

# Near-Infrared Optical Mammography for Breast Cancer Detection with Intrinsic Contrast

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(Received 24 July 2011; accepted 9 September 2011; published online 5 October 2011)

Associate Editor Daniel Elson oversaw the review of this article.

**Abstract**—Optical methods to detect breast cancer on the basis of its increased opacity have been explored for some time. These methods have matured to a point in which they are capable of quantifying the optical properties of breast tissue and translating them into measures of concentrations of relevant tissue components. In particular, near-infrared spectroscopy has been employed to determine the concentrations of hemoglobin, water, and lipids, as well as oxygen saturation of hemoglobin and optical scattering properties in normal and cancerous breast tissue. Dynamic optical measurements can also identify abnormal hemodynamic patterns associated with breast cancer. We review, in this article, a number of results in the field, which show that cancerous tissue is associated with higher hemoglobin and water concentrations, and a lower lipid concentration with respect to normal breast tissue. Indications that breast cancers are characterized by lower hemoglobin saturation and stronger scattering decay as a function of wavelength are less robust, with variable results reported in the literature. Intrinsic sources of optical contrast associated with breast cancer can also be used to monitor individual response to neoadjuvant therapy.

**Keywords**—Breast cancer, Diffuse optical imaging, Photon migration, Intrinsic optical contrast, Hemoglobin concentration.

## INTRODUCTION

Optical mammography is a diffuse optical imaging technique that aims at detecting breast cancer, characterizing its physiological/pathological state, and/or monitoring the efficacy of therapeutic treatment. The basic idea is to illuminate the breast with red/near-infrared light that is then detected after it has propagated through breast tissue. The detected optical signals provide information on the spatial distribution of the

optical properties of breast tissue, which are in turn associated with features that bear diagnostic potential. This article reviews the sources of intrinsic optical contrast featured by breast cancer, their biological, physiological, and pathological correlates, their measurements reported in the literature, and typical optical breast imaging methods.

## SOURCES OF INTRINSIC OPTICAL CONTRAST IN BREAST TISSUE

The useful spectral window for optical mammography, i.e., the wavelength range over which light transmission is appropriate for transillumination of the female breast, extends from ~600 to ~1100 nm. This spectral region determines the sources of intrinsic optical contrast in breast tissue, which are associated with optical scattering and light absorption, either in static or dynamic measurements. This section covers such sources of optical contrast and associated biologic features of normal and cancerous breast tissue.

### *Scattering Contrast*

At the wavelengths used for diffuse optical mammography (600–1100 nm), breast tissue is highly scattering, and the reduced scattering coefficient ( $\mu'_s \sim 6\text{--}15 \text{ cm}^{-1}$ ) is significantly greater than the absorption coefficient ( $\mu_a \sim 0.02\text{--}0.12 \text{ cm}^{-1}$ ). The reduced scattering coefficient and its wavelength dependence are optical parameters that reflect tissue structure at cellular and subcellular levels, as well as tissue architecture.<sup>42</sup> For this reason, scattering amplitude (associated with the value of the reduced scattering coefficient, and denoted with  $a$ ) and scattering power (associated with its wavelength dependence, and denoted with  $b$ ) are optical parameters that reflect

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intrinsic contrast associated with tissue structure as well as size and spatial distribution of cellular and subcellular units. The scattering amplitude and power can be defined by the following equation<sup>51</sup>:

$$\mu'_s = a \left( \frac{\lambda}{\lambda_0} \right)^{-b}, \quad (1)$$

where  $\lambda_0$  is a reference wavelength. According to Eq. (1),  $a$  has units of  $\text{cm}^{-1}$  and represents the reduced scattering coefficient at  $\lambda_0$ , whereas  $b$  is dimensionless and describes the wavelength dependence of the reduced scattering coefficient. A slightly different definition of scattering amplitude ( $A$ ) and power ( $B$ ) is ubiquitous in the literature, namely,  $\mu'_s = A\lambda^{-B}$ , but this definition raises the question: what are the units and the physical meaning of  $A$ ? Furthermore, it does not decouple the two coefficients (in fact  $A = \mu'_s(\lambda_0)\lambda_0^B$ ), which can explain the strong correlation between  $A$  and  $B$  that has been reported.<sup>10</sup> However, the information content of the scattering power according to the two definitions ( $b$  and  $B$ ) is the same. Values of the scattering power  $b$  in breast tissue vary significantly with tissue composition and are typically within the range of 0.4–1.6.<sup>9,14</sup>

#### Absorption Contrast

The absorption of oxy-hemoglobin and deoxy-hemoglobin dominates at the shorter wavelengths (600–850 nm) of the spectral window for optical mammography. The molar extinction coefficient of oxy-hemoglobin and deoxy-hemoglobin at the isosbestic point of ~800 nm is ~2000  $\text{cm}^{-1} \text{M}^{-1}$  (for a full hemoglobin molecule (four heme groups) and extinction coefficients defined to base  $e$ ). The absorption of lipids and water are relevant at longer wavelengths (900–1000 nm) [as a result of absorption peaks at 925 nm (lipids) and 975 nm (water)], and collagen content can be characterized by means of even longer wavelengths (1000–1100 nm) as a result of a collagen absorption peak at ~1,025 nm.<sup>51,53</sup> Quantification of oxy-hemoglobin ([HbO]) and deoxy-hemoglobin ([Hb]) concentrations in breast tissue allows for measurements of tissue oxygen saturation  $\{\text{StO}_2 = [\text{HbO}] / ([\text{HbO}] + [\text{Hb}])\}$  and total hemoglobin concentration  $([\text{HbT}] = [\text{HbO}] + [\text{Hb}])$ . The absorption spectrum resulting from typical concentrations of HbO, Hb, lipids, and water in breast tissue, namely,  $[\text{HbO}] = 36 \mu\text{M}$ ,  $[\text{Hb}] = 17 \mu\text{M}$ ,  $[\text{Water}] = 16\%$ , and  $[\text{Lipid}] = 66\%$  (see references in Table 1) is reported in Fig. 1, where one can appreciate the relatively low absorption of breast chromophores at wavelengths between 600 and 1,000 nm. The molar extinction coefficients of

oxy-hemoglobin and deoxy-hemoglobin, as well as the absorption of fat,<sup>58</sup> were taken from data tabulated by Scott Prahl (<http://omlc.ogi.edu/spectra>), whereas the absorption spectrum of water was taken from Hale and Querry.<sup>23</sup> Figure 1 also shows the reduced scattering spectrum given by Eq. (1), with  $\lambda_0 = 670 \text{ nm}$ ,  $a = 10.5 \text{ cm}^{-1}$ , and  $b = 0.8$ , which are typical values for breast tissue (see references in Table 1).

#### Optical Indices

A variety of optical indices have been introduced to identify optical measurements that best correlate with the pathological state of breast tissue or with tissue density levels. For example, tissue optical indices (TOI) aimed at enhancing contrast between cancerous and healthy tissue have been defined as follows: Shah *et al.*<sup>47</sup>

$$\text{TOI}_1^{(\text{cancer})} = \frac{[\text{H}_2\text{O}][\text{HbT}]}{[\text{Lipid}]\text{StO}_2}, \quad (2)$$

Cerussi *et al.*<sup>10</sup>

$$\text{TOI}_2^{(\text{cancer})} = \frac{[\text{H}_2\text{O}][\text{Hb}]}{[\text{Lipid}]}, \quad (3)$$

Choe *et al.*<sup>12</sup>

$$\text{TOI}_3^{(\text{cancer})} = \frac{[\text{HbT}] \mu'_s}{\text{StO}_2}. \quad (4)$$

The definitions in Eqs. (2)–(4) are based on some results indicating that, in comparison with healthy tissue, breast cancer may feature (1) a greater hemoglobin concentration, water content, and reduced scattering coefficient; and (2) a lower lipid content and hemoglobin saturation. These findings are described below in “**Optically Measured Features of Breast Cancer**” section and discussed in “**Discussion**” section. A synthetic tissue optical index that is hypothesized, on the basis of breast physiology, to correlate with mammographic tissue density has been defined by Taroni *et al.*<sup>52</sup> as follows:

$$\text{TOI}^{(\text{tissue density})} = \frac{[\text{H}_2\text{O}][\text{Collagen}] b}{[\text{Lipid}]}. \quad (5)$$

#### Dynamic Responses to Pressure Perturbations and Physiological Challenges

Pressure-induced microvascular changes can differentiate tissue regions characterized by different mechanical properties. In fact, externally applied pressure induces a spatial distribution of interstitial

TABLE 1. Optically measured parameters of normal breast tissue and breast cancer.

Reference	<i>n</i> Cancer	Scattering ( <i>a</i> or $\mu'_s$ ) Cancer	Scatter power ( <i>b</i> )		[HbT] ( $\mu\text{M}$ )		StO <sub>2</sub> (%)		[Water] (%)		[Lipid] (%)	
			Normal	Cancer	Normal	Cancer	Normal	Cancer	Normal	Cancer	Normal	Cancer
37	5	—	—	—	18(5)	130(100)	69(6)	60(9)	—	—	—	—
11	44	—	—	—	—	↑	—	↓	—	—	—	—
50	32	↓	~0.7	→	12(6)	↑	71(10)	→	—	—	—	—
22	87	↑	1.0(3)	1.4(7)	17(6)	53(30)	74(7)	72(4)	—	—	—	—
25	14	—	0.5(2)	—	20(4)	28(9)	70(8)	68(16)	38(21)	41(16)	—	—
10	58	↑	0.6(2)	0.7(3)	17(7)	24(9)	68(9)	68(8)	19(10)	26(13)	66(10)	59(15)
16	19	↓ → ↑	—	—	—	↑	—	↓ →	—	—	—	—
12	41	↑	—	—	—	↑	—	→	—	—	—	—
61	3	→	1.0(2)	1.3(2)	17(2)	28(4)	68(4)	64(5)	15(4)	26(2)	69(18)	45(7)
65	61	—	—	—	39(15)	70(18)	—	—	—	—	—	—
18	26	↑	0.91(1)	—	19(6)	27(14)	73(6)	75(6)	—	—	—	—

*n* is the number of cancerous lesions investigated. Numbers in parenthesis indicate standard deviations. Arrows indicate whether the corresponding parameter in breast cancer is smaller (↓), comparable (→), or greater (↑) than in normal breast tissue. Multiple arrows in a cell indicate different results observed across subjects.

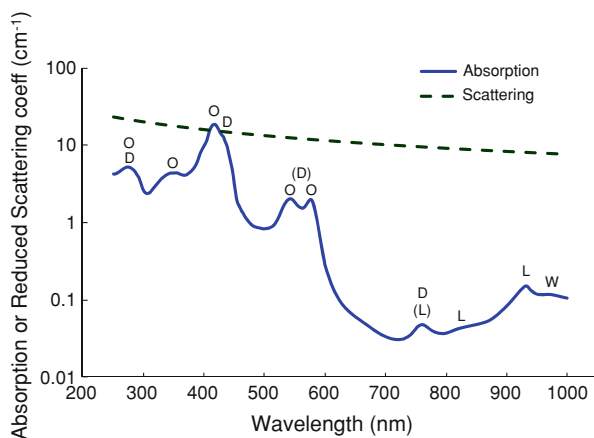


FIG. 1. The continuous line is the absorption spectrum resulting from typical concentrations of HbO, Hb, lipids, and water in breast tissue, namely [HbO] = 36  $\mu\text{M}$ , [Hb] = 17  $\mu\text{M}$ , [Water] = 16%, and [Lipid] = 66% (see references in Table 1). The dashed line is the reduced scattering spectrum given by Eq. (1) with  $\lambda_0 = 670 \text{ nm}$ ,  $a = 10.5 \text{ cm}^{-1}$ , and  $b = 0.8$ , which are typical values for breast tissue (see references in Table 1). The chromophores associated with specific absorption peaks are indicated as O (oxy-hemoglobin), D (deoxy-hemoglobin), L (lipids), and W (water). Absorption peaks of individual tissue chromophores giving minor contributions to the overall absorption spectrum are indicated in parenthesis [(D), (L)].

fluid pressure (IFP) that reflects local tissue stiffness. In turn, perturbations to the IFP determine transient changes in the vascular architecture, blood flow, blood volume, and tissue saturation that can be measured with non-invasive optical techniques to reveal tissue dynamics characteristic of healthy tissue, benign lesions, and cancerous tissue. An intrinsic spatial distribution of IFP in tissue can also result in a source of contrast for the hemodynamic response to a number of physiological challenges.

### Physiological Basis for the Diagnostic Value of Intrinsic Optical Contrast

Cellular organization, subcellular morphology, size, and density of cellular organelles all contribute to the tissue-reduced scattering coefficient and to its wavelength dependence.<sup>42</sup> Light scattering spectroscopy (LSS), a single-scattering technique, has been employed to detect early cancerous changes in a variety of organs.<sup>38</sup> Elastic scattering spectroscopy (ESS), a diffuse reflectance technique, has been applied to breast cancer diagnosis as an optical biopsy approach.<sup>3</sup> These optical scattering diagnostic techniques reveal cancer-induced structural changes at a cellular level, as well as changes in size and density of subcellular components (nuclei, mitochondria, etc.).<sup>34</sup>

Total hemoglobin concentration in tissue ([HbT]), which is directly related to blood volume, is affected by vascularization changes induced by tumor growth. Such vascularization effects include (a) perturbations to the morphology and functional viability of pre-existing host vessels, and (b) neovascularization due to tumor angiogenesis factors.<sup>1,59</sup> The abnormal vascular architecture of cancerous tissue (including dilatation of blood vessel, vascular tortuosity, formation of cystiform blood vessel, etc.), neovascularization, and blood cell extravasation (hemorrhage) all contribute to a local increase in [HbT].

In healthy tissue, the oxygen saturation of hemoglobin (StO<sub>2</sub>) is the result of the balance of oxygen supply (as determined by arterial saturation, blood hemoglobin concentration, and blood flow) and oxygen demand (as determined by the tissue metabolic rate of oxygen). In cancerous tissue, there are a number of complicating factors, such as the structural and functional disruption of the microvasculature, altered

diffusion conditions that may impair effective oxygen transport to the tissue,<sup>24</sup> and a right shift in the hemoglobin dissociation curve as a result of tissue acidosis,<sup>19,59</sup> which determines lower hemoglobin saturation values for a given partial pressure of oxygen. One has to keep in mind that the value of  $StO_2$  measured with optical methods reflects the oxygen bound to hemoglobin or, more exactly, the fraction of hemoglobin that binds oxygen within the volume probed by the optical sensor. In a situation where the vasculature is structurally and functionally disrupted, cystiform, or tortuous blood vessels, unstable direction, and speed of blood flow, obstruction of microvessels, arteriovenous shunts, and blood extravasation are all elements that play a role in determining the value of  $StO_2$ . Consequently, blood flow and oxygen consumption are the only two of a number of factors that determine  $StO_2$ . Blood flow in non-necrotic breast cancer tissue has been reported to be greater ( $0.07\text{--}0.40\text{ mL g}^{-1}\text{ min}^{-1}$ ,<sup>2</sup>  $0.35\text{ mL g}^{-1}\text{ min}^{-1}$ ,<sup>49</sup>) than blood flow in post-menopausal normal breast tissue ( $\sim 0.04\text{ mL g}^{-1}\text{ min}^{-1}$ ,<sup>2</sup>). The range of oxygen consumption rates in breast cancer ( $3\text{--}10\text{ }\mu\text{L g}^{-1}\text{ min}^{-1}$ ) has been reported to include higher values than that in the postmenopausal breast ( $3\text{--}6\text{ }\mu\text{L g}^{-1}\text{ min}^{-1}$ ), albeit the two ranges overlap.<sup>59</sup> However, the partial pressure of oxygen ( $pO_2$ ), a measure of the amount of oxygen actually available for cellular metabolism, was found to be significantly lower in breast cancers [median: 24 mmHg for pathological stages  $T_1\text{--}T_2$  ( $n = 10$ ); median: 35 mmHg for pathological stages  $T_3\text{--}T_4$  ( $n = 5$ )]<sup>60</sup> than in normal breast tissue [median: 65 mmHg ( $n = 16$ )]. Furthermore, direct measurements of intracapillary oxygen saturation of hemoglobin in animal tumor models<sup>43</sup> and in human tumors of the oral cavity<sup>35</sup> have been found to be significantly lower than hemoglobin saturation values measured in normal tissues. Finally, diffuse reflectance spectroscopy performed by a biopsy-needle-based optical sensor *in situ*, before surgical resection of breast tumors, has found significantly lower  $StO_2$  values in malignant tissues ( $\sim 45\%$ ) vs. non-malignant tissues ( $\sim 82\%$ ).<sup>4</sup>

An *ex vivo* magnetic resonance spectroscopy (MRS) study in animal models has shown that cancerous tissue has a higher percent water content ( $\sim 80$  to  $93\%$ ) with respect to normal tissue ( $\sim 66$  to  $77\%$ ).<sup>30</sup> *In vivo* MRS studies on human subjects have found that breast cancer shows an elevated water-to-fat ratio with respect to benign lesions and normal breast tissue.<sup>26,55</sup> This finding is consistent with the  $[H_2O]/[Lipid]$  factor in the TOI of Eqs. (2) and (3) that are aimed at enhancing tumor contrast in optical images. It has also been reported that, with respect to normal tissue,

breast cancer features a decreased tissue collagen content.<sup>6</sup>

Invasive breast cancers are associated with higher IFP than benign tumors and normal breast tissue,<sup>36</sup> which affects local hemodynamics. Breast cancer is also typically stiffer than normal tissue; Young's modulus values of  $\sim 3$  kPa for normal breast tissue and  $10\text{--}42$  kPa for different breast cancers have been measured *ex vivo*,<sup>44</sup> and a cancer-to-normal tissue elasticity contrast of  $\sim 6.4$  has been reported *in vivo*.<sup>33</sup> This contrast in the IFP and in the mechanical properties of cancerous tissue can affect cancer hemodynamics both at baseline and in response to physiological challenges or externally applied mechanical perturbations to the tissue.

### OPTICALLY MEASURED FEATURES OF BREAST CANCER

A near-infrared spectroscopy study has quantified the concentration of the main chromophores in breast tissue (oxy-hemoglobin, deoxy-hemoglobin, water, and lipids), and their intra- and inter-subject variabilities in healthy subjects.<sup>41</sup> A review of clinical studies involving optical mammography has been recently published, and it is a valuable reference for optical measurements on healthy and diseased breasts.<sup>32</sup> Table 1 reports a number of optically measured parameters of normal breast tissue and breast cancer taken from the recent literature. Numbers in Table 1 are average values of the parameters over multiple subjects, with associated standard deviations indicated in parentheses. When no specific values are provided, an arrow in the "cancer" column indicates whether the corresponding parameter is smaller ( $\downarrow$ ), comparable ( $\rightarrow$ ), or greater ( $\uparrow$ ) in breast cancer compared to normal breast tissue.

#### Scattering Properties

The two parameters that characterize scattering properties are the scattering amplitude  $a$  (or the value of  $\mu'_s$  at a reference wavelength) which is mainly associated with the density of the scattering centers, and the scatter power  $b$  (or the wavelength dependence of  $\mu'_s$ ), which is mainly associated with their size distribution. The scattering amplitude was found to be smaller,<sup>50</sup> comparable,<sup>61</sup> or greater<sup>10,12,18,22</sup> in breast cancer compared with normal breast tissue.<sup>16</sup> A more consistent result of a greater scatter power in breast cancer vs. normal tissue has been reported, even though such cancer-induced increase in scatter power may be small,<sup>10</sup> and some studies have not detected any scatter power contrast in malignant tumors.<sup>50</sup>

### *Concentration and Oxygen Saturation of Hemoglobin*

As discussed in “[Absorption Contrast](#)” section, the absorption contrast provided by breast cancer at the shorter wavelengths (600–850 nm) of the diagnostic spectral window is mostly associated with the tissue concentrations of oxy-hemoglobin and deoxy-hemoglobin. In turn, their sum is associated with the blood volume and their ratio is associated with the oxygen saturation of hemoglobin. As shown in [Table 1](#), breast cancer is consistently associated with a greater [HbT] with respect to normal breast tissue. While this appears to be a strong optical signature of breast cancer, it is also not highly specific as other benign breast lesions can also be associated with higher levels of blood volume. The oxygen saturation of hemoglobin in tissue (StO<sub>2</sub>), with its functional information content related to blood flow, tissue metabolic rate, vasculature viability, and efficiency of oxygen diffusion, holds promise for being a more specific parameter for cancer detection. However, while there are reports of oxygen desaturation in breast cancer,<sup>11,37,63</sup> a number of studies have reported inconsistent results across subjects,<sup>16,61</sup> or have not detected a significantly lower cancerous vs. normal tissue StO<sub>2</sub>.<sup>10,18,22,25,50</sup>

### *Water and Lipid Content*

Optical measurements, especially if spectrally extended at wavelengths beyond 900 nm, can quantify water and lipid content in tissue. As reported in [Table 1](#), these measurements have consistently found a higher water content and a lower lipid content in cancerous tissue vs. normal breast tissue. This is consistent with the MRS studies mentioned in “[Physiological Basis for the Diagnostic Value of Intrinsic Optical Contrast](#)” section.<sup>26,30,55</sup>

### *Dynamic Features*

Optical measurements, with their strong sensitivity to hemodynamics and blood distribution, lend themselves to dynamic measurements under baseline conditions, in association with externally applied pressure to breast tissue, or in response to physiological challenges.

Diffuse correlation measurements based on the temporal decay of the optical autocorrelation function have shown a significantly greater blood flow in human breast cancers with respect to measurements on healthy tissue.<sup>15</sup> This is consistent with the results obtained with dynamic positron emission tomography.<sup>2,49</sup>

Studies of the hemodynamics following breast compressions in healthy volunteers have found that the

externally applied pressure induces changes in [HbT] and StO<sub>2</sub>,<sup>28,29</sup> which can also be employed to estimate tissue blood flow and oxygen consumption.<sup>5</sup> These pressure-induced dynamic changes in the hemodynamics have the potential to provide additional physiological parameters of diagnostic value in optical mammography. In fact, a study of the hemodynamic changes induced by externally applied pressure has found significantly different rates of change of [HbT] and StO<sub>2</sub> in breast cancer vs. healthy tissue.<sup>62</sup> Furthermore, a dynamic optical breast imaging study, based on the optical transmission variability during externally applied pressure to the breast (a sequence of 15 s at 5 mmHg, 30 s at 10 mmHg, 15 s at 5 mmHg), found that a monotonic intensity change during pressure application (as opposed to oscillatory or no change) is indicative of malignancy.<sup>20</sup>

A study of the response to a Valsalva maneuver (named after the Italian physician Antonio Maria Valsalva), which consists of forcibly attempting expiration with the nose and mouth closed, has found that during such maneuver breast cancer features a greater increase in deoxy-hemoglobin concentration than normal tissue.<sup>45</sup> The Valsalva maneuver is just one example of a physiological challenge that can affect tissue hemodynamics and identify tissue regions with compromised vascularization, elevated IFP, and/or abnormal metabolic rate such as the case for cancerous tissue.

## **OPTICAL IMAGING APPROACHES TO BREAST CANCER DETECTION**

[Figure 2](#) gives a visual summary of the kinds of images generated by optical mammography. In general, these are low-resolution images because of the diffusive nature of light propagation in tissue. The value of these images rests on the contrast provided by breast cancer on the basis of a number of physiological parameters as described above. The images of [Fig. 2](#) are representative of the state of the field, and we will not attempt to describe them in great detail here. Interested readers are directed to the references provided in the caption of [Fig. 2](#) for their detailed description (instrumentation, method of image reconstruction, study protocol, information content, etc.). Nevertheless, it is useful to go over the major features of those images, which are all based exclusively on intrinsic contrast, to get a sense of the range of imaging approaches in the field of optical mammography.

Instrumentation for optical mammography employs continuous-wave (CW) methods (i.e., time-independent illumination) ([Fig. 2b, e, f, i, l, m](#)), time-domain methods (i.e., pulsed illumination) ([Fig. 2c, g, h, j](#)),

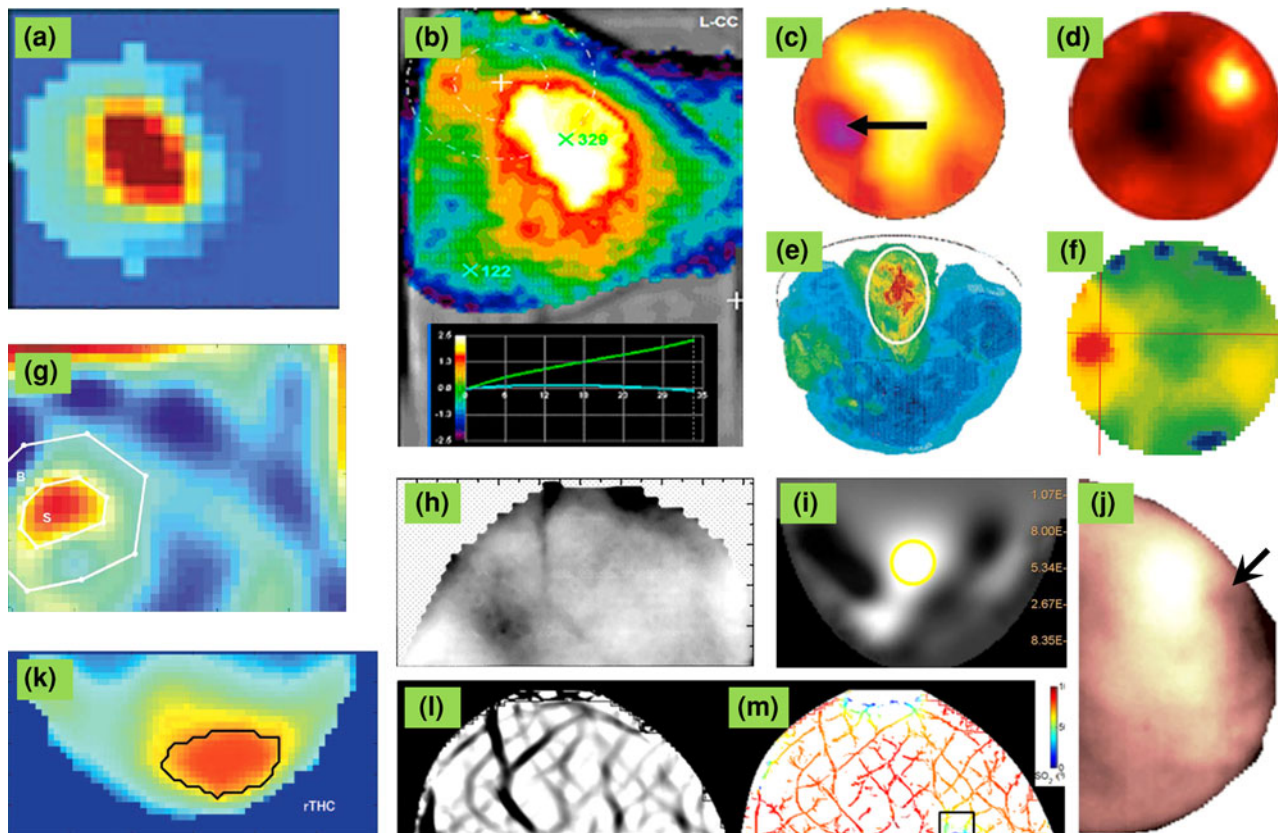


FIG. 2. Representative optical mammograms from the published literature. (a) [HbT] image of a 0.6-cm invasive ductal carcinoma.<sup>65</sup> (b) Dynamic optical image of an intraductal carcinoma during external pressure application to the breast.<sup>20</sup> (c) Hemoglobin saturation image of a 1.3-cm intracystic carcinoma.<sup>16</sup> (d) [HbT] image of 3.4-cm infiltrating ductal carcinoma.<sup>61</sup> (e) Dynamic [Hb] image of a ductal carcinoma during a Valsalva maneuver.<sup>45</sup> (f) Optical tomography image of a 1-cm adenocarcinoma.<sup>13</sup> (g) Absorption image of a 2-cm infiltrating carcinoma.<sup>25</sup> (h) Absorption image of an invasive ductal carcinoma.<sup>21</sup> (i) Absorption image of an invasive ductal carcinoma.<sup>57</sup> (j) Late-gated intensity image of a 1.5-cm lobular invasive carcinoma.<sup>54</sup> (k) [HbT] image of 2.2-cm invasive carcinoma.<sup>12</sup> (l) Spatial second-derivative image and (m) hemoglobin saturation image of a ductal carcinoma in situ (DCIS).<sup>63</sup>

frequency-domain methods (i.e., sinusoidally modulated illumination) (Fig. 2a), or hybrid frequency-domain/CW methods (Fig. 2d, k). Light sources and optical detectors can be placed at a number of fixed locations (Fig. 2a–f, i, k) or can be mechanically scanned over breast tissue (Fig. 2g, h, j, l, m). Measurements can be performed on the pendulous breast immersed in an optically matching fluid (a liquid with optical properties similar to those of breast tissue) (Fig. 2c, f, i, k) possibly involving a mild compression between Plexiglas plates (Fig. 2g). A planar geometry involving a slight breast compression between glass plates is also common (Fig. 2b, h, j, l, m), as well as a circular arrangement of optical fibers brought in contact with the pendulous breast (Fig. 2d, e). Finally, hand-held optical probes are also used, such as those that generated (Fig. 2a).

Optical mammograms can be based directly on the measured optical intensity after proper processing such as late-gating in time-domain measurements (Fig. 2j),

spatial second-derivative filtering (Fig. 2l), or tomographic back-projection reconstruction (Fig. 2f). Absorption images can be obtained by an algebraic reconstruction technique and a first-order perturbation to a diffusion model for a flat (Fig. 2g) or circular (Fig. 2i) geometry, or they can represent an effective absorption coefficient by means of a diffusion model for a homogeneous, infinite slab (Fig. 2h). By measuring the absorption coefficient at multiple wavelengths, it is possible to generate images of hemoglobin concentration and saturation, such as those of Fig. 2a (wavelengths: 780 and 830 nm), Fig. 2c (wavelengths: 780 and 815 nm), Fig. 2d (wavelengths: 661, 761, 785, 808, 826, 849, 903, 912, and 948 nm), Fig. 2k (wavelengths: 650, 690, 750, 786, 830, and 905 nm), and Fig. 2m (continuous spectrum 650–900 nm). Optical mammograms can also be based on dynamic measurements reflecting the temporal evolution of the transmitted optical intensity through the breast (Fig. 2b), or of the tissue concentration of deoxy-hemoglobin (Fig. 2e).

Instruments for optical imaging of the breast seek to find an optimal compromise between the requirements of maximal information content of the collected data and a clinically acceptable duration of the optical imaging procedure. In particular, the information content of the collected optical data determines the ability to measure:

- *tissue optical properties* (time-resolved methods are typically more powerful than CW methods);
- *spatial features* (planar raster scanning of sources and detectors can achieve a higher spatial sampling rate than fixed source-detector locations, at the possible cost of generating data with limited information content toward tomographic reconstruction);
- *dynamic tissue responses* (a fast temporal sampling rate from a fixed set of sources and detectors is ideal);
- *spectral features* (broadband spectroscopy can be significantly more powerful than measurements at a set of discrete wavelengths).

## DISCUSSION

This review article has focused on sources of intrinsic contrast for breast cancer detection using optical mammography. It is well established that breast cancer is consistently associated with an elevated hemoglobin concentration. However, the limited specificity of this parameter has pushed the research community toward the search for additional signatures of breast cancer; a search that has gone even beyond optical mammography as a stand-alone modality, or beyond sources of intrinsic contrast. In fact, intrinsic optical markers such as scattering properties and hemoglobin saturation have not shown to be robust indicators of malignancy, while optical measurements of water and lipid content are prone to significant uncertainties as demonstrated by the standard deviations in Table 1. Given that cancerous tissue has a reduced oxygen tension<sup>60</sup> and a lower intracapillary oxygen saturation of hemoglobin,<sup>35,43</sup> it is somewhat surprising that measurements of  $\text{StO}_2$  have not been more efficient at discriminating cancerous tissue from normal tissue and other benign lesions. This may be a consequence of the fact that macroscopic measurements of tissue  $\text{StO}_2$  represent some kind of spatial averaging of a highly inhomogeneous blood and oxygenation distribution in cancer tissue. Furthermore, as discussed in “[Physiological Basis for the Diagnostic Value of Intrinsic Optical Contrast](#)” section, tissue  $\text{StO}_2$  results from the interplay of oxygen supply, oxygen demand, and oxygen delivery, which are

affected by a number of physiological and pathological conditions that can vary significantly over cancer types or stages, tissue location, individuals, subject’s age, menopausal states, etc. The latter issues are generally relevant for optical mammography studies, as it has been demonstrated that the optical properties of breast tissue are significantly affected by subject’s age,<sup>7</sup> premenopausal, postmenopausal, and hormone replacement therapy conditions,<sup>46</sup> and phase of menstrual cycle.<sup>14,39</sup> These results indicate the importance of age stratification, and suggest the potential value of synchronizing optical mammography exams with the subject’s menstrual cycle.

There is one application of optical mammography that can take advantage of its high sensitivity to the hemoglobin concentration of cancerous tissue, without suffering from the limited specificity of this measure. In fact, a non-invasive technology such as intrinsic-contrast-based diffuse optical imaging, which can be safely performed repeatedly on the same subject at regular time intervals, is particularly suited for monitoring individual response to neoadjuvant cancer therapy.<sup>17</sup> It has been reported that, in patients who respond to therapy, treatment induces a decrease in hemoglobin concentration, water concentration, and scattering power [ $b$  of Eq. (1)] at the cancer location,<sup>8,48</sup> and an increase in the lipid concentration<sup>64</sup> (one study also found an increase in  $\text{StO}_2$ <sup>27</sup>). Consequently, these results suggest that optical measurements based on intrinsic contrast may provide a valuable predictor for individual response to neoadjuvant therapy.

In this article, we have specifically focused on studies that aim at translating measurements of optical contrast of breast cancers into a contrast in optical absorption, scattering, hemoglobin/water/lipid content, or dynamic features. It is important to mention that there are other alternative approaches that do not attempt at translating optical measurements into parameters that are then tested for their level of association with malignancy. For example, from broadband spectral measurements, one may introduce dedicated metrics to classify spectral features associated with either benign and malignant tumors.<sup>31</sup>

## CONCLUSION

The potential of diffuse optical imaging does not rest on its spatial resolution, which is intrinsically limited by tissue scattering, but rather on the combination of its high sensitivity to several physiologically relevant tissue components, its safe and non-invasive applicability, and the relatively compact and cost-effective instrumentation. There is certainly research value in exploring synergistic combinations of optical

mammography with other medical imaging techniques.<sup>40</sup> Such synergy is particularly appealing when it involves techniques like ultrasound imaging that feature safe and compact instrumentation similarly to optical imaging, or when it seeks to acquire subject-specific spatial priors that are applicable to a series of optical investigations on the same subject. The quest for optical contrast agents to enhance the sensitivity and specificity of optical detection of breast cancer is also significant, as it may introduce a new level of molecular specificity that is not achievable with intrinsic contrast.<sup>56</sup> However, the realization of diffuse optical imaging into a stand-alone modality based on intrinsic contrast would maximize the fulfillment of its potential as a safe and non-invasive technology, and would allow for its development into a widely applicable diagnostic tool.

### ACKNOWLEDGMENTS

The authors wish to acknowledge the financial support from the National Institutes of Health, Grant No. R01 CA154774.

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