval offered to the high-risk group (female relatives of breast-cancer-index cases) and to females from the general population. Each group consisted of 10,000 subjects aged 35 years and more. We also assumed that the compliance rate was 100% and that the sensitivity and specificity of the screening method (a combination of physical examination, mammography and ultrasound examination) were both 100%. For the disease, we applied the parameters in Table II to calculate predicted screen-detected cases and interval cancers for the highrisk group. The corresponding figures calculated for females in the general population were based on the pre-clinical incidence rate, 0.00018, from the Taiwan cancer registry and 3 years of MST from the Swedish Two-County Trial. The case-fatality rate without screening is 37%, based on the control group from the Swedish Two-County Trial. The efficacy of screening is assumed to be 33.3% reduction in death from breast cancer, an estimate of annual screening at the present study. Average life expectancy for women aged 35 years or older is approximately 21.38 years, projected from vital statistics in Taiwan. Costs considered here include direct cost of screening, treatment cost and terminal-care costs attributable to deaths from breast cancer. Table IX lists costs for treatment and adjuvant therapy and their probabilities. It should be noted that the probabilities of treatment and adjuvant therapy are based on the data for W-county in the Swedish Two-County Trial (Tabar et al., 1995). Table X lists results for years of life saved and costs. Clearly,

TABLE X - COST-EFFECTIVENESS ANALYSIS FOR MASS SCREENING AND HIGH-RISK-GROUP SCREENING<sup>1</sup>

Parameters	High-risk group	Mass screening
Transition rate		
no disease $\rightarrow$ PCDP	0.0057	0.00018
$PCDP \rightarrow clinical phase$	0.5250	0.30300
Predicted cancers		
first screen	108	6
second screen	44	2 1
interval cancers	12	1
Total	164	9
Lives saved	$164 \times 0.37$ (case fatality) $\times 0.33$	$9 \times 0.37$ (case fatality) $\times 0.33$
	(efficacy of screening) = 20.21	(efficacy of screening) = 1.11
Years of life saved	$20.21 \times 21.38$ (average life	$1.11 \times 21.38$ (average life
	expectancy) = 432.09 years	expectancy) = 23.73 years
Terminal-care cost saved	$$20,000 \times 20.21 = 404,200$	$$20,000 \times 1.1 = 22,000$
Physical examination + mammography + ultrasound		
first screen	$$85 \times 10,000 = 850,000$	$$85 \times 10,000 = 850,000$
second screen	$$85 \times 9,880 = 839,800$	$$85 \times 9{,}993 = 849{,}405$
Biopsy		
first	$$900 \times 108 = 97,200$	$$900 \times 6 = 5,400$
second	$$900 \times 44 = 39,600$	$$900 \times 2 = 1,800$
Total	$$900 \times 152 = 136,800$	$$900 \times 8 = 7,200$
Cost of treatment and adjuvant therapy		
first	\$443,902	\$23,563
second	\$180,849	\$7,854
interval	\$49,322	\$3,927
Total	\$674,073	\$35,344
Net cost	\$2,096,473	\$1,717,775
Cost per year of life saved	\$4851	\$72,480

<sup>&</sup>lt;sup>1</sup>For N = 10,000 assuming 100% attendance rate, sensitivity and specificity.

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an annual screening regime over 2 years, with the high-risk-group approach, leads to 432.09 life years saved per 10,000 women screened, compared with 23.73 for mass screening. In terms of cost-effectiveness ratio, cost per year of life saved for mass screening (\$72,480) is 15 times that for the high-risk group (\$4,851). Allowing for the discount rate (5%), the corresponding costs per year of life gained by the high-risk-group approach and by mass screening were \$7,196 and \$106,806 respectively. This suggests that a high-risk-group approach, as used in this study, is more cost-effective than a mass-screening programme for a country with low to intermediate incidence. It should be borne in mind that the difference may be smaller, due to the self-selection mentioned above.

Our study predicts a 33% reduction in breast-cancer mortality by annual breast-cancer screening for female relatives of breast-cancer-index cases. Such efficacy, and a more rapid progression from PCDP to clinical phase found in this study, suggest that a 1-year screening interval is appropriate for this high-risk group. From a practical aspect, breast-cancer screening based on our proposed high-risk-group approach is more cost-effective than mass screening for countries with intermediate or low incidence rates of breast cancer, and such an approach may be applied in other countries where the breast-cancer-incidence rate is intermediate or low.

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