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Mammographic density using two computer-based methods in an isoflavone trial

Masako Kataoka [a,*], Charlotte Atkinson [b], Ruth Warren [a], Evis Sala [a], Nicholas E. Day [c], Ralph Highnam [d], Iqbal Warsi [a], Sheila A. Bingham [e]

[a] *Department of Radiology, University of Cambridge, Box 218, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK*
[b] *Department of Oral and Dental Science, Bristol Dental School, Lower Maudlin Street, Bristol BS1 2LY, UK*
[c] *Strangeways Research Laboratory, Worts Causeway, Cambridge CB2 8RN, UK*
[d] *HAL Ltd., #9, 2 Hood Street, Wellington, New Zealand*
[e] *MRC Dunn Human Nutrition Unit, Cambridge CB2 2XY, UK*

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Abstract

Objectives: Mammographic density is a useful biomarker of breast cancer risk. Computer-based methods can provide continuous data suitable for analysis. This study aimed to compare a semi-automated computer-assisted method (Cumulus) and a fully automated volumetric computer method (standard mammogram form (SMF)) for assessing mammographic density using data from a previously conducted randomised placebo-controlled trial of an isoflavone supplement.
Methods: Mammograms were obtained from participants in the intervention study. A total of 177 women completed the study. Baseline and follow-up mammograms were digitised and density was estimated using Cumulus (read by two readers) and SMF. Left–right correlation, changes in density over time, and difference between intervention and control groups were evaluated. Changes of density over time, and changes between intervention group and control group were examined using paired *t*-test and Student's *t*-test, respectively.
Results: Inter-reader correlation coefficient by Cumulus was 0.90 for dense area, and 0.86 for percentage density. Left–right correlation of percent density was lower in SMF than in Cumulus. Among all women, percentage density by Cumulus decreased significantly over time, but no change was seen for SMF percentage density. The intervention group showed marginally significant greater reduction of percent density by Cumulus compared to controls ($p = 0.04$), but the difference became weak after adjustment for baseline percent density ($p = 0.06$). No other measurement demonstrated significant difference between intervention and control groups.
Conclusions: This comparison suggests that slightly different conclusions could be drawn from different methods used to assess breast density. The development of a more robust fully automated method is awaited.
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Keywords: Mammography; Mammographic density; Computer analysis; Isoflavone; Breast

* Corresponding author. Tel.: +44 1223 336891; fax: +44 1223 330915.
E-mail addresses: mk435@cam.ac.uk, makok@kuhp.kyoto-u.ac.jp (M. Kataoka).

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1. Introduction

Many studies have shown that higher mammographic density is associated with increased incidence of breast cancer and can be used to estimate breast cancer risk. Women with dense breasts on mammography are considered at greater risk for breast cancer than those with lucent patterns, and the relative risk is estimated to be about four to six [1]. Mammographic density is influenced by age, hormonal agents, and other lifestyle factors such as diet. For example, mammographic density changes in response to hormonal interventions such as hormone replacement therapy (HRT) and Tamoxifen [2]. Mammographic density is considered a useful biomarker of risk relating to the hormonal environment [3] and has been used to evaluate interventions with selective oestrogen receptor modulators (SERMS) or plant extracts with oestrogen-like activity called isoflavones [4–7].

Initially, mammographic density was described using visual evaluation methods such as Wolfe's scale [8], six-categorical assessment [9], and four-category density evaluation by the American College of Radiologists' Breast Imaging Reporting and Data System (BI-RADS). These methods, however, are based on readers' assessment and subject to inter/intra-observer variability. Recently, computer-based quantitative methods have become popular. They are less subjective than visual estimation, and potentially objective if fully automated, and can provide continuous data suitable for analysis. Currently, the most frequently used method is a computer-assisted thresholding method developed by Byng et al. [9] (Cumulus). It measures the area of dense tissue and total breast using semi-automated thresholding. This method has been examined in several studies [10–12]. They demonstrated that percentage density (the fraction of dense area in total breast area) was associated with larger gradients in the risk of breast cancer than dense area [13].

Some researchers are developing methods to assess the volume of the dense tissue in the breast, since it may be a more appropriate measurement for the breast as a three dimensional organ. One such method is a new fully automated density measurement that can be applied as a research tool for large-scale multi-institutional studies, called standard mammography form (SMF^{TM}) [14–16]. This method has not yet been validated in breast cancer case–control studies, but full automation and speed of analysis are potential advantages over the currently used visual and computer-assisted semi-automated methods. In a previous study [6], Atkinson et al. used visually estimated mammographic density to examine the effect of 1-year isoflavone supplement versus placebo on breast density. They found that breast density decreased over time, but there were no significant differences between the isoflavone and placebo groups. The purpose of this study is to compare computer-based methods of measuring mammographic density with visual assessment by radiologists using previously collected data and mammograms from the randomised placebo-controlled trial of an isoflavone supplement.

2. Materials and methods

2.1. Study population

The study population was derived from a previously published isoflavone intervention trial and has been described in detail elsewhere [6]. Briefly, mammograms from 1908 women aged 49–65 years were classified according to their Wolfe pattern [17] and women with Wolfe's P2 or DY breast pattern ($n = 1149$) were invited to participate in the intervention study. Women with a history of breast cancer and/or major breast surgery and/or were taking hormone replacement therapy (HRT) were excluded. All women who wished to participate were asked for written informed consent. A total of 205 healthy women were randomised to receive either an isoflavone tablet, containing 26 mg biochanin A, 16 mg formononetin, 1 mg genistein and 0.5 mg daidzein, or a placebo tablet per day. After 12 months, 177 women (isoflavone group 86 women and control group 91 women) completed the study.

The number of women included in the analysis using visual evaluation of percent density was 160 (76 for isoflavone group/84 for control). Since some of the mammograms were not available as digital images, the number analysed for Cumulus and SMF was 153 (74 isoflavone/79 control) and 151 (71 isoflavone/80 control), respectively. Their age (mean ± standard deviation (S.D.)) was 54.4 ± 4.3 years for women in

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