Optical study on the dependence of breast tissue composition and structure on subject anamnesis

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ABSTRACT

Time domain multi-wavelength (635 to 1060 nm) optical mammography was performed on 200 subjects to estimate their average breast tissue composition in terms of oxy- and deoxy-hemoglobin, water, lipid and collagen, and structural information, as provided by scattering parameters (amplitude and power). Significant (and often marked) dependence of tissue composition and structure on age, menopausal status, body mass index, and use of oral contraceptives was demonstrated.

Keywords: Tissue diagnostics, time-resolved diffuse optical imaging, tissue composition, breast cancer.

1. INTRODUCTION

Breast density is defined as the fibro-glandular fraction of breast tissue. It is recognized as a strong and independent risk factor for breast cancer: the risk is four to six times higher for high breast density than for low density.[1]

Breast tissue composition is responsible for breast density. However, breast density is routinely quantified by x-ray mammography that is mostly sensitive to water absorption. More generally, x-ray images are determined by the overall tissue attenuation and cannot discriminate among individual contributions.

Conversely, optical spectroscopy offers a non-invasive means for a more complete characterization of tissue composition and allows one to study the dependence on parameters that may affect density and the related risk to develop breast cancer. The present study explores the correlation of optically derived breast tissue composition (water, lipids, and collagen, oxy- and deoxyhemoglobin) and microscopic structure (through the scattering parameters a and b) with parameters of patient anamnesis that are known to affect breast cancer risk or investigated as potential risk factors (age, menopausal status, body mass index, and use of oral contraceptives).

2. MATERIALS AND METHODS

2.1. Instrument set-up[2]

The instrument is a transportable stand-alone set-up on wheels, suitable for use in a clinical environment.

It is designed to collect projection images in compressed breast geometry.

Time-resolved transmittance measurements are performed at seven wavelengths (635, 685, 785, 905, 930, 975, 1060 nm) using picosecond pulsed diode lasers. The pulses at the seven wavelengths are time-multiplexed and coupled to a single illumination optical fiber.

The compressed breast is raster-scanned continuously, moving the illumination fiber and a collecting fiber bundle in tandem, and recording data every millimeter.

The transmitted photons are detected using two separate photomultiplier tubes, sensitive respectively below and above 850 nm. Two PC-boards for time-correlated single photon counting record the transmittance curves at the seven wavelengths.

The acquisition time depends on the extension of the area to be scanned and in typically of the order of 5 minutes. Optical images are routinely acquired from both breasts in cranio-caudal and medio-lateral oblique (45°) views.

2.2. Patient study

The Institutional Review Board at the European Institute of Oncology approved the clinical study. Written informed consent was obtained from all the participants.

The study had twofold aim: i) the non-invasive assessment of breast density by optical means, and ii) the optical characterization of malignant and benign lesions (not considered here).

218 subjects enrolled in the study. 200 subjects were further considered for the present analysis.

2.3. Data analysis

Absorption and reduced scattering coefficients at each wavelength are estimated by fitting the experimental data to an analytical solution of the diffusion approximation (with the extrapolated boundary condition) for an infinite homogeneous slab.[3,4]

Information on tissue composition and structure is obtained directly from time-resolved transmittance curves measured at seven wavelengths. A spectrally constrained global fitting procedure is applied that relies on the Beer law and a simple approximation to Mie theory to estimate the concentrations of oxy- and deoxy-hemoglobin (HbO_2 and Hb, respectively), water, lipids, and collagen, together with the scattering amplitude a and power b.[5] Total hemoglobin content $tHb = (HbO_2 + Hb)$ and oxygen saturation $SO_2 = HbO_2/tHb$ are then calculated.

For each breast view and wavelength, the estimate of bulk optical properties is limited to a reference area that excludes boundaries and marked inhomogeneities, but still includes most of the breast (as described in Ref. 2). For each subject all data from the four images (cranio-caudal and oblique views of both breasts) are averaged to provide the average characterization of the breast tissue of that subject.

2.4. Statistical methods

The statistical significance of the difference between two groups was assessed using the Mann-Whitney test at alpha = 0.05. Significance was considered when $p < 0.05$.

Statistical analysis was performed using IBM SPSS Statistics Release 21 and Minitab Version 16.

3. RESULTS AND DISCUSSION

We investigated the dependence of all optically-derived parameters (tHb, SO_2 water, lipids, collagen, a and b) on: age, menopausal status, body mass index, and use of oral contraceptives. The correlation with mammographic density, which has been previously studied on a smaller number of subjects,[6] was also preliminarily considered.

3.1. Mammographic density

Mammographic density was classified using BI-RADS categories 1 (almost entirely fat) to 4 (extremely dense).[7] In agreement with what observed previously,[6] upon increasing breast density the maximum absorption wavelength shifts from 930 to 975 nm, and the scattering spectrum becomes steeper. Concerning tissue composition, except for the oxygenation saturation SO_2, all parameters are significantly different (often with $p < 10^{-4}$) for category 2 *vs.* 3, and for category 3 *vs.* 4, while the difference between category 1 and 2 was appreciable ($p = 0.0037$) only for the water content. Specifically, water, collagen, total hemoglobin content tHb increase with mammographic density, while lipid content decreases. Moreover, both scattering amplitude a and power b increase. All these observations are in agreement with what expected based on breast physiology, namely an increasing weight of the fibroglandular fraction at the expenses of the adipose fraction for increasing density of the breast tissue.

3.2. Age

Age leads to a progressive replacement of fibroglandular tissue with adipose tissue, corresponding to a gradual reduction in mammographic density. This is already apparent from the absorption and scattering spectra. Even though a high inter-subject variability is observed, on average upon increasing age the absorption at 930 nm (mostly due to lipids) increases, while the absorption at 975 nm (water absorption peak) decreases correspondingly. Moreover, the average scattering slope decreases, in agreement with a higher lipid content. These visual observations are confirmed when tissue composition and structural parameters are considered. Specifically, all parameters, except SO_2, depend significantly on age: lipid content increases, while all other parameters decrease. In particular, Table 1 shows the results obtained when women ≤ 50 y and > 50 y are considered. The difference between the two groups is highly significant ($p < 10^4$) for all parameters but SO_2.

Table 1. Average tissue composition and scattering parameters of woman aged ≤50 y and > 50 y, respectively

Age	**Water** (mg/cm^3)	**Lipid** (mg/cm^3)	**Collagen** (mg/cm^3)	**tHb** (μM)	**SO$_2$** (%)	**a** (cm^{-1})	**b** (-)
≤ 50 y (N = 101)	261.08	595.45	95.76	13.16	85.48	14.76	0.73
> 50 y (N = 99)	119.62	743.08	64.53	10.60	86.07	12.37	0.49

3.3. Menopausal status

The average absorption and scattering spectra of pre- and postmenopausal subjects are shown in Figure 1. Even though, as already mentioned more in general for the dependence on age, a significant inter-subject variability is observed, the effects of menopause on the optical properties and on all optically derived tissue parameters (relative to both tissue composition and structure) are qualitatively similar to what described for age. This is somehow expected, as premenopausal women are on average younger than postmenopausal ones. However, it is worth noting that all parameters but SO_2 and scattering power b are still significantly different ($p < 0.01$) for pre- *vs.* postmenopausal women when age-adjusted groups of subjects are compared.

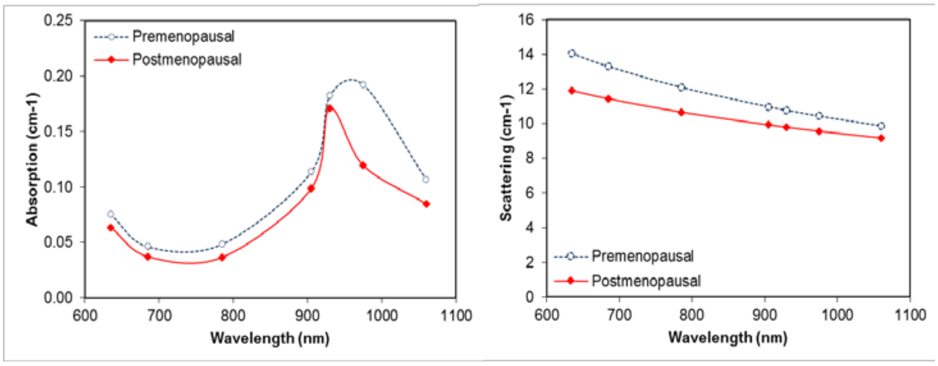

Figure 1. Average absorption spectra (left) and reduced scattering spectra (right) of premenopausal (blue, open symbol, dotted line) and postmenopausal (red, close symbol, solid line) women.

3.4. Body mass index (BMI)

The trend with BMI is also similar to what reported for age: upon increasing BMI, lipids increase progressively, SO_2 does not change significantly, while all other parameters decrease, denoting that on average higher BMI values also correspond to more adipose (*i.e.*, less dense) breasts, in agreement with what observed also with magnetic resonance imaging.[8]

3.5. Oral contraceptives (OCs)

The average absorption properties give some indication that OC use corresponds to a higher weight of the fibroglandular fraction, while the situation is not clear for the scattering properties (Figure 2). In line with what expected based on the optical properties, tissue composition is statistically different for the two groups, while scattering parameters are not significantly different. It has to be taken into account that OC users are on average younger than non-users and this might affect the results. After adjustment for age, the use of oral contraceptives still corresponds to higher collagen content and SO_2, even though the difference is only close to significance. However, it has to be mentioned that the group of non-users include women who never used OCs and women who were not using OCs at the time of the optical measurements, but may have used them in the past, and the latter subgroup may somehow confuse the comparison.

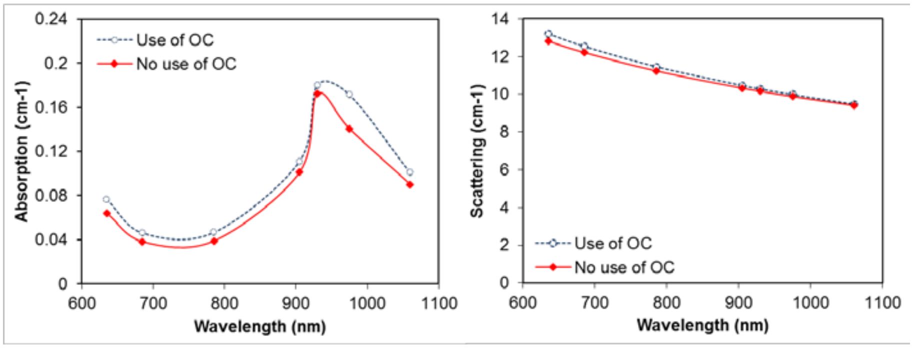

Figure 2. Average absorption spectra (left) and reduced scattering spectra (right) of users (blue, open symbol, dotted line) and non-users (red, close symbol, solid line) of oral contraceptives.

4. CONCLUSION

Optical mammography was performed on 200 subjects acquiring images at seven wavelengths in the red and near-infrared (637-10560 nm), and breast tissue composition and structure were estimated non-invasively from optical data.

The present study shows that time domain diffuse optical spectroscopy can effectively be applied to investigate the dependence of tissue composition on important risk factors for breast cancer, such as age, menopausal status, BMI and OC use.

Due to its non-invasiveness, the technique is also suitable for longitudinal monitoring studies and for testing the effectiveness of preventive interventions that aim at reducing the risk associated with breast density and may include changes in lifestyle as well as use of drugs.

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