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Multiple Detection Modalities and Disease Natural History of Breast Cancer

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Abstract and Objective

Multiple detection modalities have increasingly gained attention in population-based screening. However, the disease natural history and its efficacy have been barely addressed. We reviewed a series of articles addressing multiple detection modalities including mammography, ultrasound and magnetic resonance image between 1995 and 2005. A stochastic model was developed to estimate transition parameters pertaining to the disease natural history defined by multiple detection modalities. The effectiveness of the combination of ultrasound or magnetic resonance image (MRI) with mammography was projected using a series of computer simulation models.

The results indicated that multiple detection modalities may lead to reduced mortality. However, the benefit and the selection of detection modalities are affected by biological factors including age, breast tissue type and histological type. In addition, other social factors may also affect the utilization of multiple detection modalities.

Keywords:

stochastic model, screening, breast cancer, modality

Introduction

In Asian countries, mammography has been recommended for the early detection of breast cancers because the incidence of breast cancer has been increasing rapidly. As the occurrence of breast cancer in most Asian countries peaks at around 40-49 years, population-based breast cancer screening using mammography became controversial. This was due to the fact that mammography screening in women aged 40-49 years is less beneficial than expected in older women, and some of the associated harm is more frequent in this age group.

Recently, a series of new technologies have been used as adjunct diagnostic methods to mammography or have been proposed as possible screening tests for younger women. These include ultrasound, digital mammography and magnetic resonance image (MRI). However, as concluded in two review papers, new screening modalities are unlikely to replace mammography for screening the general population given current evidence. Therefore, they suggest that large randomized controlled trials should be conducted by comparing two or more screening tests. However, the empirical results from a larger randomized trial require long-term follow-up and enormous costs. It is timely to have a better understanding of the appropriateness and role of these new technologies in screening for the general population. The current study aimed to develop a stochastic model to describe the disease natural history for breast cancer by using different time points and screening tools based on the sensitivity of multiple modalities. Based on the estimated results, the effectiveness of the combination of ultrasound or MRI with mammography is projected using a series of computer simulation models.

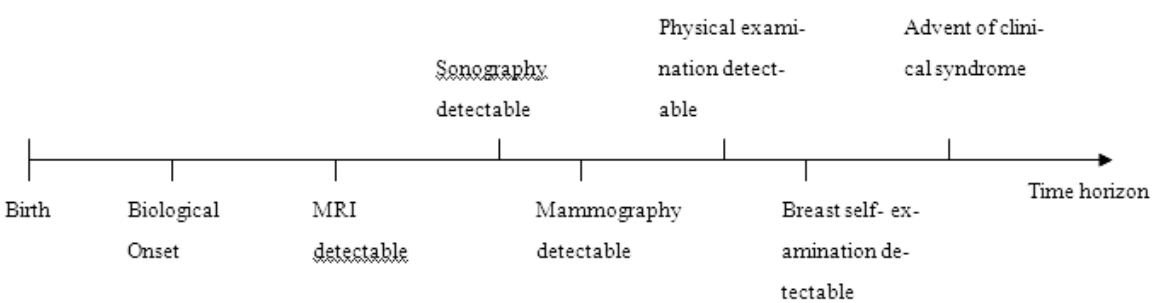

Figure 1 - Natural history of breast cancer defined by detection modalities

Methods

We reviewed a series of articles addressing multiple detection modalities for breast cancer including mammography, ultrasound and magnetic resonance image between 1995 and 2005 to obtain the performance of screening tools in terms of sensitivity and specificity. Different screening tools can detect breast cancer at different time points according to their ability to detect small or early stage breast cancer. The stochastic model to describe the progression from biological onset to the earliest detectable time point of the best screening tool, and the progress between detectable time points and between different screening tools is described below.

Estimation of transition parameters relating to disease progression with multiple detection modalities

A special case with known order of the performance of screening tools

The three available screening tools and the order of the time points with earliest detectable capability are MRI, ultrasound (US), and mammography (MA) as suggested in Figure 1. Let us treat MRI as gold standard; that is, the sensitivity of MRI is assumed to be unity. In the natural history of a special type of breast cancer, US has a better detection ability than mammography.

Patients with disease progressing beyond the earliest screening detectable point are treated as having the true disease. Since US is more capable than mammography of detecting breast cancer, the probability of detection by US or MA minus that of detection by MA only is equal to the difference of the sensitivities of the two modalities. This can be expressed as

$$P(\text{MA or US}) - P(\text{MA}) = Sen_{US} - Sen_{MA} \quad (1)$$

where P(M) denotes the probability of breast cancer being able to be detected with modality M.

The left-hand part can be written as follows:

$$\begin{aligned} &P(\text{MA}) + P(US) - P(\text{MA} \cap \text{US}) - P(\text{MA}) \\ &= P(US) - P(\text{MA} \cap \text{US}) \\ &= P(US) - P(\text{MA} \mid \text{US})P(US) \\ &= P(US)\{1 - P(\text{MA} \mid \text{US})\} \end{aligned} \quad (2)$$

Assuming constant hazard rate, the above equation is rewritten as follows:

$$\left(1 - e^{-\lambda_1 t}\right) \times e^{-\lambda_2 t} \quad (3)$$

Similarly, the relationship between MRI and MA can be expressed as follows:

$$\begin{aligned} &P(\text{MRI or MA}) \\ &= P(\text{MRI})\{1 - P(\text{MA} \mid \text{MRI})\} \\ &= 1 \times \left(P_{11}(t) + P_{12}(t)\right) = 1 - Sen_{MA} \end{aligned} \quad (4)$$

From expressions (3) and (4) together with knowledge of sensitivities of different screening tools, one can estimate λ_1 and λ_2.

Illustration

According to the Berg et al. (2004) study, the sensitivities of US and MA, and of MA only are 93.2% and 77.4%. Taking a 3-year screening interval, λ_1 and λ_2 estimated as 2.03 and 0.61. Given a constant hazard assumption, the sojourn time of staying in MRI detectable only and MRI+US detectable only are 4.6 months and 1.6 years.

Results

Types of new technologies

In addition to mammography, new technologies include ultrasound (US), magnetic resonance image (MRI), and full-field digital mammography (FFDM) with or without computer-aided detection (CAD). According to the review from Irwig et al. (2004), US together with mammography and clinical breast examination was applied to women with dense breast or normal, 'high-risk' female relatives of breast cancer patients, or high-risk women with BRCA mutation, or severe family history. MRI was further applied to even high-risk BRCA or several family members. To enhance the detection rate, FFDM with computer-aided detection was applied to average-risk women.

Natural history of breast cancer featured by multiple detection modalities

Figure 1 shows the natural history of breast cancer defined by detection modalities including US, MA, MRI, and clinical breast examination (CBE). After the onset of the biological process, the tumour can be detected by one of the modalities in the pre-clinical screen-detectable phase. Although figure 1 shows the earliest time point is detected by MRI followed by US, MA and CBE, the sequence may not be such a case. For example, certain breast tumours with micro-calcification or breasts with fatty tissue may be easily detected by MA before US. Using the information on the sensitivity of different modalities, we can calculate the probability of staying in the preclinical detectable phase (PCDP) using different modalities. The probabilities of staying in PCDP of MA+US compared with MA, given a US study by Berg et al. (2004), were shown in figure 2. The figures of dense tumour, fatty tumour and tumours with lobular type were also depicted. In addition, the time order of detecting breast cancer by these modes can be also affected by technical quality i.e. operator characteristics. To tackle this problem, we may model all possible combinations of the four modalities and quantify each type with the proportion Pi.

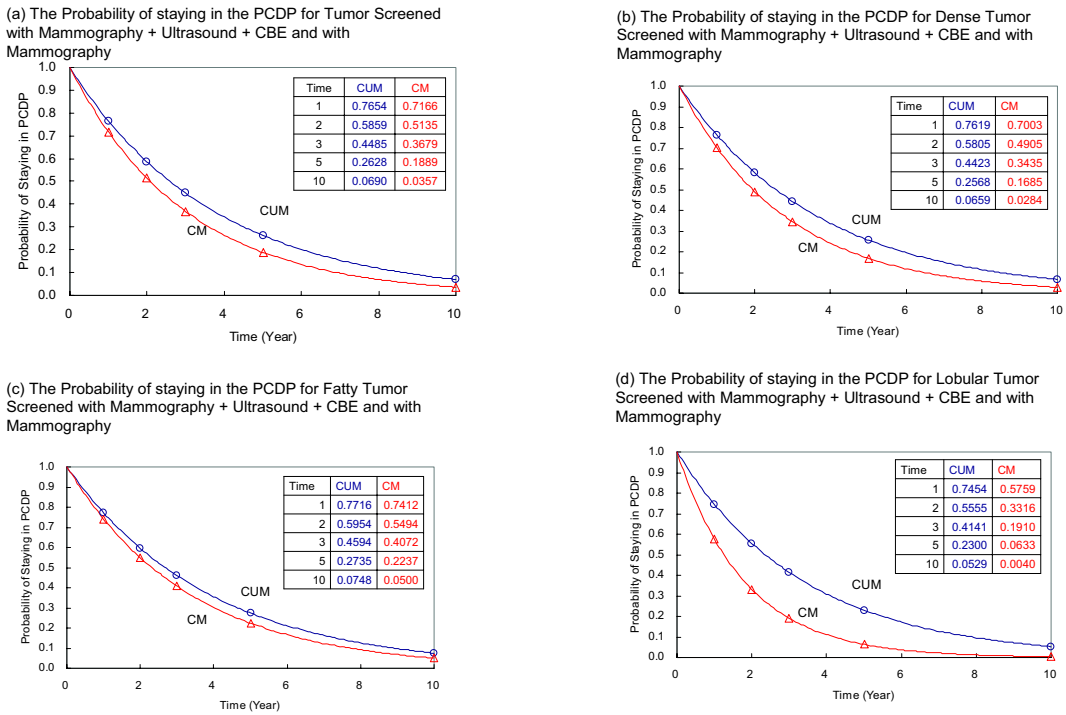

Figure 2 - The probability of staying in the PCDP for tumour screened with mammography + ultrasound + CBE and with mammography

Table 1 - The estimated results of the sojourn times between different sets of screening tools based on the stepwise method

County	Period	Partici-pants	Modality 1/Modality 2	lamda1	lamda2	Sojourn Time1	Sojourn Time2	RR of clinical cases	RR of breast cancer death
Taiwan [2]	1989-2001	105	M+C/C	0.5131	0.6127	1.9489	1.6322	0.4391	0.7273
			U+M+C/M+C	96.5106	0.3275	0.0104	3.0533	0.3333	0.6966
UK [3]	1997-2004	649	M+C/M	0.7884	0.2985	1.2685	3.3497	0.3852	0.7954
			MI+M+C/M+C	2.3220	0.5360	0.4307	1.8657	0.3704	0.8744
Nether-lands [4]	1998-2000	2020	M+C/C	1.8033	0.4957	0.5546	2.0173	0.4106	0.7402
			U+M+C/M+C	2.6597	0.9728	0.3760	1.0280	0.4957	0.7946
USA [1]	1999-2002	177	M+C/C	0.8379	0.4071	1.1934	2.4567	0.3921	0.7054
			U+M+C/M+C	2.0320	0.6143	0.4921	1.6279	0.4355	0.7656
			U+M+C/M+C(Density)	1.8349	0.5536	0.5450	1.8063	0.4173	0.7487
			U+M+C/M+C(Fatty)	2.4870	0.7460	0.4021	1.3405	0.4462	0.7756
			MI+M+C/M+C	19.0107	0.5047	0.0526	1.9814	0.3742	0.7401
			MI+M+C/M+C(Density)	13.4336	0.4477	0.0744	2.2334	0.3593	0.7288
			MI+M+C/M+C(Fatty)	63.8632	0.6296	0.0157	1.5883	0.3996	0.7580

* Lamda1 is the transition rate from the earliest screening detectable point (t_1) to the earliest detectable point with the extra screening tool in modality 1 (t_2), and Lamda2 the transition rate from t_2 to the earliest detectable point with modality 2 (t_3).

** Sojourn time 1 is the average time between t_1 and t_2, and sojourn time 2 between t_2 and t_3.

For simplification, we assume that the earliest and the latest time points detected were MRI and CBE respectively. We only make allowances for the time order changing between US and MA i.e., US followed by MA, or MA followed by US. The proportion P is used for quantifying MRI, US, MA and CBE, and 1-P for MRI, MA, US and CBE. The estimation technique has been proposed using data from literature review.

Table 1 shows the estimated results on transition rates based on the studies addressing asymptomatic breast cancers. Taking the Taiwanese study (no. 2) as an example, when comparing cancers detected by MA or CBE to CBE, the time from the earliest detectable time point to MA-detectable was estimated as 1.95 years. The time between MA-detectable and CBE-detectable was estimated as 1.6 years. When considering the modality of UA, MA and CBE combined compared to MA plus CBE combined, the first time interval was estimated at nearly no time given 100% sensitivity. However, the time lag between these two detectable points was estimated as 3 years given a comparably low sensitivity of MA plus CBE, of 62.5% of MA plus CBE. Based on a biennial screening interval in 8 years, the relative risk of being clinically detected can be obtained from a simulation technique. The 5-year survival for those breast cancer cases was projected. Results of studies from UK, Netherlands, and USA were also applied in the same way.

Effectiveness of new technologies for population-based breast cancer screening

The relative risks of being clinically detected and of breast cancer death were listed. The results show that 56% of clinically-detected cases were reduced by using the MA plus CBE regime compared to using CBE only. The reduction from using UA+MA+CBE was estimated as 67% compared to having MA plus CBE together. Using the cumulative survival by detection mode from the Swedish Two-County trial, the numbers of death from breast cancer were projected. The results suggested a 27% mortality reduction from breast cancer can be achieved with MA+CBE compared to CBE only. When the comparison was made with UA+MA+CBE to MA+CBE, the reduction was estimated as 30%.

Conclusion

Multiple detection modalities may lead to reduced mortality. However, the benefit and the selection of detection modalities are affected by biological factors including age, breast tissue type and histological type. In addition, other social factors may also affect the utilization of multiple detection modalities.

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