A clinical investigation to develop an evidence base for the use of Breastlight in examining the breast

Introduction

Mammography is currently the gold standard for the imaging of the breast and digital processing has further strengthened its role. However its value in screening dense breasts is more limited. In 1986 the Forrest Report recommended that work on other non-invasive techniques should continue in the search for an effective way of screening younger women with dense breasts. The advent of digital mammography has not negated these comments and mammography is still not very effective when imaging dense breasts. This prompted Brittenden and Watmough to develop a combined optical and Doppler ultrasound instrument for the detection of breast cancer. Clinical trials with this prototype had a sensitivity of 70-90%. These efforts culminated with the production Breastlight, a consumer based optical breast examination tool intended to facilitate self examination. It is a handheld device that transilluminates the breast with a high intensity red light (617nm) which is absorbed by haemoglobin in areas of high vascularity. The degree of light absorption is determined by the number of blood cells per unit volume of breast tissue. Cysts appear translucent whereas blood filled cysts, haematomas and neoplastic tumours appear opaque. Although the device is consumer based thus not intended for use within a healthcare environment in the UK, the company was keen to validate it in a clinical setting.

Materials and Methods

The dataset comprised 300 consenting subjects referred by their General Practitioner to the Breast Clinic at the Sunderland Royal Hospital between March to August 2009. All subjects had both breasts examined using Breastlight and photographies were taken of each transilluminated breast by a medical photographer. The examiner was not aware of the index breast. The patients then underwent a standard consultation and triple assessment technique by the same clinician. We then retrospectively identified the index breast for which a woman had been referred by her General Practitioner. This was done by three independent reviewers who blindly commented on the photographic assessments of transilluminated breasts.

Statistical analysis was performed by a medical statistics consultancy firm. The analysis of data is largely descriptive. Inter-rater reliability was performed on readings of photo assessments in a subset of 56 patients. Agreeement between assessment, ease of assessment and confidence in assessment was assessed using simple kappa statistic. Agreement between direct breastlight assessment and photographic assessment was assessed on the whole group using kappa statistic. Association between breastlight result and results of clinical, imaging and histological investigations was tested using Fishers exact test. The utility of the Breastlight assessment compared with clinical diagnosis of a lump, imaging diagnosis of a lump and histological/cytological diagnosis of a lump was expressed using sensitivity, specificity, positive predictive value and negative predictive value.

It should be noted that whilst sensitivity and specificity do not vary according to prevalence of lump, positive predictive value and negative predictive value are highly dependent upon prevalence and therefore are not transferable to other situations where the prevalence of a lump may be different.

Results

300 women underwent Breastlight and standard triple assessment. Average age was 46 (SD 15) with a range from 19 to 88 years. Primary reason for referral was a lump in 207/300 (69%) cases followed by pain 50/300 (16.67%), other 36/300 (12%) and nipple discharge 5/300 (1.67%). 6 women in the sample had previous mastectomy in the non-index breast and 10 women had breast conserving surgery (3 in the index breast, 7 in the non-index breast)

Clinical findings

The surgeon noted that 161/300 (54%) had a lump on presentation. 44/300 were considered to have probably malignant or malignant lumps. 227 women had a mammogram of which 89% revealed a lesion. Of those 89, 20 were scored as being probably malignant of malignant. Those 20 women with a lump scored as being probably malignant or malignant on mammogram were also scored as being probably malignant or malignant on ultrasound. 58 core biopsies were performed, 18 cancers were diagnosed. Of these 17 were graded of probably malignant or malignant on ultrasound and 16 were graded as probably malignant or malignant on mammogram.

Breastlight results

54/300 (18%) of the index breasts were rated as positive by Breastlight examination. All photographic assessments were obtained by photographing transiluminated breasts in a dark room. This ‘backlighting’ environment made obtaining good quality images a challenge. 266 (88%) of assessments were rated as fairly confident or confident and 252 (84%) assessments were rated as easy or fairly easy. There was a ‘fair’ agreement between the direct breastlight assessment and the photo assessment with agreement in 81% of cases (kappa 0.41). There was a significant association between the clinical findings and the Breastlight result ($p<0.001$, Fisher’s exact test), between ultrasound grade and Breastlight result ($p<0.001$, Fisher’s exact test) and mammogram versus Breastlight result ($p<0.001$, Fisher’s exact test).

Grade of Mammogram of Index Breast	Breastlight + in Index Breast Yes	No	Total
Normal	11 10.38	95 89.62	106 100.00
Benign	16 18.60	70 81.40	86 100.00
Probably Benign	4 44.44	5 55.56	9 100.00
Probably Malignant	6 66.67	3 33.33	9 100.00
Malignant	5 45.45	6 54.55	11 100.00
missing	12 15.19	67 84.81	79 100.00
Total	54 18.00	246 82.00	300 100.00

Comparison of Breastlight with Ultrasound and Mammographic Assessment

21 lumps were indicated as being probably malignant or malignant by both ultraosound and mammography; of these Breastlight was positive in 12 giving an estimated sensitivity of 57% (95% CI 34%-78%). Of the remaining 279 examinations, 237 were negative on Breastlight giving a specifiticty of 85% (95% CI 80%-89%).

Comparison of Breastlight Asessment with Histological Assessment

Of the 58 breasts that underwent biopsies 19 (33%) were positive on Breastlight examination. There was a significant association between histological findings and Breastlight result ($p<0.001$, Fisher's exact test).

Result of Aspiration /Biopsy	Breastlight + in Index Breast Yes	No	Total
Benign	7 17.50	33 82.50	40 100.00
Malignant	12 66.67	6 33.33	18 100.00
No Biopsy	35 14.52	206 85.48	241 100.00
missing	0 0.00	1 100.00	1 100.00
Total	54 18.00	246 82.00	300 100.00

Breastlight performs well against cytological/histological findings; 12 of 18 malignant tumours were detected using Breastlight giving a sensitivity of 67% (95% CI 41%-87%). 240 of 282 breasts with no malignancy found were correctly identified as negative giving a specificity of 85% (95% CI 80%-89%). Of the 54 positive results given by Breastlight, 12 turned out to be malignant tumours giving a positive predictive value of 22% (95% CI 12%-36%). Of the 246 negative results given by Breastlight only 6 turned out to be malignant tumours giving a negative predictive value of 98% (95% CI 95%-99%)

Lesion size by Breastlight result

An imaging size was provided for 115 breasts; of these 84 (73%) were Breastlight negative and 31 (27%) were Breastlight positive. Breastlight positive lumps were significantly larger than Breastlight negative lumps (P=0.02, Kruskal Wallis Test); Breastlight positive lumps were on average 18mm compared with Breastlight negative lumps which were 11mm on average.

Lesion size for malignant lumps by Breastlight result

In the subgroup of 18 malignant lumps, there was no significant difference between the size of lump picked up by Breastlight (median 26.5mm) and the size of lump not picked up by Breastlight (median 23.5mm) (P=0.9, Kruskal-Wallis Test). Breastlight picked up malignant lesions varying from 0.7cm to 3.6cm.

The percentage of positive Breastlight results did not seem to be affected by cupsize, menopausal status, and oral contraceptive pill therapy or hormone replacement therapy.

Of the 220 non-indexed breasts that were examined with Breastlight; 7 (3.2%) were positive (presumed false positive).

Discussion

Breastlight assessment appears to provide some useful information. Assessment of confidence in result or ease of decision making were not reproducible and therefore appear to be of little value. Data were not available at the time of analysis to assess the agreement between the direct Breastlight assessment and the photo assessment. This would be very useful information. All examiners felt that interpretation of the photographic evidence was challening due to inherent technical limitations of obtaining good quality pictures in a backlighting setting. Subjectively raters felt that direct Breastlight assessment would have increased the accuracy of the device. This aspect will be worked on future clinical evaluations of the device.

Breastlight results did not correlate well with clinical assessment but the value of the clinical assessment (in the absence of further imaging or diagnostic testing) is questionable and thus one might not expect a strong relationship. Estimates of sensitivity and specificity compared with the imaging results were good, as were estimates of sensitivity and specificity compared with histology/cytology. Breastlight assessments did not appear to be dependent upon bra cupsize, use of hormone replacement therapy or the oral contraceptive pill. Postmenopausal women were significantly more likely to have a positive Breastlight result overall, as were women with larger sized lumps. It is impossible to say whether menopausal status or lump size influence the use of Breastlight in the subgroup of malignant lumps because the sample of malignant lumps is so small.

Brittenden was the first to establish the effectiveness of an optical device for the detection of breast lesions in 1995. Since then researchers have looked at ways to adapt optical non invasive imaging in breast disease. Keshgar has recently described the use of an optical device for rapid intra-operative analysis of sentinel nodes with some success. Blackmore investigated the use of transillumination spectroscopy as a tool for risk assessment in breast cancer particularly for young women. Similar study was undertaken by Blyschak et al. Song looked at the feasibility of detecting lesions using near infrared light tomography. Blydon et al decribed an optical spectral imaging tool for rapid intraoperative assessment of resection margins in breast conserving surgery. Cerussi et al evaluated the utility of repeated optical imaging during breast cancer neoadjuvant chemotherapy to assess tumour physiology and response to treatment. Erickson recently evaluated a handheld near infrared optical device in conjuction with indocyanin green in breast cancer imaging. Lee showed promising results by using a near infrared optical device in addition to indocyanine green in order to assess viability of tissue in perforator flap reconstructions. Troyan successfully described the use of a near infrared fluorescence imaging system in breast cancer real time sentinel node mapping. In a review article focusing on imaging modalities in breast disease, Karellas stated that developing optical and electromagnetic imaging techniques hold significant potential for physiologic information and they are likely to be of most value when integrated with or adjunctively used with techniques that provide anatomic information. Recently Wishart and Hutchinson demonstrated the feasibility of an infra red digital scanner in the detection of breast cancer, particularly in the young age group.

While some of these studies employ high tech imaging and spectral analysis equipment and others use simple hand held devices they all work on similar principles based harvesting diagnostic information following tissue penetration of near infrared light. These recent studies show a renewed interest in fast, accurate and non invasive and non toxic diagnostic methods with potentially wide applications.

Breastlight is a device designed for consumer use in the United Kingdom. It is intended as an adjunct to self examination. Our evaluation of the device in a clinical setting showed that Breastlight can provide some useful information with a sensitivity of 67% and a specificity of 85%. While use of the Breastlight device in the clinical setting in the United Kingdom and developed countries is very limited there is currently a very strong interest in using the device as a gross screening tool in parts of the world where mammographic assessment of the population is not routine. With strong support from local clinicians, plans to develop a clinical trial using very large numbers of patients in rural India are already on the way.

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