Radiological Devices Advisory Panel
April 12, 2012

Breast Transilluminators 515(i)

Executive Summary

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Introduction

On August 25, 2010, the Food and Drug Administration (FDA or the Agency) published a proposed rule in the Federal Register[1] (75 FR 52299) for 4 preamendments devices, one of which was breast transilluminators. The current regulation for these devices is 21 CFR §892.1990 which reads as follows:

> **§ 892.1990 Transilluminator for breast evaluation.**
>
> (a) Identification. A transilluminator, also known as a diaphanoscope or lightscanner, is an electrically powered device that uses low intensity emissions of visible light and near-infrared radiation (approximately 700–1050 nanometers (nm)), transmitted through the breast, to visualize translucent tissue for the diagnosis of cancer, other conditions, diseases, or abnormalities.
> (b) Classification. Class III (premarket approval).
> (c) Date premarket approval (PMA) or notice of completion of a product development protocol (PDP) is required. The effective date of the requirement for premarket approval has not been established.
> See § 892.3.

Transilluminators, also know as lightscanners or diaphanoscopes, are electrically powered and emit low intensity visible light and near-infrared radiation on the order of 700 to 1050 nanometers (nm). The device is placed in contact with a woman's breast and is used to illuminate her mammary tissue in a darkened environment. Light in the 700 – 1050 nm range is transmitted relatively easily through breast tissue and is preferentially absorbed by hemoglobin in the blood. When used properly, the transilluminator is intended to illuminate the vasculature of the breast, and abnormalities, such as a cyst or breast cancer, would appear to the user as an area of darker absorption.

Regulatory History

Breast transilluminators are considered pre-amendment devices since they were in commercial distribution prior to May 28, 1976 when the Medical Device Amendments law became effective. On January 11, 1991, the Obstetrics and Gynecology Devices Advisory Panel[2] met to discuss and reach consensus on the classification of several pre-amendment devices including breast transilluminators.

The Agency classifies medical devices into Class I, II, or III generally determined by the risks or hazards to the patient or user associated with the device. Class I devices are those devices which are considered low risk and present minimal potential harm to a user and/or patient. The risks from harm of a Class I device can be adequately mitigated by general controls which include the following:

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[1] 75 FR 52299

[2] Obstetrics and Gynecology Devices Panel, Forty-fifth Meeting. Transcript and Meeting Minutes, January 11, 1991.

- establishment registration and listing;
- 510(k) premarket notification unless exempt;
- Good Manufacturing Practices (GMPs); and
- other regulatory controls, e.g., adverse event reporting, misbranding, adulteration of the device, etc.

Class II devices are those devices which are considered to have moderate risk such that general controls alone are not sufficient to mitigate the risks of harm to a user and for which there is sufficient information to establish special controls, existing methods specific to the device that can control the risks not controlled by the general controls. Special controls for medical devices may include:

- performance standards;
- post-market surveillance;
- patient registries;
- guidelines;
- design controls; and
- other appropriate action deemed necessary for mitigating the risks of the device.

Class III devices are those devices considered to be high risk and whose risk may not be completely mitigated by general controls and special controls alone. For Class III devices there is insufficient information to provide a reasonable assurance of safety and effectiveness so data from a well-controlled, statistically significant clinical study is needed to establish their safety and effectiveness.

Dr. Carl D'Orsi, a recognized expert in the field of breast imaging and mammography, presented a summary of findings from his study of breast transilluminators to the Obstetrics and Gynecology Advisory Panel during the 1991 meeting. He explained to the Panel that light with wavelengths in the red and near infrared range (700 – 2500 nm) was used since the absorption of light from this part of the spectrum is the greatest in biologic tissue. The fundamental basis of the research at that time was that the absorption of light in red and near infrared range would create patterns which would render cancer and non-cancerous lesions more distinguishable. The purpose of lightscan exams was to locate any areas in the breast that were unusual in their ability to transmit light.

The Spectrascan was one example cited by Dr. D'Orsi who explained that penumbra was a major problematic aspect of the device since structural shadows could obscure smaller intervening structures. Equally important was the finding that exam results were highly dependant on the examiner's technique. In order to achieve reasonable results using the Spectrascan, it was necessary to attempt to get all portions of the breast close to the skin surface in order to alleviate the penumbra effect. This would frequently require 6 or more views of the breast.

Dr. D'Orsi stated that absorption is the critical diagnostic criteria for a lightscan exam, and absorption may be focal, may occur in a larger portion of the breast, or may occur

throughout the entire breast. He also commented that there were several indirect signs which were difficult to evaluate and were not necessarily accurate. These signs included vascular asymmetry, vessel clustering, and abrupt vessel caliber changes. From his experience, Dr. D'Orsi found that vascular asymmetry was not very helpful since benign lesions have increased vascularization as much as malignant lesions.

In his opinion, Dr. D'Orsi commented to the Panel that the basic "pitfall" of the exam was that blood is the detector and will absorb light regardless whether it is in a tumor, in a vein, or free in the breast. Skin lesions filled with blood, such as blood leakage from a needle biopsy, scars, and ink from tattoos, may easily be mistaken for malignancies.

Dr. D'Orsi studied 3,000 women in an NIH-funded grant[3] to evaluate the efficacy of breast transillumination. Each lightscan case was read by 4 independent radiologists, and the study found the sensitivity of these devices ranged from 43-98%. The large variation in sensitivity was ascribed to the disparity of interpretation when lightscans were read blinded (without a mammogram) and to exam results being both device dependent and technique dependent.

Overall, the study did not find 1 case of carcinoma detected by lightscanning alone that either a physical exam and/or mammography did not detect, and the size of a carcinoma is a key factor because of the penumbra effect which may render a lesion undetectable. In Bartrum's study[4] the sensitivity of a blinded lightscan for tumors less than 1 cm was 0.44, which means breast transilluminators are not effective as a screening modality where the goal is to visualize masses smaller than 1 cm. Dr. D'Orsi summarized the results from his NIH study and concluded that breast transillumination:

- cannot be used for screening;
- cannot be used alone; and
- has no known adjunctive use (with breast self-exam or mammography).

During the discussion of the Obstetrics and Gynecology Panel meeting in 1991, 3 major risks of breast transilluminators were identified: misdiagnosis, delayed diagnosis, and delayed treatment. The Panel recommended that breast transilluminators be place in Class III because a reasonable assurance of safety and effectiveness could not be established and additional clinical studies are needed prior to approval for marketing.

On January 13, 1995, the FDA published a proposed rule in the Federal Register[5] (60 FR 3171) that would place breast transilluminators in Class III. FDA proposed to require at a

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[3] D'Orsi CJ, Smith EH: Double blind study of breast diaphanography. National Institute of Health Grant (N.I.H.) G2736 1984-1989 approved $195,196/yr RNM# 1RO1CA37970-AIA.

[4] Bartrum RJ, Crow HC: Transillumination Lightscanning to Diagnose Breast Cancer: A Feasibility Study. Am J Roentgenol 1984 Feb; 142(2): 409-14.

[5] Proposed Rule Federal Register (60 FR 3171).

later undetermined date, that device manufacturers submit a Premarket Approval Application (PMA) when notified via a future regulation under section 515(b) of the Federal Food, Drug and Cosmetic Act (the FD&C Act) (21 U.S.C. 360e(b). In February 1994, the Agency formally notified manufacturers in writing[6] that breast transilluminators had been reclassified and subsequently, the FDA published a Final Rule[7] (60 FR 36639) on July 18, 1995 that placed breast transilluminators into Class III based on the recommendation of the Obstetrics and Gynecology Devices Panel without setting a date that PMAs would be required.

Citizen's Petition

On August 25, 2010, FDA issued a proposed rule calling for PMAs for breast transilluminators. In response to the proposed rule, the Agency received a Citizens Petition on September 9, 2010, from Mr. Russell Overend of pwbHealth Ltd.[8] The petition requested a change in classification to Class I stating breast transilluminators are already Class I devices in a number of other countries around the world including Canada and the European Union. pwbHealth Ltd also states that the risks of breast transilluminators (electrical shock risk, optical radiation risk, and the potential for missed or delayed diagnosis) raised in 1991 by the Obstetrics and Gynecology Devices Panel have been adequately mitigated.

The petition also cites results from a U.K. clinical trial[9, 10] in which a breast transilluminator was found to have sensitivity of 67% (95% C.I. 41%-87%) when compared to cytological/histological findings. Specificity for this study was determined to be 85% (95% C.I. 80%-89%) as 240 of 282 breasts with no known malignancy were correctly identified as negative. The petition compares these results to x-ray mammography, considered the "gold standard," and states that mammography is 60-90% accurate depending on the age of the patient. These studies cited in the petition are posted on the petitioner's website and include an article by Bundred et al[11] from 1983 that describes an early clinical investigation of breast transillumination, and another article by Brittenden et al.[12] that clinically evaluated the combination of breast

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[6] Letter to Breast Transilluminator Manufacturers, Office of Compliance.
[7] Final Rule Federal Register (60 FR 36639).
[8] Citizens Petition from pwbHealth Ltd., U.K., September 9, 2010.
[9] Iwuchukwa O, Dordea M, and Keaney N: Analysis of Breastlight Findings in Patients with Biopsies. Abstract presented at the European Institute of Oncology's 12th Breast Cancer Conference, Milan Italy, June 17, 2010.

[10] Iwuchukwa O and Dordea M: A Clinical Investigation to Develop an Evidence Base for the use of Breastlight™ in examining the Breast. http://www.breastlight.com/clinical-evidence.

[11] Bundred N, Levack P, Watmough D, and Watmough J: Preliminary results using computerized telediaphanography for investigating breast disease. http://www.breastlight.com/clinical-evidence.

[12] Brittenden J, Watmough D, Heys S, and Eremin O: Preliminary clinical evaluation of a combined optical Doppler ultrasound instrument for the detection of breast cancer. British Journal of Radiology, vol. 68 (816): 1344-1348.

transillumination with ultrasound and found that the combined optical/Doppler instrument was not suitable for screening due to low sensitivity. However, the cited results could not be evaluated and confirmed.

Current Literature

Several MEDLINE/PubMed literature searches were performed using the key words 'breast' or 'mammary', 'lightscanner' or 'transilluminat' or 'lightscan' or 'lightscanning' or 'illuminator.' Also used was 'mammography' AND 'transilluminat,' 'breast' or 'mammary' AND 'near-infrared' or 'near infrared' along with 'breast' or 'mammary' or 'carcinoma' or 'cancer' or 'tumor' or 'malignant.' The searches were for published literature from January 1, 1995 to February 23, 2012 and yielded 322 articles reporting randomized controlled trials, observational studies, and systematic literature reviews. Articles were excluded if they were: (1) non-clinical study (i.e., editorials, commentaries, discussions, or overviews); (2) non-human studies (i.e., animal and *in vitro* studies); (3) not relevant to breast transilluminators; (4) combination devices/approaches; and (5) not relevant to the breast transilluminator device indication.

Ten of the studies were reviewed for qualitative analysis by the Division of Epidemiology, Office of Surveillance and Biometrics. The analysis primarily evaluated effectiveness and safety. Contributing factors of effectiveness considered were the primary study endpoint, adjunctive use of optical imaging, reader variability, the reference or gold standard, and performance by lesion characteristics. Although there were no reported adverse events from exposure to light from these devices or the injection of contrast agent (indocyanine green) use for diffuse optical tomography, the primary safety concern is misdiagnosis resulting from delayed treatment (i.e., false negative cases) or unnecessary biopsies (i.e., false positive case) with associated morbidity and cost.

A majority of the studies (7 of 10) used pathology as a reference which was considered a strength of the analysis. However, there was a lack of subgroup analysis for factors such as breast density, menopausal status, race, body mass index (BMI), and age to assess their impact on the effectiveness of optical imaging. There was some evidence that the effectiveness of breast transilluminators varied with reader ability, and for a retrospective study it was not known if the readers were blinded to the subject's breast cancer status.

The qualitative analysis reached the following conclusions:

- the rates of false positives and false negatives for breast transilluminators in asymptomatic women with a nonpalpable mass could not be determined;
- the current literature does not address safety concerns related to misdiagnosis with resulting delayed treatment or unnecessary biopsies; and
- additional clinical studies are needed to provide valid scientific evidence to establish the effectiveness of breast transilluminators according to their indication for use in the intended use population.

The complete report of the qualitative analysis performed by the Division of Epidemiology may be found in Appendix A. FDA identified 4 additional publications from the U.K. as related to the Citizens Petition which are briefly discussed below.

Summary and Conclusion

The Radiological Devices Panel is asked to discuss all the risks associated with breast transilluminators and their known mitigations in an effort to determine what the appropriate classification should be for this device. The Panel should discuss the benefit to risk ratio and the potential impact on public health for these devices. Based on current evidence of the safety and effectiveness of these devices either based on the Panel's knowledge and imaging expertise and the existing literature, the Panel will be asked to assess whether the evidence allows for this device to be classified as class I, II or III in accordance with the medical device regulations.

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Breast Transilluminators 515(i)

Panel Discussion Questions

1. Considering the key risks to health (missed diagnosis, delayed diagnosis, delayed treatment, electrical shock, and optical radiation) of breast transilluminators identified by the Obstetrics and Gynecology Devices Panel meeting on January 11, 1991 and your own knowledge and expertise of breast imaging, please discuss whether you agree or disagree with the inclusion of these risks to health. Please also identify any additional risks to health you feel may have been omitted.

2. Based on your understanding of general controls, e.g., establishment registration & listing, 510(k) premarket notification, Good Manufacturing Practices (GMPs), and other reporting such as adverse event reporting, discuss whether you believe these controls adequately mitigate the risks associated with breast transilluminators. Is there sufficient information to determine whether general controls alone are sufficient to provide reasonable assurance of safety and effectiveness of breast transilluminators?

3. For medical devices considered to have moderate risk such that general controls alone are not sufficient to mitigate the risk of harm, special controls are often developed, which may include performance standards, post-market surveillance, patient registries, guidelines, design controls, and other appropriate actions deemed necessary for mitigating the risks of the device. If general controls are insufficient to mitigate the risks to health associated with these devices, is there sufficient information to establish special controls for breast transilluminators in addition to general controls that would provide reasonable assurance of the safety and effectiveness of these devices? If yes, please identify the special controls needed.

4. If the device remains a class III device and becomes subject to PMA, discuss the important clinical study design features necessary to demonstrate that the device is safe and effective.

Appendix A

FDA Literature Review

FDA Literature Review of Breast Transilluminators

I. Introduction

Transilluminators, also known as lightscanners or diaphanoscopes, are electrically powered and emit low intensity visible light and near-infrared radiation on the order of 700 to 1050 nanometers (nm). The device is placed in contact with a woman's breast and is used to illuminate her mammary tissue in a darkened environment. Light in the 700 – 1050 nm range is transmitted relatively easily through breast tissue and is preferentially absorbed by hemoglobin in the blood. When used properly, the transilluminator is intended to illuminate the vasculature of the breast, and abnormalities, such as a cyst or breast cancer, would appear to the user as an area of darker absorption.

A team at FDA conducted a systematic literature review to assess the safety and effectiveness of breast transilluminators by analyzing the existing clinical literature. We sought to address the following questions:

1. What is the evidence for the effectiveness of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?
2. What are the reported adverse events associated with the use of breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities?

II. Methods

A systematic search of the literature was conducted on February 23, 2012 using the MEDLINE database. The following terms were used to capture clinical studies regarding breast transilluminator devices:

MEDLINE/Pubmed

#1	("breast or mammary") AND ("lightscanner" OR (transilluminat*) OR "light scan" OR "light scanning" OR "illuminator")
#2	("mammography") AND transilluminat*
#3	#1 OR #2, Limits: English, Publication Date from 1995/01/01 to 2012/02/23
#3	#1 OR #2, Limits: English, Publication Date from 1995/01/01 to 2012/02/23
#4	("breast or mammary") AND ("near-infrared" OR "near infrared") Limits: English, Publication Date from 1995/01/01 to 2012/02/23
#5	("breast or mammary or carcinoma or cancer or tumor or malignant") AND ("optical") Limits: English, Publication Date from 1995/01/01 to 2012/02/23
#6	#3 OR #4 OR #5, Limits: English, Publication Date from 1995/01/01 to 2012/02/23
#7	#3 OR #4 OR #5, Limits: Human, English, Publication Date from 1995/01/01 to 2012/02/23

Results were limited to articles published in English from January 1, 1995 to the present. The initial search yielded 332 results. Titles, abstracts, and full text when needed were reviewed for clinical studies involving breast transilluminators. Randomized controlled trials, observational studies, and systematic literature reviews were considered for inclusion. Articles were excluded for the following reasons: (1) non-clinical study (i.e., editorials, commentaries, discussions, or overviews); (2) non-human studies (i.e., animal and *in vitro* studies); (3) not relevant to Breast Transilluminators; (4) combination devices/approaches; and (5) not relevant to the breast transilluminator device per indication. The list of 322 articles that were excluded is provided as **Appendix.**

Ten articles were included as part of the qualitative synthesis [1-10]**.** A summary of article retrieval and selection is provided in **Figure 1**.

III. Results

The results of our systematic literature review are presented for the use of Breast Transilluminators for the detection of cancer, other conditions, diseases, or abnormalities. In this literature review, we included studies that contained clinical data to evaluate the diagnostic accuracy of the breast transilluminators. We provide a brief description of the studies, main findings regarding effectiveness, concerns on safety, and discussion of the critical findings.

IV. Overview of Published Literature

Imaging modalities that were evaluated included the hand-held transilluminator[2], optical mammography[1,3,7] (e.g., Time-domain optical mammography) and optical tomography[4-6,8-10] (e.g., Dynamic optical tomography with or without contrast agents, diffuse optical tomography). Ten articles were identified; two articles[3,7] that studied different technical aspects, but used identical clinical data, and eight independent studies are considered in this review**.** Most studies were conducted in European countries such as France[1], Germany[3-5,7,8] and the Netherlands[9,10]. There were only two studies that were conducted in the United States[2,6]. Nine of the ten studies were cross-sectional[1,2,4-10] where optical imaging and reference, i.e., pathology and conventional radiology, were performed in the same time interval. One study was retrospective[3] where the reference, i.e., histopathology, was performed prior to the optical imaging . None of the studies were prospective or a randomized controlled trial. Sample size ranged from 18 to 154 breast lesions or patients. The optical imaging modalities were compared to histopathological findings in 7 of the studies[1-5,7,8]. In the remaining 3 studies, conventional breast imaging[6,9,10] (x-ray mammography, ultrasound, MRI) was used as reference.

The Citizens Petition from Mr. Russell Overend of pwbHealth Ltd (Citizens Petition from pwbHealth Ltd., U.K.), received by FDA on September 9, 2010, cites results from a United Kingdom clinical trial where a breast transilluminator was found to have a sensitivity of 67% (95% C.I. 41%-87%) when compared to cytological/histological findings and a specificity of 85% (95% C.I. 80%-89%). To our knowledge, this reference is not peer-reviewed and an abstract of the clinical trial was presented at the

European Institute of Oncology's 12th Breast Cancer Conference in Milan on 17th June 2010 (http://www.breastlight.com/clinical-evidence, last accessed 2012/03/01).

A. Effectiveness

Primary Study endpoints
The primary endpoints in the ten studies included were sensitivity, specificity and area under the curve (AUC) estimated in receiver operator curves analyses (ROC). The scale of reporting for all studies was categorical, i.e., cancer/non-cancer or malignant/benign; none reported on a continuous probability rating scale or as an actionable item (e.g., no action versus follow-up or biopsy).

Most of the studies were estimates of sensitivity and specificity using histologically-confirmed malignant lesions or mammographic lesions coded as Breast Imaging Reporting and Data System (BI-RADS) 4/5. The reported sensitivity for optical imaging in detecting malignant lesions included: 30%[10] (6 of 20 for absorption images) and 65% with physiological maps[9] (13 of 20 cysts), 85.7%[8] (12 of 14 malignant lesions) and 90%[3,7] (92 of 102 tumors). Poplack *et al*. reported a modest AUC of 0.67 (95% confidence interval, 0.52, 0.82) that discriminates 97 mammograms classified as BIRADS 4/5 with 53 women with normal mammograms using hemoglobin properties derived from the optical imaging[6]. Van den Ven *et al.* estimated discriminatory values for the presence of malignancy of 0.92-0.93 and 0.97-0.99 for quantitative and qualitative ROC[10] .

Only one estimated sensitivity for benign cyst (>10mm) was reported where the sensitivity was 30% using absorption images and 65% via physiological maps[9].

No study estimated the sensitivity and specificity in women with negative screening mammographic findings of BI-RADS category 1. Thus, there was limited information on the rate of false positives and false negatives of optical imaging modalities in asymptomatic women with no palpable mass.

Adjunctive use of optical imaging
In terms of study hypotheses and possible translation to indication of use, four study designs evaluated the adjunctive use of the optical imaging modalities, not use in the standalone mode. The lesions were localized in x-ray mammography[1,2,4,5] prior to optical breast imaging. Thus, the study results are not interpretable for assessment of the effectiveness of the breast transilluminators for the detection of cancer, other conditions, diseases, or abnormalities.

Athanasious *et al*. reported a sensitivity of 73% and specificity of 38% for 72 malignant lesions in non-palpable BIRADS 4/5 mammograms[1]. Their false positive results were seen in benign proliferative lesions. However, Athanasious[1]excluded women with submuscular breast implants, tattoos, piercing, inflammatory breast or skin disease. Their assessment of the performance of optical imaging may not reflect the performance expected in the United States general population as these factors are thought to contribute

to false positive rates and lower specificity for detecting breast lesions. Cheng *et al.* included 48 women with anomalous mammograms and biopsies with the objective of distinguishing subjects with benign lesions from mammogram-positive patients[2]. They reported an overall 92% sensitivity and 67% specificity. Based on ROC curve analyses, Poellinger *et al.* presented a mean AUC difference of 0.07 between optical imaging (computed tomography laser mammography) and x-ray mammography modality versus x-ray mammography alone in 82 patients[5]. Poellinger *et al.* estimated a mean sensitivity of 92% and a mean specificity of 75% with three-dimensional optical imaging obtained with contrast agent injection (indocyanine green)[4].

Reader variability

Only two studies [4,10] estimated intra- and inter-observer agreement for the optical imaging devices. In a German study population from a single center[4], the agreement between two independent, blinded, untrained radiologists in optical imaging with indocyanine green infusion was as follows: κ=0.48, precontrast, κ =0.41, late fluorescent; and κ =0.24 early fluorescent. In comparison, the agreement for x-ray mammography was κ=0.43. In a Dutch study population[10], the agreement of region of interest between two readers was as follows: Intraobserver agreements: κ 0.88 and 0.88; interclass correlation, ICC 0.978 and 0.987. Interobserver agreements: κ 0.77–0.95; ICC 0.96–0.98.

Reference

In terms of reference for comparison with optical imaging modalities, seven[1-5,7,8] studies used histologically-confirmed breast lesions that is considered as the gold standard in breast cancer classification. Of these seven, only one[2] has a United States study population; six were from Western European populations. In the European studies, information was insufficient with regards to the comparison to the standard United States breast cancer classification practices, e.g. the type of histopathological classification (e.g., WHO classification) and grading (e.g., Scarff-Bloom-Richardson system or Nottingham grading system). One study[6], in a US population, employed x-ray mammography as reference. Two [9,10] studies used magnetic resonance imaging for comparisons with their 3-dimensional optical images. These two studies were in a Dutch population and their classification used the same BI-RADS lexicon commonly used in United States mammography reading.

Performance by lesion characteristics

The performance of optical imaging modalities are thought to differ by lesion size and lesion depth[11]. Five studies[4,5,8-10] included information regarding lesion sizes. The ranges varied 8mm to 80mm for malignant lesions and 10mm to 52mm for benign (fibroadenoma) lesions. Of these, none reported subgroup analyses of quantitative differences in optical imaging modalities across lesion sizes. Two studies did qualitatively report in their discussion that their optical imaging devices performed relatively worse for lesions smaller than 10 mm[1] and 6 mm[8]; formal statistical analyses with the corresponding estimates of diagnostic performance and statistical significance were not presented . None of the studies provided diagnostic performance by lesion depth.

B. Safety

There are no reported adverse events associated with the exposure to near infrared light which is utilized in breast transilluminators nor from injection of contrast dye (indocyanine green) in the 3-dimensional optical imaging (diffuse optical tomography). However, the safety concern related to this device is misdiagnosis which may lead to either delayed treatment (i.e., false negative cases) or unnecessary biopsies (i.e., false positive cases) with attendant morbidity and cost.

C. Discussion of Strengths and Limitations

In the published literature, there were ten studies that evaluated the effectiveness and safety of breast transilluminators. For the assessment of effectiveness of breast transilluminators, the highest level of evidence can be obtained by randomized controlled trials. However, no randomized controlled trials have been reported. The vast majority of the studies (n=9) were cross-sectional; there was one retrospective study. There was lack of information in the retrospective study if the readers were blinded to the breast cancer status of the optical scans. None of the studies were prospective studies where the patients are followed and imaged again at a later time point.

The studies included women with suspicious breast lesions and ages ranging from 22 to 93 years. However, none of the studies performed subgroup analysis for women with high breast density versus low breast density which may be influenced by the menopausal status, race, BMI and age. The effect of breast density on device performance is not clear.

Two studies[4,10] provided information on the variability of readers evaluating the results of optical imaging. The effectiveness of the optical imaging devices is influenced by reader variability.

A strength of the studies was the use of pathology results as reference, which is the gold standard for the detection of abnormalities in the breast. The majority of the studies (n=7) compared optical findings to histopathological results from biopsies.

V. Conclusions

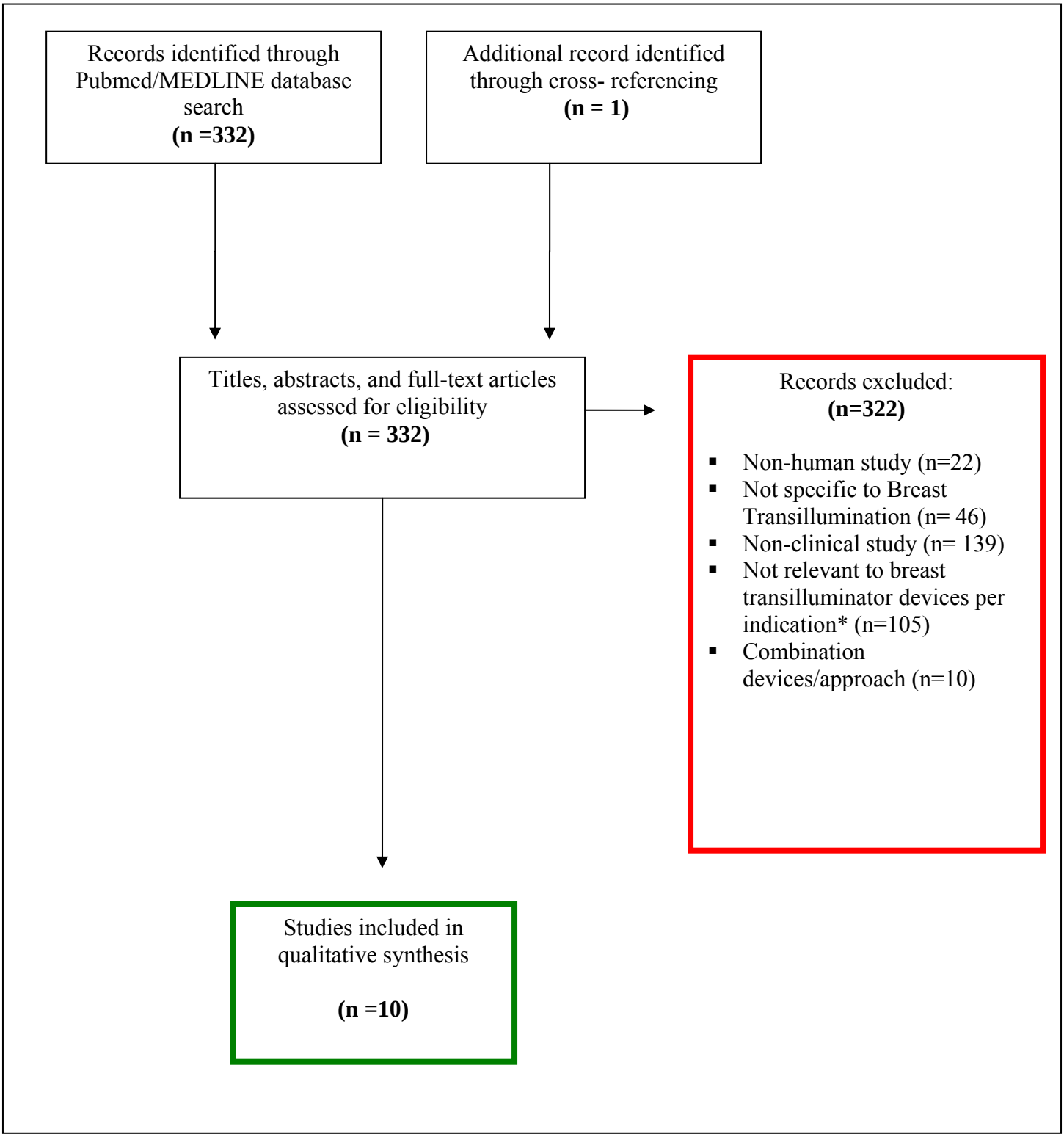
In the published literature, the limited number of studies does not adequately demonstrate the effectiveness of breast transilluminators. The rate of false positives and false negatives of optical imaging modalities in asymptomatic women with no palpable mass could not be ascertained. Thus, the current literature does not address the safety concerns regarding the extent of misdiagnosis resulting in delayed treatment or unnecessary biopsies in asymptomatic women.

There is a need for additional studies which will address the effectiveness and safety of transilluminators for the detection of cancer, other conditions, diseases, or abnormalities.

VI. Attachments

Figure 1: Inclusion and exclusion of articles from literature search
Appendix: List of articles which were not included in the literature review

Figure 1. Article Retrieval and Selection



*Other cancers, breast reconstruction, lymph nodes, margin, physiological properties MRI-guided near-infrared spectral tomography, Ultrasound (US)-guided optical tomography

References:

1. Athanasiou, A., Vanel, D., Fournier, L. & Balleyguier, C. Optical mammography: a new technique for visualizing breast lesions in women presenting non palpable BIRADS 4-5 imaging findings: preliminary results with radiologic-pathologic correlation. *Cancer Imaging* **7**, 34-40 (2007).
2. Cheng, X., *et al.* Breast cancer detection by mapping hemoglobin concentration and oxygen saturation. *Appl Opt* **42**, 6412-6421 (2003).
3. Grosenick, D., *et al.* Time-domain scanning optical mammography: II. Optical properties and tissue parameters of 87 carcinomas. *Phys Med Biol* **50**, 2451-2468 (2005).
4. Poellinger, A., *et al.* Breast cancer: early- and late-fluorescence near-infrared imaging with indocyanine green--a preliminary study. *Radiology* **258**, 409-416.
5. Poellinger, A., *et al.* Near-infrared laser computed tomography of the breast first clinical experience. *Acad Radiol* **15**, 1545-1553 (2008).
6. Poplack, S.P., *et al.* Electromagnetic breast imaging: results of a pilot study in women with abnormal mammograms. *Radiology* **243**, 350-359 (2007).
7. Rinneberg, H., *et al.* Scanning time-domain optical mammography: detection and characterization of breast tumors in vivo. *Technol Cancer Res Treat* **4**, 483-496 (2005).
8. Schneider, P., *et al.* Fast 3D Near-infrared breast imaging using indocyanine green for detection and characterization of breast lesions. *Rofo* **183**, 956-963.
9. van de Ven, S., *et al.* Diffuse optical tomography of the breast: initial validation in benign cysts. *Mol Imaging Biol* **11**, 64-70 (2009).
10. van de Ven, S.M., *et al.* Diffuse optical tomography of the breast: preliminary findings of a new prototype and comparison with magnetic resonance imaging. *Eur Radiol* **19**, 1108-1113 (2009).
11. Leff, D.R., *et al.* Diffuse optical imaging of the healthy and diseased breast: a systematic review. *Breast Cancer Res Treat* **108**, 9-22 (2008).

Appendix- List of articles which were not included in the literature review

1. The palpable breast lump: information and recommendations to assist decision-making when a breast lump is detected. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. CMAJ 158 Suppl 3, S3-8 (1998).
2. Abdalla, M.O., et al. Enhanced noscapine delivery using uPAR-targeted optical-MR imaging trackable nanoparticles for prostate cancer therapy. J Control Release 149, 314-322.
3. Adams, K.E., et al. Comparison of visible and near-infrared wavelength-excitable fluorescent dyes for molecular imaging of cancer. J Biomed Opt 12, 024017 (2007).
4. Akers, W., Lesage, F., Holten, D. & Achilefu, S. In vivo resolution of multiexponential decays of multiple near-infrared molecular probes by fluorescence lifetime-gated whole-body time-resolved diffuse optical imaging. Mol Imaging 6, 237-246 (2007).
5. Akers, W.J., et al. Targeting of alpha(nu)beta(3)-integrins expressed on tumor tissue and neovasculature using fluorescent small molecules and nanoparticles. Nanomedicine (Lond) 5, 715-726.
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