

## Mammography-detected ultrasound-negative asymptomatic micro-calcifications in Chinese women: Would it be safe to watch and wait?



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### ABSTRACT

Although mammography (MG) has been widely used for breast cancer screening in the western world, over-diagnosis remains controversial. Milestone studies showed that ultrasound (US) was an effective primary screening test for breast cancer both in the western world and in China. US improves the sensitivity of screening in Chinese women who have denser breasts and develop breast cancer earlier than Caucasian counterparts, and is used as the primary imaging test in the hospital-based opportunistic screening among asymptomatic self-referred women. Our previous work showed that US result might further differentiate the MG-detected breast cancers into low risk (US+) and ultra-low risk (US−). Indeed, most of the MG+/US− breast cancers would be ultra-low risk cancers and almost always present as MG micro-calcifications. Furthermore, majority of the commonest MG+/US− abnormal finding of micro-calcification is usually benign. Biopsy of benign breast disease increases not only the risk of breast cancer, but the expenses of screening and healthcare. Our hypothesis proposes that mammography-positive ultrasound-negative (MG+/US−) asymptomatic micro-calcifications might not need immediate invasive procedures and be safe to observe until the micro-calcifications increase significantly or become US-positive. If this hypothesis is proved, US would serve as the primary imaging test for breast cancer screening in China, with MG as the selective screening test and diagnostic tool for surgical plan. Unnecessary biopsy or surgery might be avoided with screening expenses considerably decrease.

### Introduction

Mammography (MG) has been widely used for breast cancer screening in the western countries, following the publications of the Greater New York Health Insurance Plan (HIP) trial and the Swedish Two-County trial (TCT) [1,2]. However, the Nordic Cochrane group questioned the methodological quality of those randomized trials in 2000 [3]. The debate had heightened when the concern of over-diagnosis was taken into account. Two randomized trials conducted in Canada found no significant reduction in breast cancer deaths associated with MG screening compared to screenings with clinical breast examination [4,5]. The increase of early stage breast cancer detected by MG did not lead to the decrease of the incidence of late stage lethal cancers [6]. In the Netherlands, the participation rate in screening of women 50–74 years old had always been high (around 80%) and the incidence of stage I or in-situ breast cancers increased by three times. However, the incidence of stage II–IV breast cancers had not changed

for 23 years among women aged 50 years (168/100,000 in 1989 and 166/100,000 in 2012) [7,8]. In the United States, the incidence of ductal carcinoma in situ (DCIS) in women aged  $\geq 50$  years rose from 10/100,000 in the 1980s to around 90/100,000 in the 2000s. The excess incidence in 2008 was estimated to be 31% of all breast cancers diagnosed, consisting mainly of DCIS and of stage I cancers [9]. Studies compared changes in mortality from breast cancer between early and late (10–15 years later) implementation of MG screening and found no difference in changes of breast cancer mortality rates over time [10,11].

This is explained that MG-detected breast cancer is fundamentally low-risk cancer. Studies showed that MG detection in screening was an independent prognostic factor of breast cancer which was associated with a more favorable long-term survival [12,13]. Compared to interval cancers, MG-detected invasive cancers had the clinicopathological characteristics of less aggressive tumors [14–16]. Studies have suggested that 60–70% of MG-detected breast cancers were DCIS [17,18], and the detection of DCIS contributed quite little to the reduction of

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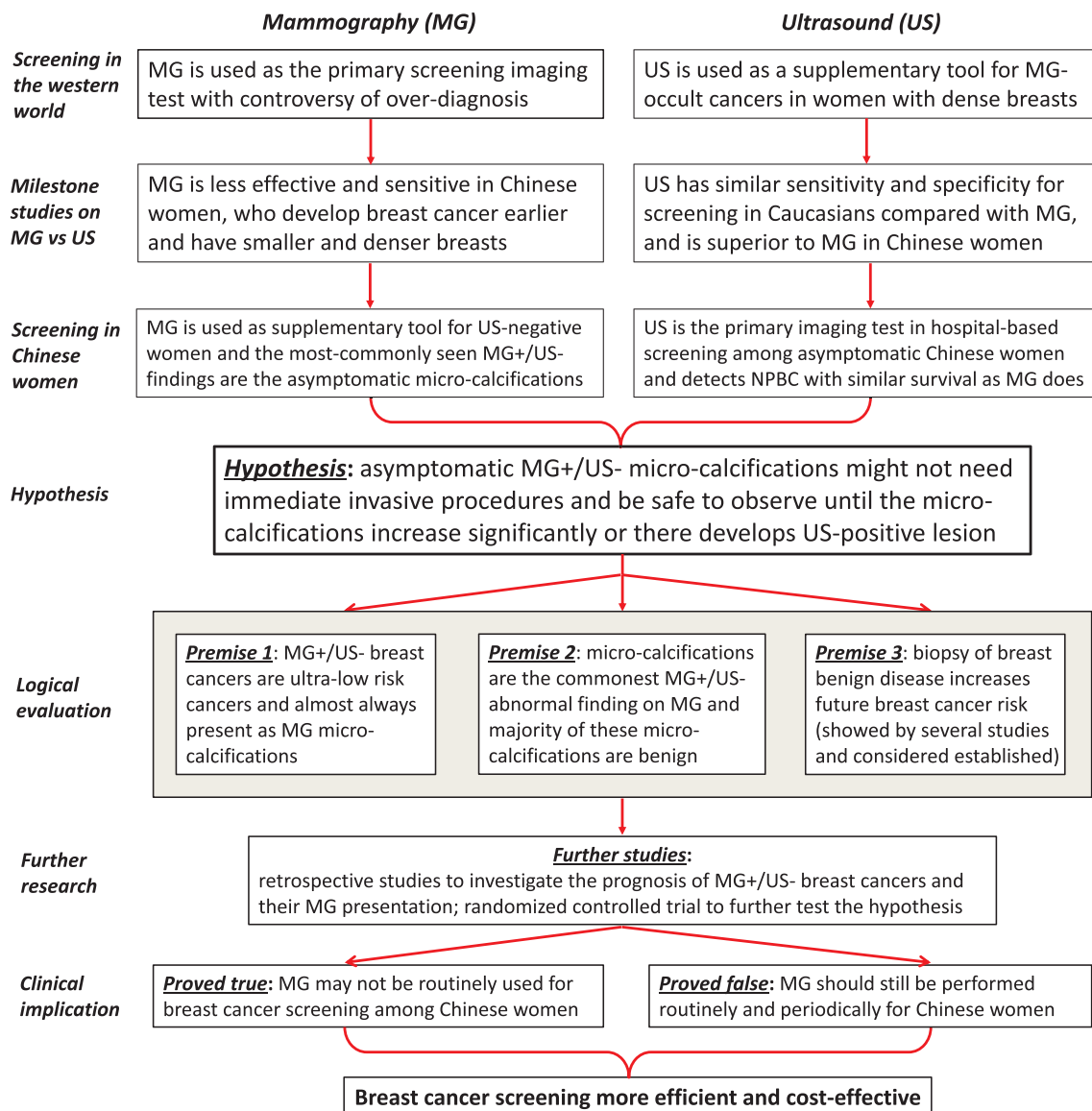


Fig. 1. Diagram of the background, development, evaluation and clinical implication of the hypothesis, and further studies to test the hypothesis.

breast cancer mortality [19]. Among invasive cancers, MG has a high sensitivity for luminal A subtype and low sensitivity for aggressive cancers such as triple-negative breast cancer (TNBC) [20,21].

Ultrasound (US) is usually used as a supplementary imaging tool to MG in the western world for women with dense breasts or elevated risk [22–27]. The ACRIN 6666 study suggested that cancer detection rate with US was comparable with MG, with a greater proportion of invasive and node-negative cancers among US detections, while MG detected more DCIS ( $P < 0.001$ ) [28]. However, there is still very limited data concerning the biology and survival of those mammography-positive ultrasound-negative (MG+/US-) breast cancers. In China, incidences of breast cancer have been dramatically increased during the past two decades and is now the most common cancer among women [29]. Chinese women tend to have small and dense breasts, which are known to reduce the diagnostic accuracy of MG. Studies showed that US was not only a useful supplementary imaging modality of MG, but an effective primary screening test for breast cancer both in the western world and in China [28,30–32].

In our previous work, we showed that with a multi-center randomized controlled trial, ultrasound US could detect breast cancer with improved sensitivity and accuracy in high risk Chinese women [33].

Then we demonstrated within a consecutive cohort on a hospital-screening basis that US and MG detected non-palpable breast cancer (NPBC) had similar long-term survival [34]. Interestingly, we found that the prognosis of the MG+/US- breast cancers was very satisfactory with “ultra-low risk” amongst those low-risk screening-detected NPBCs [34]. We speculated that US result might further differentiate the MG-detected breast cancers into low risk (US+) and ultra-low risk (US-), and these MG+/US- cancers seemed to be too “gentle” to become symptomatic or life-threatening. Accordingly, a retrospective study reviewed material 158 micro-calcification cases examined with US, MG+/US- cancers totaled 32, including 26 DCIS, 4 IDC, 2 invasive lobular carcinoma (ILC) [35].

Breast mass/nodule is the most common abnormal finding in MG and calcifications the second commonest [17,18]. MG-detected breast mass/nodule is usually (if not always) positive to US, and macro-calcification alone is almost always considered benign. Thus micro-calcification could be regarded as the most common MG+/US- abnormality. Calcium deposits are frequent positive findings in asymptomatic DCIS and early breast cancer, and X-ray based techniques are exquisitely sensitive in spotting these deposits. It is true that almost all the MG+/US- asymptomatic breast cancers present as MG micro-

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