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学位論文内容の要旨

博士の専攻分野の名称：博士（保健科学）　　氏名：Jeffrey Wang

Imaging biomarkers of breast cancer derived from breast parenchyma
（乳腺から派生した乳がんのイメージバイオマーカー）

Background

Radiology is in the process of transitioning from a largely qualitative practice into the quantitative era through technological advances of computers, imaging devices, and analysis methods. Imaging biomarkers as surrogate endpoints for disease outcomes have helped to make a great impact in the respect of personalizing medicine.

Breast cancer is the most common invasive cancer among women and its incidence is increasing. X-ray mammography continues to be the standard for screening and MR imaging has also been recognized as tremendously sensitive in breast cancer diagnosis. Over recent years, the ability to stratify patients based on genetic, hormonal, lifestyle, and more recently imaging biomarkers, has proven to be of great value toward individualized healthcare, dropping breast cancer to the second leading cause of cancer death with women in developed nations, and further developments are expected to enhance it even further.

Recent research has shown that a tumor’s microenvironment also contains information about the nature of the cancer, potentially defining and regulating its progression. With breast cancer, it is being gradually recognized as the key contributor to aggressiveness. Characteristics of fibroglandular parenchyma breast tissue appear to be related to risk and subtypes of breast cancer and are being investigated heavily.

Computer-Aided Diagnosis (CAD) systems have been making major contributions to improving healthcare for many years, with early successes realized in breast cancer imaging. As imaging and computing technologies develop, image processing and bioinformatics tools are now able to extract large numbers of quantitative features from images, producing data mineable for information reflecting any underlying pathophysiology. This extension of CAD, known as radiomics, is poised to advance classification, prognosis of treatment response or other disease outcomes, and monitoring disease status. Driven by this recent progress due to data availability in parallel with computational scale, new statistical and machine learning approaches can be exploited to discover and validate useful biomarkers and elucidate relationships in the complexity of cancer and radiomics datasets.

Understanding key characteristics of breast parenchyma tissue as potential cancer biomarkers has become clinically meaningful and to investigate and facilitate new approaches to their discovery and inclusion into clinical practice becomes more and more

important. The aim of the studies integrated in this thesis addresses two areas concerning precision medicine: identification and validation of imaging biomarkers derived from parenchyma breast tissue in predicting outcomes of breast cancer and in parallel investigate radiomics and machine learning methods in the discovery and measurement of imaging surrogates of breast cancer.

Materials and Methods

Firstly, three novel automated techniques for quantifying breast parenchyma tissue volumetrically by digital mammography are compared with one derived from MRI. The current standard of scoring breast tissue density manually is highly subjective and expensive. Automatic methods exist, but whether these techniques are accurate is not well known. The accuracy of the three mammographic methods are investigated in a screening population.

Next, a fully automated machine learning algorithm is investigated for calibrating mammographic systems for quantitative analysis of breast parenchyma tissue. Artificial Neural Network (ANN) modeling is used to estimate measures of breast density as a surrogate for breast cancer risk. The method is validated against phantom data, intra-patient, against a qualitative scoring standard, against MRI measures, and against classical risk factors of breast cancer as well as cancer status.

Lastly, the added discriminative value of detailed quantitative characterization of background parenchymal enhancement (BPE) in addition to the tumor itself on dynamic contrast-enhanced (DCE) MRI in identifying “triple-negative" breast cancers is investigated using radiomics and machine learning approaches.

Results

Automatic measures of breast parenchyma tissue volume from 2-dimensional imaging (mammography) are shown to be in substantial agreement with MRI as a standard for 3-dimensional anatomical imaging and could be used in clinical practice to enhance risk assessment and prevention of breast cancer.

ANN modeling is shown to extract reasonable measures of breast parenchyma tissue volume from digital mammography, as validated with phantoms, with existing measures of breast tissue density, and with classical biomarkers of breast cancer risk.

Considering a breast tumor’s surrounding parenchyma on DCE-MRI for radiomic image phenotyping is shown to provide useful information for identifying triple-negative breast cancers. Heterogeneity of BPE appears to add significant value to differentiation models of breast cancer subtype.

Conclusion

It appears key characteristics of breast parenchyma tissue imaging act as clinically meaningful biomarkers for breast cancer. We reinforce previous findings describing the importance of considering the microenvironment in which cancer may develop for predicting cancer outcomes. Exploiting radiomics and machine learning methods is also shown to be beneficial. Accurate and reproducible discovery and measurement of cancer imaging biomarkers are facilitated with their use. Prospective validation studies are warranted to confirm these findings and determine potential implications.