Abstract

Breast cancer is one type of disease that persists to have high incident rates among women. International agency for research on cancer (IARC) estimates more than one million cases of breast cancer happens yearly in the world and in each year large numbers of women pass away as a result of this disease. Despite of the variety of the modalities that can be utilized in the detection of breast cancer disease; these modalities still suffer of many drawbacks such as high false positive and negative rates accompanied with mammography, the side effects of the patient exposure to ionization radiation and the impracticability due to the high cost and time consuming for screening large population and, invasiveness of tissue biopsy. All of these weaknesses are a strong motivation for further investigation. Some evidences have been found that urine and saliva can be exploited as biomarkers for the detection of many diseases. The aim of this study was to evaluate the biomarkers of body fluids (urine & saliva) whether it can determine the stage of breast cancer. This is carried out by the measurement of the sample's response to the applied microwave energy. The urine and saliva samples were measured by network vector analyzer between 10MHz to 20GHz. The significant differences in permittivity across the different stages were also investigated. Significance differences were found across all the groups in all parameters over certain frequency range, while no significant difference found in all dielectric parameters of saliva. The results suggest that it is possible to differentiate between different stages of breast cancer based on the dielectric properties of urine.

Abstrak

Kanser payudara merupakan kanser yang paling umum di kalangan wanita. Agensi Penyelidikan Kanser Antarabangsa (IARC), menganggarkan lebih daripada satu juta kes kanser payudara berlaku setiap tahun dan di setiap tahun lebih dari 400,000 wanita meninggal dunia akibat penyakit ini. Walaupun pelbagai modal yang boleh digunakan dalam pengesanan kanser payudara; modaliti masih mengalami banyak kelemahan penting seperti kadar positif dan negatif palsu yang tinggi dengan mamografi, kesan sampingan dari pendedahan pesakit kepada radiasi pengionan dan ketidakpraktisan yang disebabkan oleh kos yang tinggi dan masa panjang untuk menapis populasi yang besar dan, biopsy tisu yang invasif. Semua kelemahan ini adalah motivasi yang kuat untuk penyelidikan lebih lanjut. Beberapa bukti telah dijumpai bahawa air kencing dan air liur boleh digunakan sebagai biopenanda untuk mengesan pelbagai jenis penyakit. Tujuan penyelidikan ini adalah untuk menilai biopenanda cecair tubuh (air kencing dan air liur) samaada mereka boleh digunakan untuk menentukan tahap kanser payudara. Ini dilakukan dengan pengukuran tindak balas sampel terhadap tenaga gelombang mikro. Sampel air kencing dan air liur diukur dengan Analisa Rangkaian Vektor antara 10MHz hingga 20GHz. Perbezaan yang signifikan dalam kebertelusan di tahap yang berbeza juga diselidiki. Signifikansi perbezaan yang ditemui di semua parameter pemalar dielektrik, faktor kehilangan dan tangen kehilangan urin, sementara tiada perbezaan yang signifikan ditemui pada semua parameter dielektrik air liur. Keputusan kajian mencadangkan bahawa ia bermungkinan untuk menganggarkan tahap kanser payudara berdasarkan sifat dielektrik air kencing.

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List of Abbreviations

ANOVA: One-Way Analysis of Variance

BSE: Breast Self Exam

CBE: Clinical Breast Exam

COM: Component Object Model

CT: Computed Tomography

IARC: International Agency for Research on Cancer

MRI: Magnetic Resonance Imaging

MUT: Material Under Test

TNM: Tumor Node and Metastasis

CHAPTER 1

INTRODUCTION

1.1 Breast Cancer

Breast cancer is type of dangerous cancer which is considered as the most cancer that happens for woman (Eltoukhy, et al., 2010). According to the estimation of the international agency for research on cancer (IARC), each year more at least one million cases of breast cancer will happen in the world and annually not less than four hundred thousand women pass away as a result of this disease. After skin cancer, breast cancer has the highest incident rates among cancers that may happen for women (Gibbins et al., 2010)

Diagnosis of the disease and plan treatment decisions are important for decreasing life fatalities which is done after determining the stage of the breast cancer as an essential step in disease diagnosis and classification, it plays an essential role in decreasing mortality and morbidity rates with subsequent effective treatment.

Breast cancer is a disease that has high incident rates. Breast cancer is a malignant tissue that grows from the breast cells, metastasize abnormally and invade other parts of the body. As mentioned before, this disease has high incident rates in women but it seldom found in men (Stang, 2008)

Early mortality is one of the most negative results of breast cancer. Those women maybe die due to the late of detection of their disease; this attenuation permits the disease to propagate and to spread all over the body in uncontrollable way where it was possible to be cured if it was detected at early stage. So, detection of breast cancer at

early stage and determining accurately the stage of the disease play a primary role in choosing proper treatment plans.

Staging is a way which is introduced to explain and express the development of the cancer. Stages of the cancer are determined according to the information acquired from the doctors and data obtained from laboratory tests in addition to the data revealed by the different imaging technologies such as mammography, and X-Ray.

Stage of the breast cancer is characterized by the size of the tumor, the invasiveness of the tumor and the number of lymph nodes involved. So each stage indicates how much the cancer is extended through the body. Based on this information treatment plan suitable for each patient will be decided. Staging system has been introduce in order Arrange the different elements and some of the personal features in classes that provides a depiction of the patient's status which in role helps the doctors and the specialists to decide the best way of treatment and guide them into a common standard of treatment plans, so that the result of any treatment plan can discussed and analyzed.

1.2 Research Problem and Problem Statement

Determining the stage of breast cancer plays a key role in choosing a suitable treatment plan for the patients and in rescuing their lives. X-ray mammography is a common method utilized for detection and staging of breast cancer; it is considered as a gold standard among other used methods. Unfortunately, this method still suffer many limitations, which include, difficulty in imaging woman with dense breast, missing 10-30% of breast cancers, high number of false positives. Furthermore, the frequency of screening is limited due to the ionizing properties of X-rays.

These problems motivate this study to seek for new staging methods purposes to overcome those limitations through the assessment of the possibility using Quantitative values of permittivity of urine and saliva in the differentiating between different stages of breast cancer.

1.3 Significance of the Study

This study seeks for a non invasive, low cost, easy method to acquire the stage of the breast cancer. Currently used methods for staging breast cancer still suffer some limitations. Although these methods have proved their efficiency in screening the breast and detecting the tumors, but there are some drawbacks that still challenge these modalities. For example, in ultrasound technique sometimes it fails to detect the tumors due to the similarity in acoustic properties between fats of the breast and tumor masses (Kalogerakos, et al., 2008), and the small possibility of determining the nonpalpable lesions using ultrasound (Elsdon et al., 2007) Moreover, the high cost of ultrasound are considered as factors that limits the efficiency of this technique. These limitation decreases the accuracy of ultrasound to detect tumors. In the MRI technique, the false positive rate is high relatively to other methods. All of these factors leads to the need of finding a new way to detect classify different stages of breast cancer.

This study attempted to introduce a non invasive method able to classify various stages of the cancer of the breast through the utilization of the quantitative values of their permittivity.

1.4 Scope of the Study

Many technologies were exploited for the sake of staging and detecting of breast cancer. These methods have been applied widely in the diagnosis field. Breast cancer staging can be done using various techniques. Many studies have been done and many technologies with updated features have been implemented for staging of breast cancer. The purposes to introduce a new non invasive method fast and high accuracy in order to detect the stage of the breast cancer that will make it easier to make a decision for Treatment plan suits for the status of the patient.

Two types of samples were obtained from breast cancer patients and normal subjects: urine and saliva. However, the use of other types of body fluids such as blood, tears and sweat were excluded. These samples were collected with taking into account to collect samples only from patients prior to surgery while they were still carrying the lumps. The age range of both patient and healthy control is between 40 to 60 years of age. Patients and normal subjects participated in this study were involved Malays, Chinese and Indians, all from Malaysia. These samples were analyzed with slim form probe using Agilent network analyzer at room temperature. The measurements were recorded over a frequency range between 10 MHz – 20GHz. One way ANOVA in SPSS was applied, the significant difference across the groups (different stages of breast cancer and normal subjects) was obtained.

1.5 Objective of the Study

1) To determine the permittivity of saliva and urine of subjects with different stages of breast carcinomas.

2) To determine the significant difference in permittivity between the stages of breast carcinomas.

1.6 Organization of the Dissertation

This study includes five chapters. In each chapter subtopics were discussed and many figures, tables, data and references are showed.

Chapter one introduces the topic of the thesis through the explanation of the breast cancer; by discussing the origin of breast cancer and different stages of breast cancer, it also mentions the aim and objective of this study.

Chapter two previews the literature and focuses on the current methods employed in breast cancer staging, competencies of saliva and urine in breast cancer detection, and the application of microwaves in the medical field.

Chapter three in particular deals with types of samples collected and method of collection to conduct the study, it explains in steps the procedure followed in analysis data obtained from samples, focus is also laid on research instrument and statistical method employed for analysis.

Chapter four shows the output of data analysis of significant differences of urine and saliva's permittivity across different breast cancer stages in tabular form; it also explains the significance of the study as compared with recent methods in literatures.

Chapter five summarizes the results of the study and inclusion in breast cancer detection and staging and also gives idea for future work.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of Breast Cancer

Tumor masses which grow from From the cells of the breast is known as breast cancer. As malignant tumors grow, they become more obvious and easy to be detected on imaging techniques such as mammography, X-Ray and MRI.

Breast cancers when studied using imaging techniques it appear as masses, parts of architectural distortion and collection of calcifications play a significant role in breast cancer diagnosing and staging (2009). Currently, the most common utilized technique for breast cancer staging and detection. The significant feature of this technique which makes it useful and powerful is that its ability to detect small (less than 1cm) lymph node negative breast cancers with an accurate prognosis which in turn enables the identification of the disease at early stage and reducing the mortality of the breast cancer.

2.2 Normal Breast

Breast cancer is considered as a very dangerous cancer that may happen for women. Knowing more about breast anatomy can help early breast cancer detection, prevention and understanding the disease, It is essential to have a knowledge about the structure of normal breast.

The structure of breast is shown in Figure 2.1. The breast is attached to lymph nodes by lymphatic vessels. Lymph nodes function for is gathering bacteria, cancerous cells and other unhealthy materials. There are groups of these Small lymphatic masses under the

arm and behind the breast bone as while as in other parts of the body. Each breast consists of lobes, lobules and ducts. The lobes consist of smaller lobules that contain groups of tinny non producing glands. When the breast is producing milk it passes through the ducts into the nipple where it exits the body. Breast cancer is mostly developed in the lobules, glands and ducts of the breast.

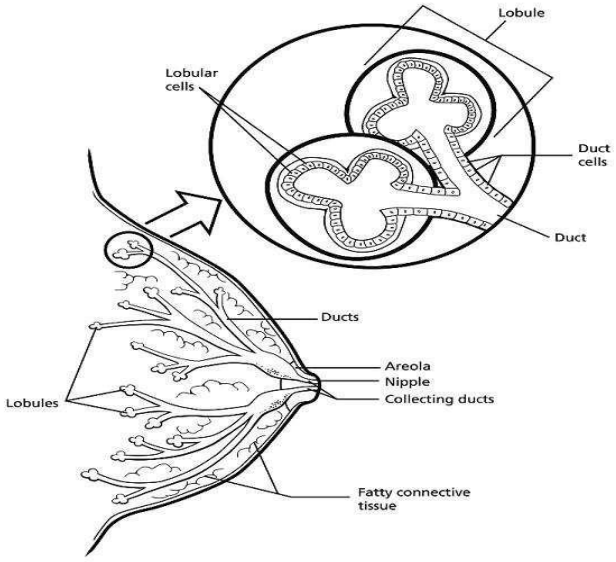

Figure 2.1: Structure of the normal breast

Adapted from: http://caredm.org/whatisbreastcancer.html

2.2.1 Lymphatic System

To understand the lymphatic system, it helps to comprehend the paths through which breast tumors can spread. Lymph nodes are small, bean shaped masses of immune cells which are attached to each other by lymphatic vessels. Lymphatic vessels same as small veins in their function but the difference between them is that lymphatic vessels carry lymph while small veins carry blood. Lymph is colorless, consists of fluid of tissue and waste, as well in addition to immune system cells.

Lymphatic vessels are connected to axillary nodes (nodes under the arm), internal mammary nodes (nodes inside the chest) and supraclavicular or infraclavicular nodes (above or below the collarbone). Breast cancer cells can go inside the lymphatic vessels and start growing in lymph nodes. Determining whether cancer cells have reached to lymph nodes has a significant important in identifying if it spread into the bloodstream and extended to other organs. The greater number of involved lymph nodes means the higher possibility that the cancer has reached to other organs. Knowing the extent of cancer spread through the body directly affects the treatment plans and the disease management (Atoum MF, 2010).

So, in summary; basically female breast comprises lobules, ducts and stroma. Lobules are glands which produce milk. Ducts are tinny channels which transfer the milk from the lobules to the nipple. Stroma is a fatty tissue and connective tissue which surrounds the ducts and lobules, blood vessels and lymphatic vessels (2009). The structure of lymphatic system is shown in Figure 2.2.

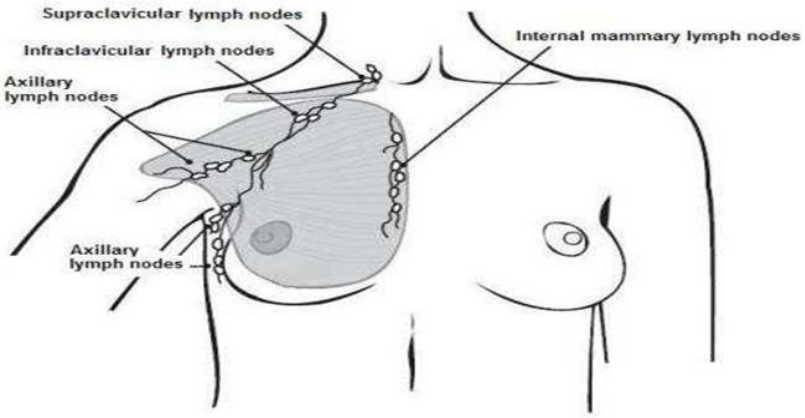

Figure 2.2: Lymphatic system

Adapted from: http://caredm.org/whatisbreastcancer.html

2.3 Staging and Progression of Breast Cancer

Breast cancer is developed in multiple stages, each stage has it is specific properties which are classified according to the size of the tumor, invasive or non-invasive, and whether it is metastasizing or not. Stage 0 is non invasive, in this stage there is no expansion of the tumors into the neighboring breast tissue beyond the duct or lobule (Atoum MF, 2010).

Progression of cancer in stage 1 is shown in Figure 2.3. Stage 1 is considered an early stage of invasive breast cancer, the tumor is less than 2 cm in diameter an there is no extension beyond the breast.

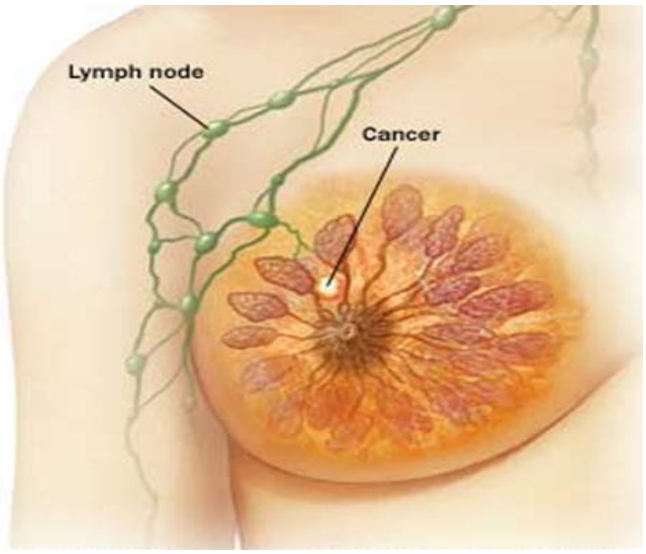

Figure 2.3: Stage 1 of the breast cancer

Adapted from: http://www.mayoclinic.com/health/stage-of-breast-cancer/BR00011&slide=3

Stage 2 is classified into two classes of 2a and 2b. stage 2a is invasive breast with tumor is either a maximum up to 2 cm in diameter and has reached to the lymph node under the arm or the tumor is between 2-5 cm in diameter but no lymph nodes are involves. Stage 2b is a little different in that the tumor is either between 2-5 cm and has reached

under arm lymph nodes or the tumor is larger than 5 cm but has not extended to the under arm lymph nodes. Stage 2 of breast cancer is shown in Figure 2.4.

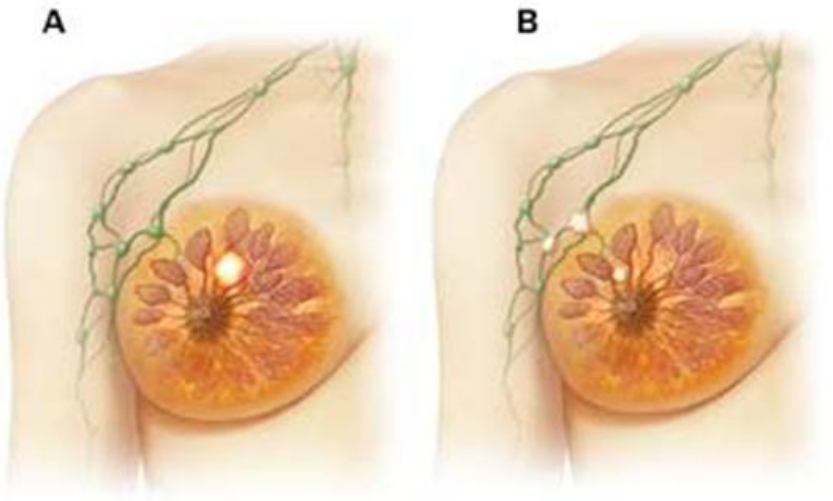

Figure 2.4: a. stage 2a of the breast cancer, b. stage 2b of the breast cancer

From: http://www.mayoclinic.com/health/stage-of-breast-cancer/BR00011&slide=4

Stage 3 is considered a locally breast cancer and it is also divided into subcategories of 3a, 3b and 3c. There are two main scenarios that can occur with stage 3a, in the first one the tumor is not larger than 5 cm in diameter but it has spread under arm lymph nodes that are growing into each other forming clumps. The cancer may also have spread to the lymph nodes near the breast bone. The second scenario for stage 3a is very similar with the exception that the tumor is larger than 5 cm in diameter and the under arm lymph nodes are not adhered to one other or to other tissues. Unlike the other stages, in stage 3b the tumor maybe any size and has spread to the skin of the breast or chest wall. This stage may also include lymph in the skin of the breast or swelling of the breast.

In stage 3c the tumor may also be of any size but it has also spread to the lymph node areas above or below the clavicle, the chest wall and the skin of the breast. Stage 3 of breast cancer is illustrated in Figure 2.5 and Figure 2.6.

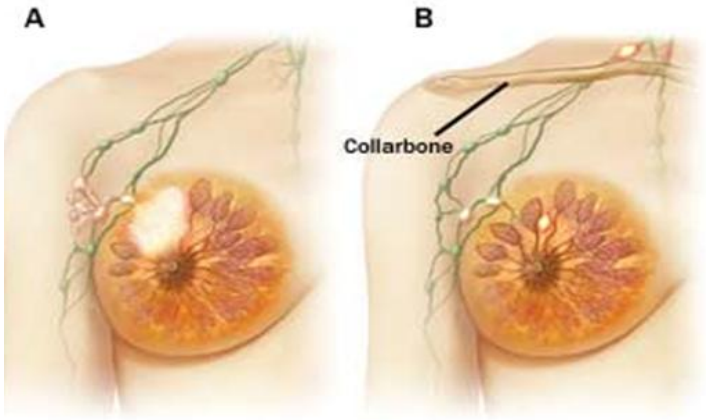

Figure 2.5: a. stage 3a of the breast cancer, b. stage 3b of the breast cancer

http://www.mayoclinic.com/health/stage-of-breast-cancer/BR00011&slide=5

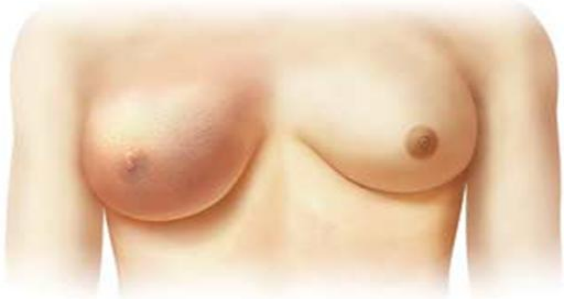

Figure 2.6: stage 3c of the breast cancer

From: http://www.mayoclinic.com/health/stage-of-breast-cancer/BR00011&slide=6

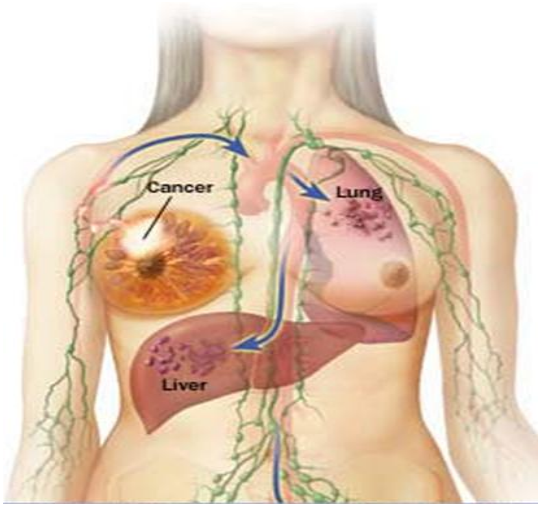

Figure 2.7: stage 4 of the breast cancer

http://www.mayoclinic.com/health/stage-of-breast-cancer/BR00011&slide=4

Stage 4 of the breast cancer is shown in Figure 2.7. In Stage 4 cancer has expanded to other organs and parts of the body.

2.4 TNM (Tumor Node and Metastasis) Staging System

Suitable treatment plans and prognosis determination extremely depends on staging of breast cancer. Appropriate staging provides a language that enables for different treatment outcomes to be compared from various centers.

The most widely used staging system is TNM classification, TNM stands with tumor nodes and metastasis. This system takes classify the stages according to the size of the tumor, the number of nodes involved and the extension of the cancer through the body. classification system of breast cancer stages can range from 0-4, stage 0 is in situ carcinoma, in this stage cancerous cells have not expanded as well as they have not reached to neighboring organs. In stage 1 the size of the tumor is 2 cm or less and have not reached to surrounding organs. Stage 2 is classified into two classes. Stage 2a,

tumor measures 2 cm or less, 2 to 5 cm of the lymph node is included but the there is no inclusion for the auxiliary lymph nodes. Stage 2b, the tumor measures 5 cm or more in cross section and auxiliary lymph nodes are involved. Stage three is also classified into three types. Stage 3a, in this stage the cancer is spread locally, the tumor measures 5 cm or more in greatest dimensions and there is inclusion for axillary lymph nodes. Stage 3b, in this stage the tumor can be of any size but has spread into the skin, chest wall, or internal lymph nodes of mammary glands. Stage 3c, tumor is similar to 3b but with the surrounding tissues are more invaded. In stage 4, the tumor masses propagation reaches to parts which are distant from the chest (Atoum MF, 2010).

2.5 Techniques Used for Staging of Breast Cancer

Cancer screening is globally believed to be an effective method of cancer detection and staging and beneficial for reducing mortality rates. Any screening method used for detection and staging of breast cancer has three significant measures of utility include sensitivity which is defined as the potency to determine those with cancer, specificity (the potency do determine those without cancer) and positive predictive value (the percentage of cases reported as malignant).

For any cancer screening program, efficacy and effectiveness should be assessed. Efficacy it is the extent to which an intervention can be beneficial while effectiveness indicates whether the intervention is beneficial or not in real conditions (Demartini et al., 2008).

Recently, introduction of diagnostic and detection means of breast cancer has been increased drastically as an urgent demand accompanied by the sharp increase of cancer morbidity and particularly the high false positive cases detected.

2.5.1 Currently Used Staging Methods

2.5.1.1 Lymph Node Biopsy

Figure 2.8 shows lymph node biopsy technique for staging breast cancer. Lymph node biopsy is an investigational procedure used for staging breast cancer this technique includes two basic methods: sentinel node biopsy and axillary node biopsy.

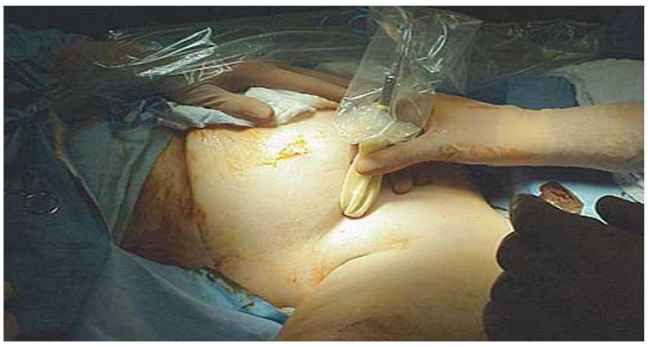

Figure 2.8: Lymph node biopsy

http://findmeacure.com/wp-content/uploads/2009/03/lymph-node-biopsy.jpg

It is a technique in which the specialists extract the lymph nodes to obtain the cancerous cells. This is can be achieved by the injection of contrast material besides the cancerous mass or it can be injected under the nipple. Then the colored nodes can be screened and then it can be removed and examined.

This test provides information about the extension of the cancer through the body. When cancerous cells are found in axillary lymph nodes, this means that the disease has spread to other parts of the body (Krag, 1999).

2.5.1.2 Magnetic Resonance Imaging (MRI)

Figure 2.9 shows magnetic resonance imaging instrument. Magnetic resonance imaging (MRI) is a technology which is utilized in the medical field to perform detection and diagnosis in a non invasive way. This method uses strong magnetic pulses to form images of internal parts of the body. After the pictures are formed, they can be viewed using a monitor and then can be tested and analyzed. Moreover these pictures can be saved on a CD. These pictures can reveal the status of the internal structures and can show diseases that cannot be diagnosed using other methods (Kearney and Murray, 2010).

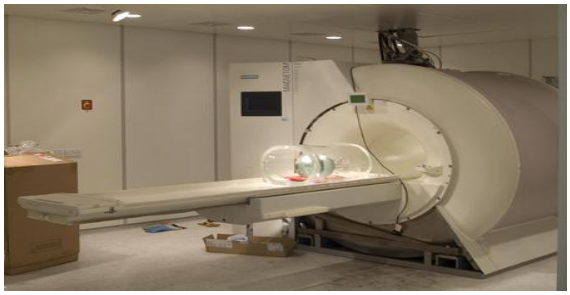

Figure 2.9: Magnetic resonance imaging

Adapted from: http://congenital-heart-defects.co.uk/images/MRI%20Scan.jpg

Breast magnetic resource (MRI) is a significant technique in the imaging for the staging and diagnosis of breast carcinoma, MRI for cancer evaluation has been shown to be beneficial in imaging patients at high risk, assessment of patients with a new malignancy diagnosis, screening treatment response in patients receiving chemotherapy and diagnosing patient who has metastatic axillary carcinoma with unknown primary site (Boulevard and Brook, 2010). MRI extracts significant data related to the status of the breast. These data offered by MRI cannot be obtained by other imaging techniques, such as mammography and ultrasound (Jochelson and Morris, 2011). Strength and weakness points of MRI technique are summarized in Table 2.1.

Table 2.1: strength and weakness of MRI modality

Weakness	Strength
Due to the similarity of the characteristics between benign and normal tissues it has low specificity and high sensitivity	Can detect breast cancer at early stage with high sensitivity.
High cost	It can detect cancers that are missed on mammography, ultrasound and clinical breast examination.
Long examination time (Brem et al., 2006).	Density independent especially when dealing with young population (Demartini et al., 2008)

2.5.1.3 Computed Tomography (CT) Scan

CT scan instrumentation is shown in figure 2.10. CT scans are specially exploited to image the lungs or the liver which the breast cancer has already extended to them. X-Ray machine takes pictures for the chest and the abdomen. This x-ray machine is connected to a computer to view the pictures. Radioactive substance can be injected into the blood stream in order to make abnormal parts more obvious.

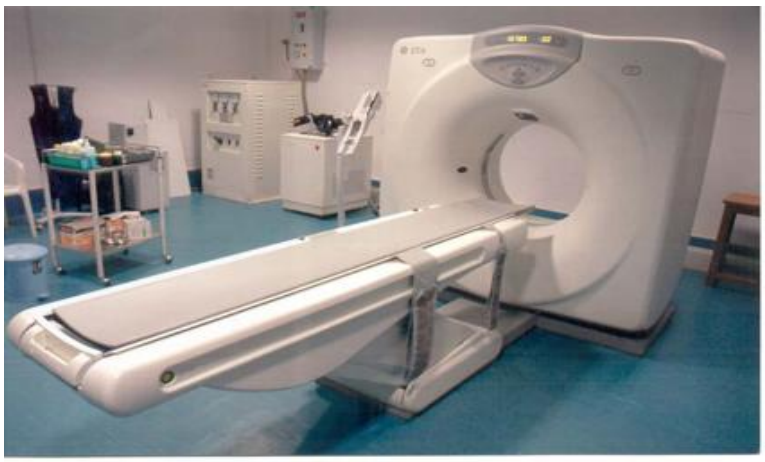

Figure 2.10: CT scan instrumentation

From: http://blogs.discovermagazine.com/80beats/files/2009/12/Ct-scan425.jpg

2.5.1.4 Bone Scan

In this method a contrast material is inserted into the bloodstream and collected in the bones, then the radiation can be scanned and pictures of the bones can be formed. This pictures reveal whether the breast cancer has reached to the bones or not (2009).

2.5.1.5 Agilent 85070E Dielectric Probe kit

Agilent network vector analyzer is shown in figure 2.11. Each material has a special and certain molecular structure. Because of the variety of the molecular structure dielectric properties varies relatively as well. Agilent network vector analyzer was exploited to find the permittivity values. According to the dielectric properties further properties of the material can be found (2011).

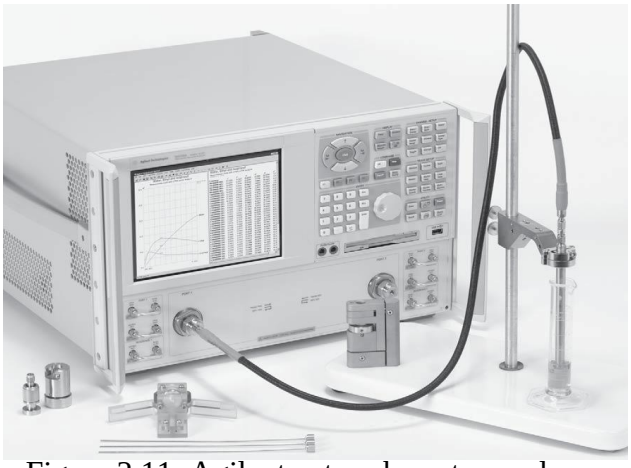

Figure 2.11: Agilent network vector analyzer

Principle of operation: the material is illuminated by RF or microwave energy then the backscattered pulses is measured by the network vector analyzer. The RF is reflected to the material under test (MUT). Complex permittivity can be computed in a very short

time and it can be viewed in different formats such as: dielectric constant and dielectric loss factor (2011).

Slim Form Probe

The slim form probe is shown in Figure 2.12. the slim shape of this probe permits it to be used for tasks that uses small samples and small opening containers (2006).

The Slim Form probe is made up of holder which has two diameters of 2.2 mm and 10 mm, respectively and also adapters and bushings. The probe sends a signal into the sample which is under test and within seconds the analyzer yields output of complex permittivity quantitative values in two formats as a function of frequency (from 0.41 GHz to 20 GHz).

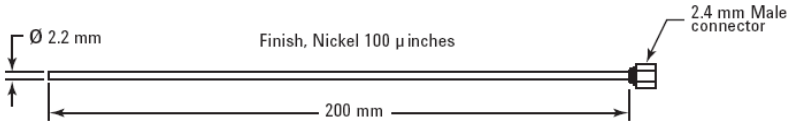

Figure 2.12: Slim Form probe

Adapted from: http://cp.literature.agilent.com/litweb/pdf/5989-0222EN.pdf

2.6 Use of Microwaves in Breast Cancer Investigation

Currently, X-ray mammography, MRI and ultrasound are widely used methods for breast cancer staging and detection. Although X-ray mammography is considered as a gold standard among other used methods, but unfortunately this method still suffer many limitations, which include, difficulty in imaging woman with dense breast, missing 10-30% of breast cancers, high number of false positives. Furthermore, the frequency of screening is limited due to the ionizing properties of X-rays. MRI is a

significant technique implemented to screen the breast carcinoma, MRI for cancer evaluation has been shown to be beneficial in imaging patients at high risk, assessment of patients with a recent malignancy diagnosis, screening treatment response in patients receiving chemotherapy and diagnosing patient who has metastatic axillary carcinoma with unknown primary site (Boulevard and Brook, 2010). Moreover; Although MRI can extract information that cannot be obtained using other techniques, such as mammography and ultrasound (Jochelson and Morris, 2011). However; the high false positive rate of this imaging modality relatively to other detection methods (Whitman et al., 2006), Long examination time (Brem et al., 2006), and high cost are considered as factors that limits the use of this technique. Inability of ultrasound to detect breast cancer (Kalogerakos et al., 2008), (Elsdon et al., 2007) in addition to the high cost of this technique (Kopans, 2006) These reasons limits the ability of ultrasound to detect breast cancer.

The aforementioned problems motivate this study to seek for new staging method aims to overcome those limitations through the utilization of microwave technology and the assessment of the permittivity of urine and saliva in the differentiation between different stages of breast cancer. Microwaves are electromagnetic waves which have a frequency range from 0.3 GHz to 300 GHz. These waves are utilized to measure a significant property which is specific for each material called complex permittivity (Gabriel C., 1996); it is given by:

$$\varepsilon = \varepsilon' - j\varepsilon'' \quad (1)$$

Permittivity is a characteristic of the dielectric material. It indicates the ability of charges to move in the material as a response to an electric field (Tyna and Sian, 2004).

Complex permittivity consists of two parts real (ε′), and imaginary (ε″) (Neves, 1996). The imaginary stands to the loss in energy when a dielectric material is inserted in an electric field while the real part refers to how much energy is stored. Relative permittivity is the complex permittivity divided by permittivity of the space ($\varepsilon_0 = 8.85\ldots \times 10^{-12}$ F/m) and it means that the value of permittivity has a proportional relation with the dielectric characteristics of a vacuum (Choi et al., 2004). Complex permittivity values at particular frequencies show the specific electromagnetic properties of various materials (Kao et al., 1999). Permittivity of materials can be influenced by several factors include: temperature, sample age, history and water content (Fricke and Morse, 1926; Smith and Foster, 1985; Suroweic et al., 1988).

Interest and research in studying the electrical properties of breast tumors began several decades ago. All of these studies are based on the consensus is that breast tumors electrical properties are different than that for healthy tissues. Fricke and Morse have conducted a study to investigate the electrical characteristics of cancerous breast tissue. They found out that the quantitative values of permittivity of cancerous tissues at 20 KHz are greater than for normal tissues (Kao et al., 1999). Roberts and cook observed higher values of permittivity in the loss factor and in the dielectric constant of tissues illumenated by x-rays (Roberts and Cook, 1952)**.** Same conclusion has been confirmed by Singh et al. (Singh et al., 1979). Chaudhary et al conducted a study to measure the dielectric properties of two groups of breast tissues: cancerous tissues and normal tissues at frequency range from [3MHz-3GHz] (Chaudhary et al., 1984)**.** In 1988, Surowiec et al. carried out in vitro tests. They used network analyzer to find out the differences of characteristics between two main groups, the first contained cancerous tissues and the second contained a mix of cancerous tissue and normal tissues on frequency range between 20 kHz to 100 MHz. They found out that the conductivity and

the dielectric constants of tissues of carcinoma are different across the sample groups (Suroweic et al., 1988). Figure 2.13 shows the dielectric constant data of breast cancerous tissues obtained by previous studies.

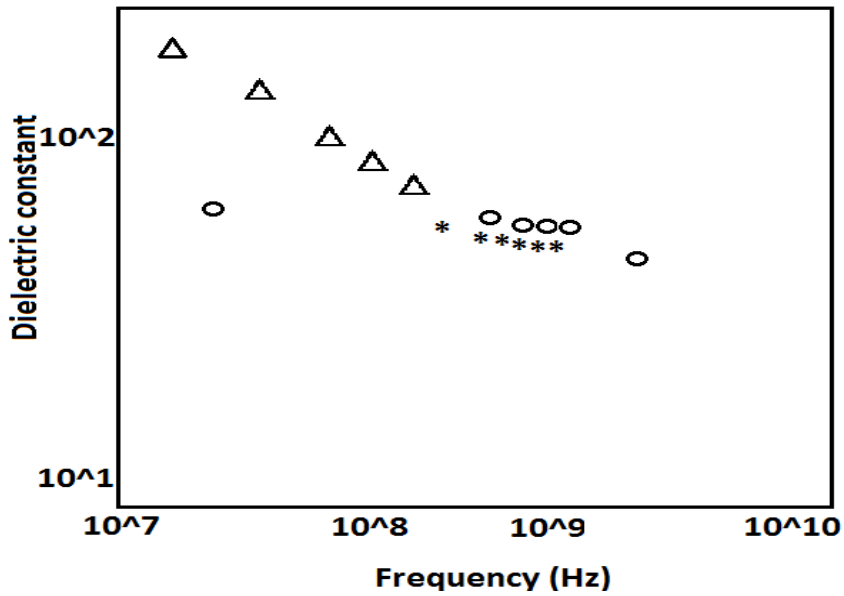

Figure 2.13: The dielectric constant data of breast cancerous tissues obtained by previous studies. (○:Data obtained by(Chaudhary et al., 1984) , △: Data obtained by (Suroweic et al., 1988), * : Data obtained by (Joines et al., 1994)).

The electrical impedance of breast cancerous tissue was measured by Morimoto et al. in vivo (Morimoto et al., 1993) (Morimoto et al., 1990). This was achieved by inserting a fine needle electrode into the cancerous tissue using a three-electrode method. The extracellular resistance, the intracellular resistance, and the membrane capacitance were figured out according to a model circuit and the measured complex impedance. The model circuit encompassed the combination of the extracellular resistance in parallel with of the intracellular resistance and the capacitance connected in series. The frequency of operation was in the range of 0–200 kHz. The conclusion was that there are significant differences between breast tumor and normal tissue. Swarup et al. measured the MCA1 fibrosacroma mouse tumors and they investigated the onset of the high values of relative permittivity and conductivity it was found that the relative

permittivity and conductivity values vary with the size of the tumor but no significant difference was found in their values with tumor age (Swarup et al., 1991).

Jossinet (Jossinet, 1996; Jossinet, 1998; Jossinet and Schmitt, 1999) investigated the impedance of breast tissue for six groups over frequency range from 488 Hz to 1 MHz. The impedance spectra were measured for 120 samples collected from 64 patients, with the sample groups classified into three groups of healthy breast tissue, two groups of benign tissue, and tumor. The first study studies the changes in the impedance output within each type by evaluating the standard deviation and calculating the reduced standard error (Jossinet, 1996). In the second study, the plot of the complex impedance was depicted as a function of frequency as an initial step to obtain the Cole–Cole parameters. These parameters contributed as a tool to differentiate tumor tissue samples (Jossinet, 1998). It was concluded that there is more significant difference in properties of tumor tissues at frequencies higher than 125 kHz. In the third study, Jossinet and Schmitt tried to introduce a new group of parameters that can be used to distinguish tumor tissue from other tissues (Jossinet and Schmitt, 1999). They found out that it is more efficient to recognize the tissue by many parameters spanning a range of frequency than using one parameter at a specific frequency point. Chauveau and colleagues (Chauveau et al., 1999) attempted to determine whether it is necessary to find out the value of bio-impedance parameters over a range of frequency. For ex vivo healthy samples and cancerous tissues, the bio-impedance parameters were measured over frequencies from 10 KHz to 10 MHz based on these measurements and a model of a constant phase element, the extracellular resistance, the intracellular resistance, and the membrane capacitance were computed. The output revealed that these parameters would permit tumor tissues to be distinguished from healthy tissues.

Qiao et al. performed a study to investigate the impedance of normal and cancerous suspensions of breast cells to acquire the electrical properties of a single cell. It was observed that the conductivity values of late stage breast cells is between the conductivity values of early stage and invasive cancer cells (Qiao et al., 2010). Table 2.2 summarizes the literature review of microwave in breast cancer detection.

Table 2.2: Summary of the literature review on the use of microwave in breast cancer investigation

Authors/year	Method	Result
Fricke H. & Morse S. (1926)	Electrical capacity was measured for malignant and healthy tissues.	It was found that the capacity of malignant tumors is higher than in healthy tissues
Roberts J. E.& Cook H.F. (1952)	Dielectric constant and loss factor of normal breast and breast fibrosed by X-rays was measured.	Breast tissue fibrosed by X-rays showed higher dielectric constant and loss factor than in normal tissue.
B. Singh, C.W. Smith & R. Highes (1979)	Relative permittivity and dielectric loss of body tissues were measured using spectrometer over frequency range of 0.1 Hz to 100 KHz.	Breast tumors revealed higher permittivity and dielectric loss than normal breast tissues.
Chauhdary et al. (1983)	The relative permittivity and conductivity of normal and malignant breast tissues obtained from 15 patients were measured over frequency range {3MHZ-3GHz].	Over the frequency range considered in the study conductivity and relative permittivity values of malignant tissue exceed the values of normal tissues.
Suroweic et al. (1988)	Relative permittivity of cancerous breast tissue and the surrounding tissues was measured over frequency range of 20 KHz to 100 MHz at 37˚C	Structural and cellular inhomogeneties of the tumor tissue. Tumor's adjacent cells show an increment in their conductivity.
Swerup et al. (1991)	Onset of the high values of relative permittivity and conductivity was studied by the measurement of MCA1 fibrosacroma mouse tumors at 7, 15 and 30 days after inception.	No significant difference of relative permittivity and conductivity with tumor age but significant difference was found with the size of the tumor at frequencies above 0.5 GHz.
Morimoto et al. (1993)	Electrical impedance of various tumors was measured in vivo in patients with different breast diseases. Measurements were made using three electrode system over frequency range of	Extracellular resistance and intracellular resistance in breast tumors were higher than in malignant and normal where membrane capacitance in breast tumors were lower than in

	0 to 200 KHz.	benign and normal.
Joines et al. (1997)	They measured the electrical conductivity and the relative permittivity of malignant and normal human breast tissues at frequencies from 50 to 950 MHz .Measurements were made between 23˚C and 25˚C using a network analyzer.	In general, at all frequencies tested both conductivity and real permittivity were greater in malignant tissue than in normal tissue. Differences in permittivity and conductivity of mammary glands were about 233% and 577%, respectively.
Jossinet et al. (1999)	They nvestigated the impedance of breast tissue for six groups over frequency range from 488 Hz to 1 MHz.	It was concluded that there is more significant difference in properties of tumor tissues at frequencies higher than 125 kHz.
Chauveau et al. (1999)	Ex vivo bioimpedance of normal and cancer female breast tissues was measured.	Electrical properties of normal tissue, surrounding tissues and cancerous tissues are significantly different.
Qiao et al. (2010)	The impedance of normal and cancerous suspensions of breast cells was measured.	It was concluded that it can be differentiated between the normal and different stages of cells using their impedance values..

2.7 Review of Current Modalities Used For Staging of Breast Cancer

Currently there are three widely used screening methods for breast cancer detection and staging, they are mammography, CBE and BSE. Table 2.2 shows a brief review which is available in literature.

Table 2.3 comparison of current modalities used for staging of breast cancer

Modality	**Sensitivity**	**Specificity**	**Positive predictive value**	**Strength**	**Weakness**
Mammography	39%-89%	94%-97%	2%-22%	Mortality reduction up to 44% (Demartini et al., 2008)	Imperfect examination with 10-15% of breast cancers not visible on mammographic examination. Can only identify abnormalities and not definitely differentiate between benign and malignant findings (Brem et al., 2006).
CBE	40%-69%	88%-99%	4%-50%	It can find node negative tumors< 2 cm in diameter. It can find 15% of tumors that can't be seen with mammography. The only breast cancer screening maneuver that can be done by virtually all women without the aid of expensive machinery or expert health care professionals. Non invasive inexpensive	Insufficient evidence of effectiveness (Demartini et al., 2008).
BSE	26%-89%	66%-81%	Up to 45%	It can find tumors at early stage Smaller projection of death Reduces mortality May find 15% of tumors that are not picked up by mammography. Inexpensive Non invasive	Insufficient evidence of effectiveness.

CHAPTER 3

METHODOLOGY

3.1 Introduction

In this study permittivity of normal, malignant and benign subject's urine sample will be measured by using Agilent 85070E Dielectric Probe kit. Vector analyzes data provided by Agilent 85070E Dielectric Probe kit will be statistically analyzed using Self-Propelled Semi-Submersible (SPSS) software, at the end graph results will be plotted using Excel. Flow chart in figure 3.1 shows a summary for the methodology.

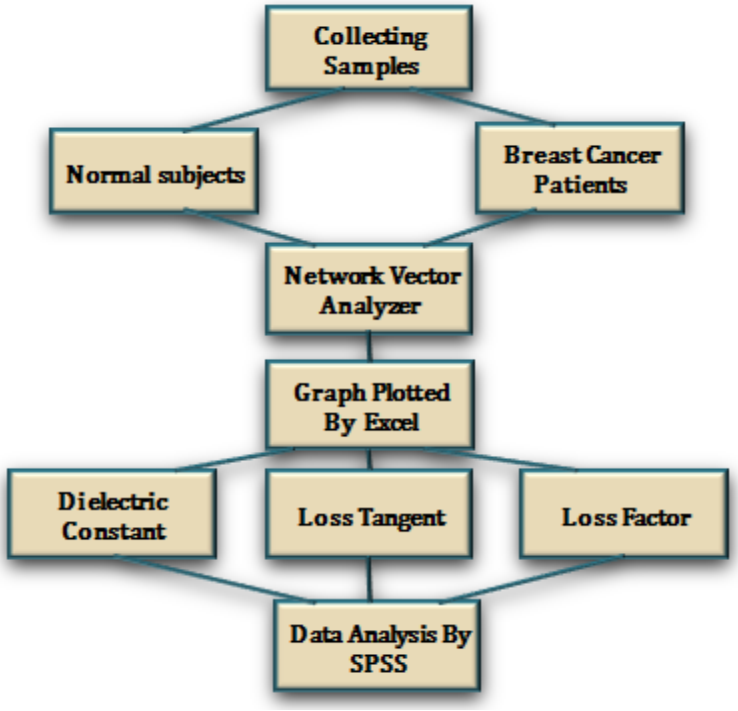

Figure 3.1: Methodology summary

3.2 Samples Collecting

Urine and saliva samples were collected from volunteers separated into two groups, first: normal subjects (5 normal; mean of the age: 49.2 years) and second: 18 breast cancer subjects (stage 1: 6, stage 2: 7, stage3: 5; mean of age: 49.77 years). The number

of the samples was limited because it was difficult for the patients to give sufficient amount of saliva specially that the samples were collected in the morning before they take their breakfast. Moreover samples were collected from the primary clinic this clinic was held once per week. Samples were collected in the morning before subject takes any food and after drinking 250ml mineral water, also the samples need to be kept in containers in a way that prevents changes in their temperature and pressure, shaking of samples or any factor which may affect permittivity. When urine samples are collected it is important to maintain them from any factor causes change of urine properties; thus Samples were analyzed within 1 hour after collecting them. Table 3.1 and table 3.2 shows patients' profiles normal subjects' profile; respectively.

Table 3.1: Patients' profiles

No	HISTO TYPE	Stage	**TUMOR SIZE**	**RACE**			**AGE (YR)**
				I	C	M	
1	IDC	3b	11 cm Stage 3b		/		32
2	IDC	1	1.2			/	51
3	IDC	1	1.5		/		48
4	IDC	2a	3		/		49
5	IDC	1	2			/	56
6	IDC	2a	3.5	/			67
7	DCIS	1(DCIS)	1.4		/		70
8	IDC	2A	1	/			52
9	IDC	2A	2		/		77
10	DCIS with microinvasion	1	0.7		/		41
11	IDC	2A	3.2		/		36
12	IDC	3A	6		/		53
13	IDC	2B	5.5		/		53
14	IDC	3C	3		/		71
15	IDC	2A	3.1		/		53
16	IDC	1	1.4		/		51
17	ILC	3B	5		/		46
18	IDC	3A	6		/		43

Table 3.2: Normal subjects' profiles

No	**RACE**			**AGE (YR)**
	I	C	M	
1			/	41
2			/	56
3	/			47
4		/		43
5			/	59

3.3 Data Measurement and Analysis

Complex permittivity of the collected samples of urine and saliva was measured using Network Vector Analyzer. This is done by putting the slim probe in the samples. Calibration was done before each measurement. Calibration involves several steps starts with choosing frequency range from 10MHz to 20GHz, and selecting slim form probe then setting temperature at 25˚C.

3.4 Refresh of calibration

Before each measurement, in a very short time the system is calibrated automatically. This refreshment is important to remove drift errors and the artefacts due to the movement of the cables (2006). Figure 3.2 shows a graph for the permittivity values of the water with and without calibration.

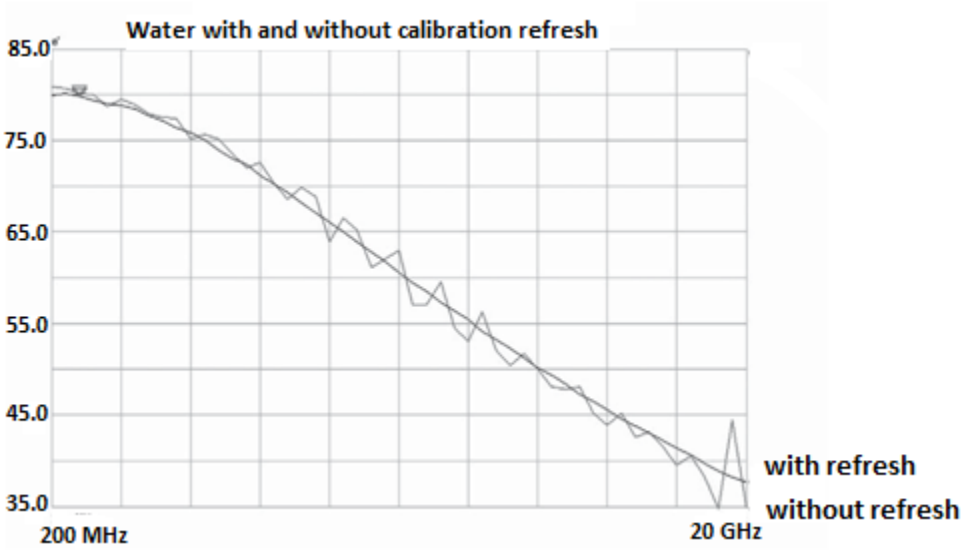

Figure 3.2: water permittivity values with and without calibration

Permittivity values of urine and saliva which are measured by network vector analyzer then will be transferred to Excel for further calculations. In fact transferring the data to Excel has three purposes: first, to arrange the data in such a way to make it ready to be inserted in SPSS for statistical analysis. Second: to calculate the means of all the groups (normal and different stages of breast cancer) and to draw their mean graphs separately to expect by vision the relation between the groups and the possibility of the significant difference to exist across them. Third: to calculate the values of loss tangent based on the obtained values for real part and imaginary part using the equation:

$$\delta = \frac{\varepsilon''}{\varepsilon'} \qquad (2)$$

After the data was transferred to SPSS for statistical analysis, the method compare means using one-way ANOVA was selected. One-way ANOVA was selected because this method is implemented to compare the means of three groups or more, according to the following formula

$$H_0: \mu_1 = \mu_2 = \mu_3 = \cdots = \mu_k \qquad (3)$$

Where; μ is the mean and k is the group number. One-way ANOVA is followed by Turkey which is inserted under post hoc to show how the means of the groups differ from each other. Statistical significance was set at $P < 0.05$. After SPSS analysis was run statistical analysis output was obtained. Using this data the significant difference point were extracted with their relative frequency points. These data then arranged and summarized in tables 4.1- 4.8 which are represented in chapter four.

CHAPTER 4

RESULTS AND DISCUSSIONS

4.1 Introduction

This chapter discusses the results which are obtained from SPSS statistical analysis and it interprets the graphs of permittivity obtained for both urine and saliva. Graphs were plotted after outliers were removed and they were presented in three formats: dielectric constant, loss factor and loss tangent. Dielectric parameters with the highest five F numbers (the ratio of the difference between the groups to the difference within the same group) were compared between the groups of subjects and they were summarized in tables. Moreover, the output of the statistical analysis for both urine and saliva were summarized in tables revealing the existence of the significant difference between the groups among different types of dielectric parameters. Summary of the statistical output for all the frequency points were a significant difference was found are included in the appendix (App.1- App.3) section at the end of this report.

4.2 Implication of the Graphical Output of Dielectric Parameters as a Function of Frequency

Generally, graphs are used to show relationships between variables in order to depict their relationships and their behaviours visually. In this study graphs served as a tool to depict whether a significant difference exists across the groups stage 1, stage 2 , stage 3 and normal where the probability of the differentiation between the groups decreases as the graphs curves are closer to each other and vice versa.

4.2.1 Dielectric Parameter as a Function of Frequency for Saliva Samples

Graphs 4.1-4.3 show the dielectric parameters as a function of frequency for saliva samples. The shape of the graphs for stage1, stage2, stage3 and normal follow almost the same trend. Another common trend can be observed that the permittivity of saliva of normal subjects is higher than for stage 2 in dielectric constant, loss factor and loss tangent at frequency range of (0.41 GHz to 12.41 GHz), (2.41 GHz to 4.41 GHz) and (15 GHz to 16 GHz and 17.41 to 19.41), respectively. Meanwhile, the permittivity of saliva of normal subjects is lower than all stages in dielectric constant, loss factor and loss tangent at frequency range of (16 GHz to 16.41 GHz and 18.41 GHz to 20 GHz), (10 GHz to 12 GHz, 13.41 GHz to 14.41 GHz, 16.41 GHz to 17.41 GHz and 19 GHz to 20 GHz), respectively. This observation agrees with the results obtained by Chaudhary, Fricke, Roberts and Singh, in all of these studies it was found that the dielectric properties of malignant tissue is greater than for normal tissue (Chaudhary et al., 1984; Fricke and Morse, 1926; Roberts and Cook, 1952; Singh et al., 1979). The trend of the curves in the dielectric constant where The dielectric property decreases with increasing frequency is consistent with what is revealed in many studies for the plot of the relative permittivity and Dielectric constant as a function of frequency for normal breast tissue (Chaudhary et al., 1984) (Joines et al., 1994) (Suroweic et al., 1988). Although the general shape of each group of subjects follow the same pattern but stage1 is only taking the lead value for dielectric constant parameter over all frequency range considered while it takes the least values for loss factor and loss tangent parameters. Meanwhile it is obvious that in all graphs for all parameters, all the groups have curves close to each other which indicates that the groups are not well separated and that there is no significant difference between the groups can be found using saliva. The reason is due to the small amount of saliva that could be collected from the patients as it was

difficult for them to give the required sufficient amount needed for the accomplishment of the study.

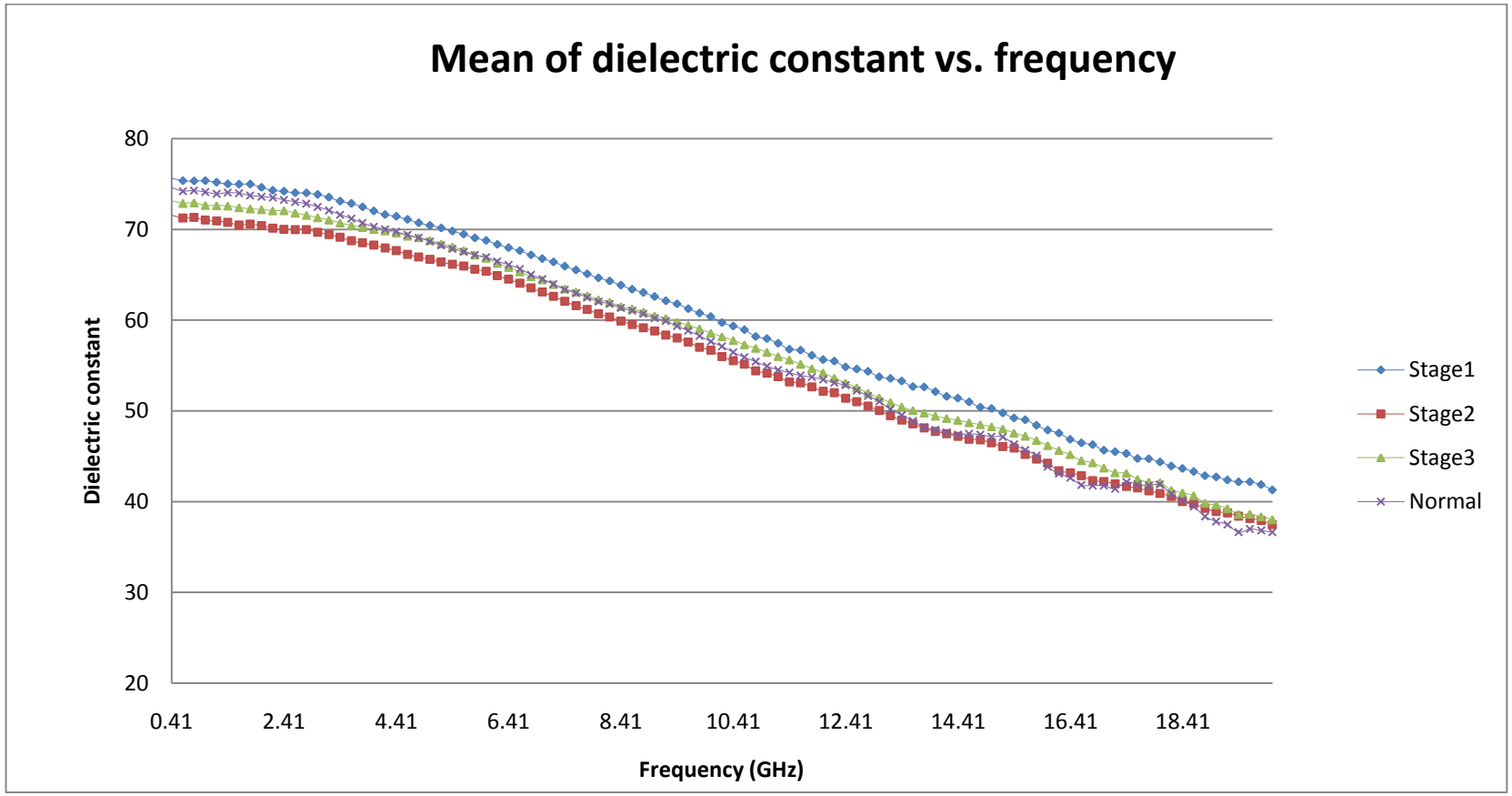

Figure 4.1: Dielectric Constant of saliva for different stages of breast carcinomas

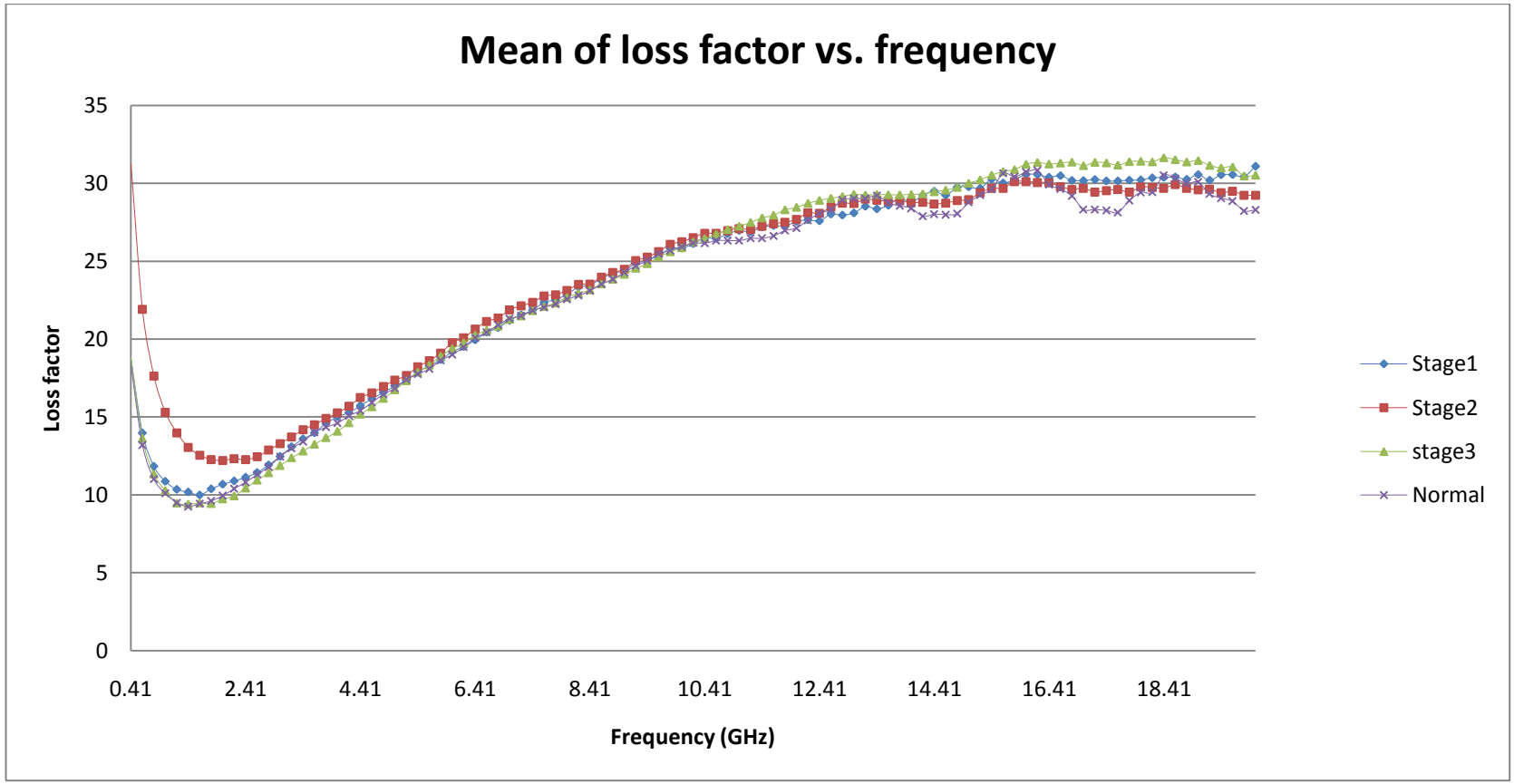

Figure 4.2: Loss factor of saliva for different stages of breast carcinomas.

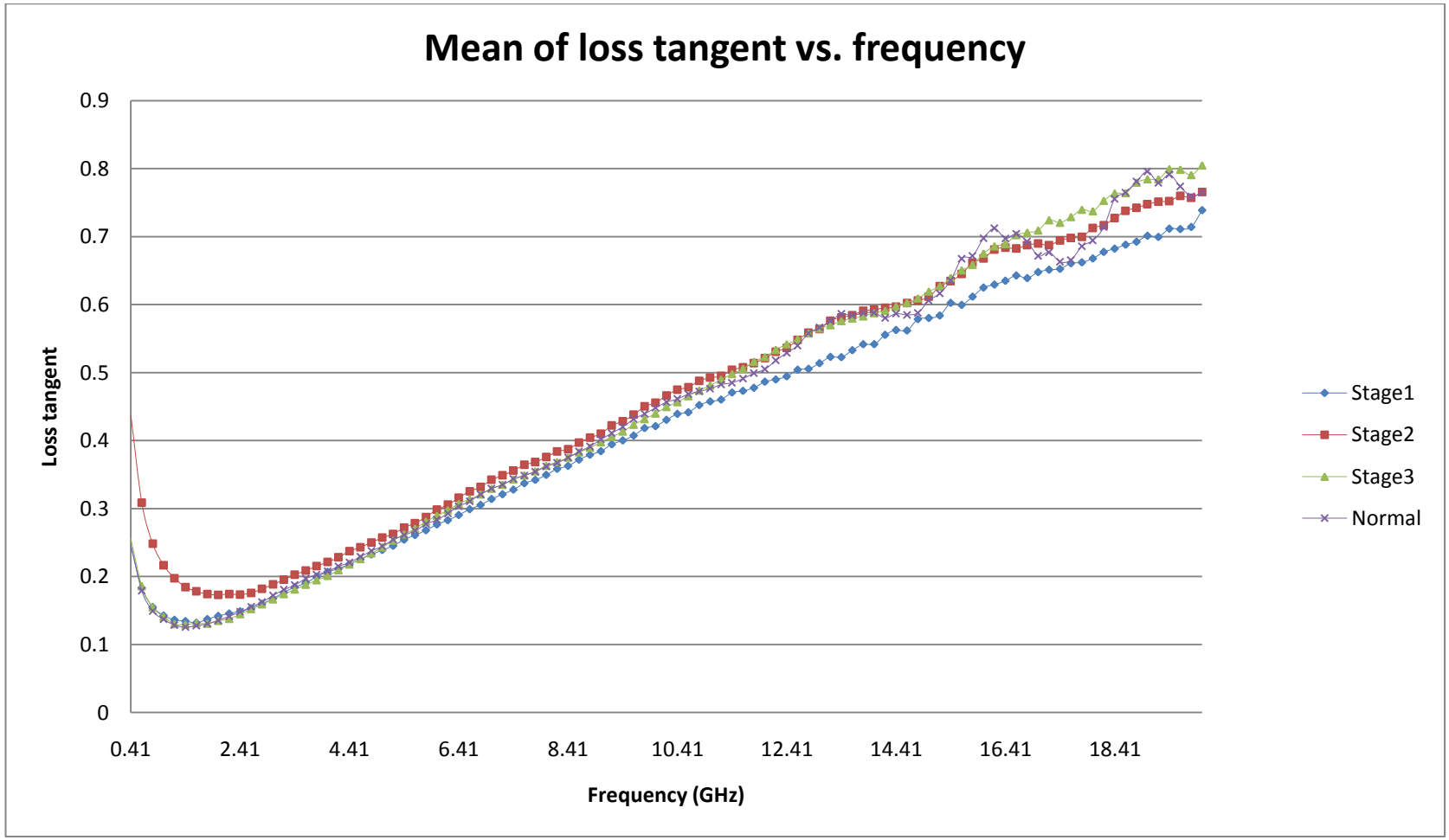

Figure 4.3: Loss tangent of saliva for different stages of breast carcinomas

4.2.2 Dielectric Parameter as a Function of Frequency for Urine Samples

According to the graphs represented in figures 4.4-4.6 the shape of the graphs for stage1, stage2, stage3 and normal subjects follow almost the same trend. However another common trend observed that stage1 appears to have the leading value for dielectric constant parameter, while normal subjects have the lowest values for both loss tangent and loss factor parameters over the considered microwave frequency range. This result is directly opposite with what was observed in permittivity values of saliva and with what was revealed in the literature for breast cancerous tissues, as the permittivity of saliva of breast cancer patients is higher than the permittivity of saliva of normal subjects and the permittivity of malignant breast tissue is higher than the permittivity of healthy breast tissue. This is maybe due to the rise of the mucoprotein levels in the urine of breast cancer patients (Lockey et al., 1956). Lockey et al. found that the mucoprotein mean values in the urine of breast cancer is 238 ± 17.26 mg/24 hours where the relative urine concentration is 1.58 ± 0 .121. Meanwhile; the mucoprotein mean value of the urine of normal subjects is 134.5 ± 6.06 mg/24 hours where the relative urine concentration is 0.598 ± 0.024 which means that the water content in urine of breast cancer patients is lower than in the urine of normal subjects. According to the study conducted by Gabriel et al. (Gabriel et al., 1996) they have compared the permittivity of high content water tissue with low content water tissue as a function of frequency, they found that the permittivity of high water content tissue is greater than the permittivity of low water content tissue. This means that water content has a proportional relation with permittivity in other words water content is the driving force of the difference in dielectric properties between normal tissue and cancerous tissue. Henceforth, our results show lower permittivity values of the breast cancer subjects' urine. However; the appearance of stage 1, stage3 and normal has a seemingly overlapping presentation for dielectric constant parameter even some intersection points can be observed this

indicates that these groups are close from each other and the difference between their mean in this parameter is small in other words that the possibility of finding a significant difference among them is low. Although normal and stage1 are overlapping in loss tangent parameter at some frequency points, they are very far from each other at frequency points between 16.4 to 20 MHz. Moreover, in all the figures it can be seen that the graphs of stage 3 is between the graphs of stage 1 and stage 2 which is also agree with what was found by Qiao et al. for the conductivity values. He observed that the conductivity values of late stage breast cells is between the conductivity values of early stage and invasive cancer cells (Qiao et al., 2010).

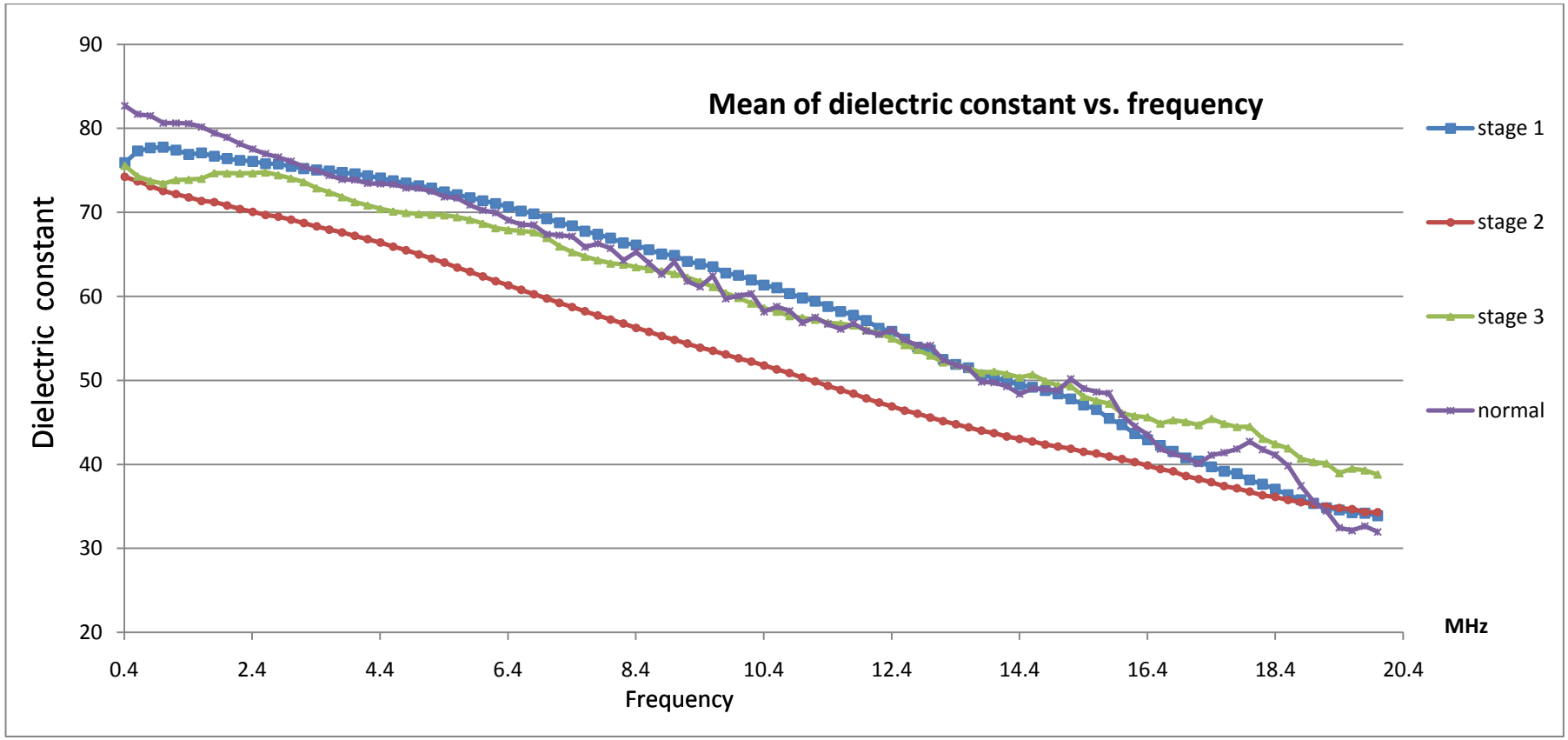

Figure 4.4: Dielectric constant of urine for different stages of breast carcinomas

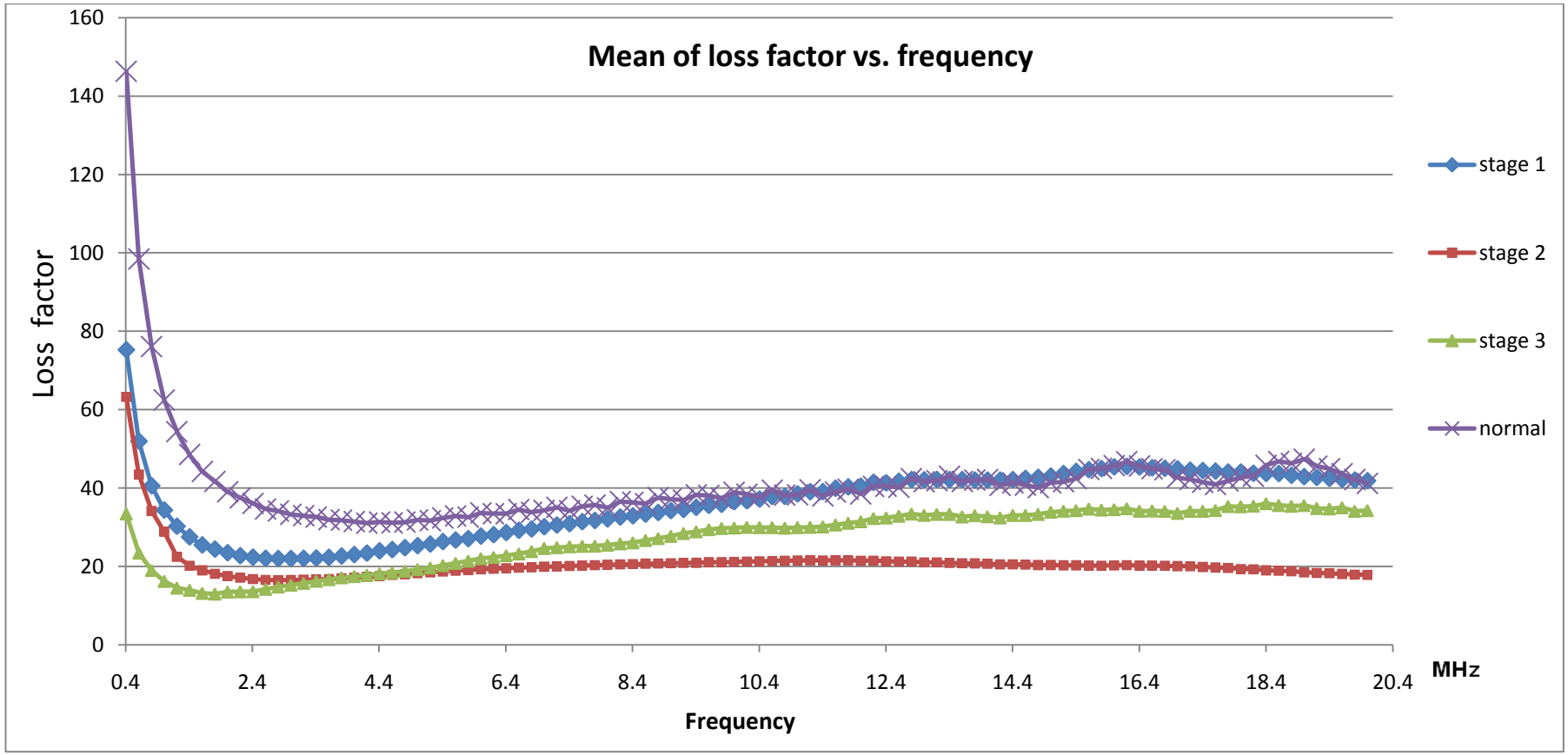

Figure 4.5: Loss factor of urine for different stages of breast carcinomas

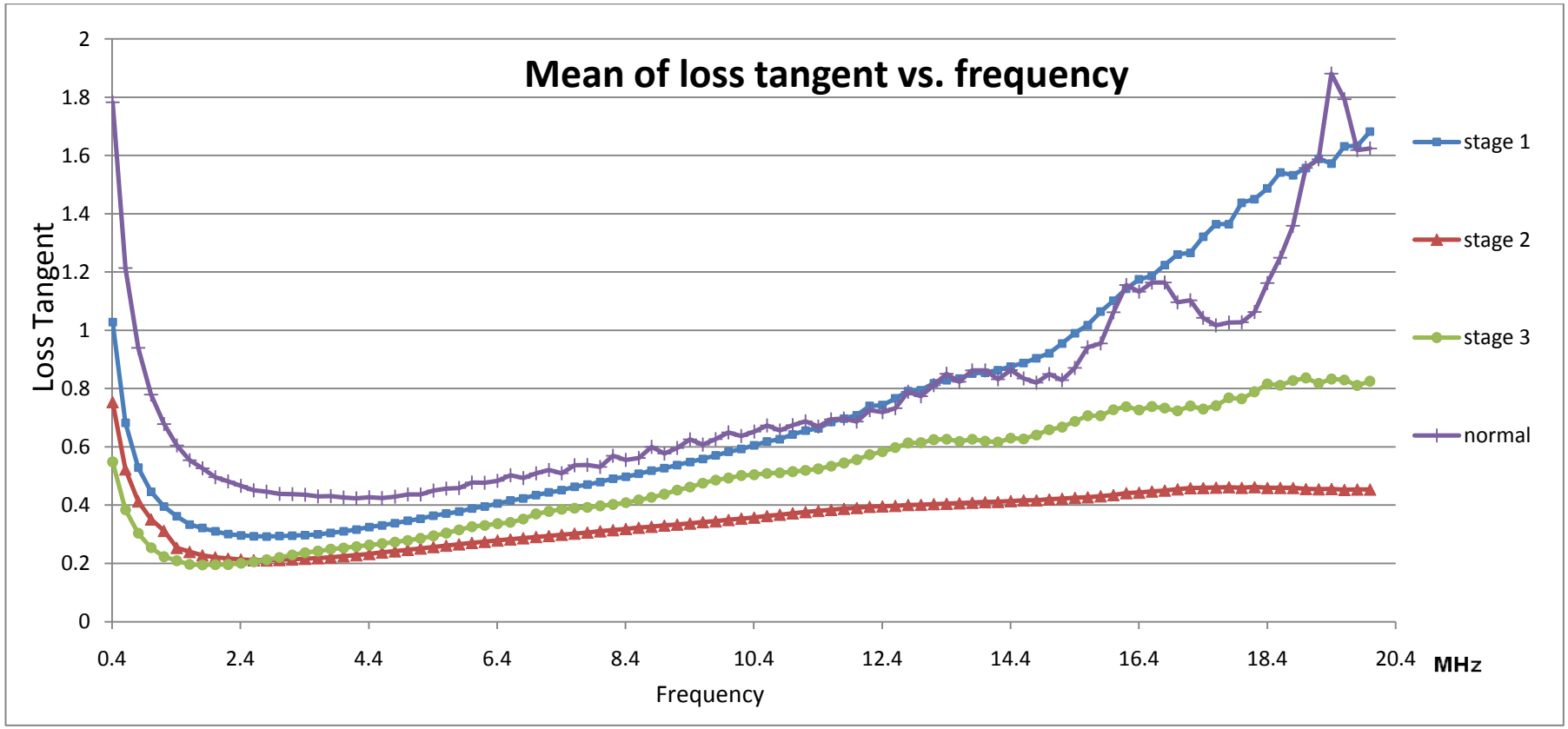

Figure 4.6: Loss tangent of urine for different stages of breast cancer

4.3 Summary of Urine Sample Analysis

Table 4.1: Multiple comparisons between the groups of subjects for dielectric constant of urine with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 8.622, P = 0.001 at frequency 12 GHz	F =8.437, P= 0.001 at frequency 11.8 GHz	F =8.241, P= 0.001 at frequency 12.4 GHz	F =7.935, P= 0.001 at frequency 11.6 GHz	F = 7.895, P= 0.001 at frequency 12.2 GHz
Stage1	Stage2	**.002**	**0.002**	**.003**	**0.002**	**0.003**
	Stage3	.961	0.953	.986	0.925	0.993
	Normal	.997	0.993	.993	0.931	1
Stage2	Stage1	**.002**	**0.002**	**.003**	**0.002**	**0.003**
	Stage3	**.009**	**0.009**	**.011**	**0.012**	**0.009**
	Normal	**.01**	**0.01**	**.005**	**0.02**	**0.01**
Stage3	Stage1	.953	0.953	.986	0.925	0.993
	Stage2	**.009**	**0.009**	**.011**	**0.012**	**0.009**
	Normal	.996	0.996	.942	1	0.997
Normal	Stage1	.993	0.993	.993	0.931	1
	Stage2	**.01**	**0.01**	**.005**	**0.02**	**0.01**
	Stage3	.996	0.996	.942	1	0.997

As depicted in table 4.1, the significant difference between the groups is appreciable because the F numbers quite high; with the highest being 8.622 at 12 GHz and the least is 7.895 at 12.2 GHz. In general, differentiation can be made from urine sample analysis considering loss factor parameter as a function of microwave frequency range considered.

Table 4.2: Multiple comparisons between the groups of subjects for loss factor of urine with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 24.176, P = 0.000 at frequency 4.61 GHz	F =23.997, P= 0.000 at frequency 4.81 GHz	F =23.604, P= 0.000 at frequency 4.21 GHz	F =22.694, P= 0.000 at frequency 4.01 GHz	F = 22.513, P= 0.000 at frequency 5.21 GHz
Stage1	Stage2	**0.003**	**0.003**	**0.009**	**0.015**	**0.002**
	Stage3	**0.016**	**0.015**	**0.028**	**0.04**	**0.017**
	Normal	**0.005**	**0.008**	**0.002**	**0.001**	**0.019**
Stage2	Stage1	**0.003**	**0.003**	**0.009**	**0.015**	**0.002**
	Stage3	0.981	0.965	0.994	0.998	0.904
	Normal	**0**	**0**	**0**	**0**	**0**
Stage3	Stage1	**0.016**	**0.015**	**0.028**	**0.04**	**0.017**
	Stage2	0.981	0.965	0.994	0.998	0.904
	Normal	**0**	**0**	**0**	**0**	**0**
Normal	Stage1	**0.005**	**0.008**	**0.002**	**0.001**	**0.019**
	Stage2	**0**	**0**	**0**	**0**	**0**
	Stage3	**0**	**0**	**0**	**0**	**0**

As depicted in table 4.2, the significant difference between the groups is appreciable because the F numbers are very high; with the highest being 24.176 at 4.61 GHz and the least is 22.513 at 5.21 GHz. In general, differentiation can be made from urine sample analysis considering loss factor parameter as a function of microwave frequency range considered.

Table 4.3: Multiple comparisons between the groups of subjects for loss tangent of urine with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 10.059, P = 0.000 at frequency 2.21 GHz	F =9.923, P= 0.000 at frequency 1.81 GHz	F =9.776, P= 0.000 at frequency 2.41 GHz	F =9.626, P= 0.001 at frequency 1.41 GHz	F = 9.611, P= 0.001 at frequency 2.01 GHz
Stage1	Stage2	0.368	0.393	0.342	0.423	0.373
	Stage3	0.256	0.218	0.293	0.216	0.239
	Normal	**0.019**	**0.022**	**0.022**	**0.025**	**0.025**
Stage2	Stage1	0.368	0.393	0.342	0.423	0.373
	Stage3	0.978	0.946	0.994	0.928	0.968
	Normal	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**
Stage3	Stage1	0.256	0.218	0.293	0.216	0.239
	Stage2	0.978	0.946	0.994	0.928	0.968
	Normal	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**
Normal	Stage1	**0.019**	**0.022**	**0.022**	**0.025**	**0.025**
	Stage2	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**
	Stage3	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**

As depicted in table 4.3, the significant difference between the groups is likewise appreciable because the F numbers are quite high; with the highest being 10.059 at 2.21 GHz and the least is F = 9.611at frequency 2.01 GHz. In general, differentiation can also be made from urine sample analysis considering loss tangent parameter as a function of microwave frequency range considered.

Table 4.4: Significant differences in urine's permittivity across the groups of subjects

No	Group	Significant Difference	Parameter	Frequency
1	Stage1-Stage2	Yes	Dielectric constant Loss factor Loss tangent	(4.61 GHz to13.2 GHz) (3.61 GHz to 20 GHz) (1.6 GHz, 2.4 GHz, 7.2 GHz to 16 GHz)
2	Stage1-Stage3	Yes	Loss factor	(12.1 GHz to 13 GHz)
3	Stage2-Stage3	Yes	Loss factor	(14.4 GHz to 20 GHz)
4	Normal-Stage1	Yes	Loss factor Loss tangent	(0.41 GHz to 5.61 GHz) (1.4 GHz to 3.4 GHz)
5	Normal-Stage2	Yes	Dielectric constant Loss factor Loss tangent	(1.21 GHz to 13 GHz) (0.41 GHz to 19.8 GHz) (0.41 GHz to 15 GHz)
6	Normal-Stage3	Yes	Loss factor Loss tangent	(0.41 GHz to 4.01 GHz) (0.41 GHz to 5.8 GHz)

Table 4.4 above summarises the statistical result output for this study considering only the urine sample. Significant difference across all the groups was found; hence all the groups could be successfully classified at the frequency shown.

4.4 Summary of Saliva Sample Analysis

Table 4.5: Multiple comparisons between the groups of subjects for dielectric constant of saliva with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 1.352 at frequency .4098 GHz	F =1.326 at frequency .6097 GHz	F =1.287 at frequency .8096 GHz	F =1.286 at frequency 1.2094 GHz	F = 1.211 at frequency 1.0095 GHz
Stage1	Stage2	.429	.474	.514	.586	.562
	Stage3	1.000	1.000	.999	.990	.998
	Normal	1.000	.999	.996	.988	.995
Stage2	Stage1	.429	.474	.514	.586	.562
	Stage3	.400	.403	.410	.371	.424
	Normal	.296	.291	.298	.306	.324
Stage3	Stage1	1.000	1.000	.999	.990	.998
	Stage2	.400	.403	.410	.371	.424
	Normal	1.000	1.000	1.000	1.000	1.000
Normal	Stage1	1.000	.999	.996	.275	.995
	Stage2	.296	.291	.298	.985	.324
	Stage3	1.000	.1.000	1.000	.938	1.000

Table 4.5 above shows the summary of saliva samples output after one way analysis of variance (ANOVA) was applied. as the F numbers are low the significant differences between the groups are not appreciable, Which means that no differentiation can be made using saliva sample considering dielectric constant parameter as a function of microwave frequency range considered in this study.

Table 4.6: Multiple comparisons between the groups of subjects for loss factor of saliva with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 1.315 at frequency 19.4003 GHz	F =1.274 at frequency 19.6002 GHz	F =1.241 at frequency 19.8001 GHz	F =1.194 at frequency 20.00 GHz	F = 1.034 at frequency 19.2004 GHz
Stage1	Stage2	.603	.519	.523	.507	.634
	Stage3	.641	.620	.615	.630	.730
	Normal	.220	.242	.253	.275	.321
Stage2	Stage1	.603	.519	.523	.507	.634
	Stage3	1.000	.998	.999	.997	.998
	Normal	.908	.968	.973	.985	.963
Stage3	Stage1	.641	.620	.615	.630	.730
	Stage2	1.000	.998	.999	.997	.998
	Normal	.881	.917	.931	.938	.911
Normal	Stage1	.220	.242	.253	.275	.321
	Stage2	.908	.968	.973	.985	.963
	Stage3	.881	.917	.931	.938	.911

Table 4.6 above shows the summary of saliva samples output after one way analysis of variance (ANOVA) was applied. as the F numbers are low the significant differences between the groups are not appreciable, Which means that no differentiation can be made using saliva sample considering loss factor parameter as a function of microwave frequency range considered in this study.

Table 4.7: Multiple comparisons between the groups of subjects for loss tangent of saliva with the 5 highest F numbers

GROUP	GROUP	SIGNIFICANT LEVEL				
		F = 1.768 at frequency 1.2094 GHz	F =1.751 at frequency .4098 GHz	F =1.737 at frequency .6097 GHz	F =1.692 at frequency .8096 GHz	F = 1.65 at frequency 1.0095 GHz
Stage1	Stage2	.374	.287	.316	.346	.366
	Stage3	.998	1.000	1.000	1.000	1.000
	Normal	.996	1.000	1.000	.999	.999
Stage2	Stage1	.374	.287	.316	.346	.366
	Stage3	.262	.303	.302	.309	.313
	Normal	.186	.205	.197	.201	.210
Stage3	Stage1	.996	1.000	1.000	.1.000	1.000
	Stage2	.262	.303	.302	.309	.313
	Normal	1.000	1.000	1.000	.999	1.000
Normal	Stage1	.996	1.000	1.000	.999	.999
	Stage2	.186	.205	.197	.201	.210
	Stage3	1.000	1.000	1.000	.999	1.000

Table 4.7 above shows the summary of saliva samples output after one way analysis of variance (ANOVA) was applied. as the F numbers are low the significant differences between the groups are not appreciable, Which means that no differentiation can be made using saliva sample considering loss tangent parameter as a function of microwave frequency range considered in this study.

Table 4.8: Significant differences in saliva's permittivity across the groups of subjects

No	Group	Significant Difference	Parameter
1	Stage1-Stage2	NO	None
2	Stage1-Stage3	NO	None
3	Stage2-Stage3	NO	None
4	Normal-Stage1	NO	None
5	Normal-Stage2	NO	None
6	Normal-Stage3	NO	None

Table 4.8 above summarises the statistical output for this study considering saliva samples only. No significant difference found between the groups and therefore no differentiation could be made between them in the frequency range considered in this study.

CHAPTER 5

CONCLUSION AND FUTURE WORK

5.1 Conclusion

This research is carried out in order to find a new non invasive breast cancer staging method. Urine and saliva samples were collected from normal subjects, and breast cancer patients, dielectric parameters were measured using Agilent network vector analyze in the frequency range (10MHz-20GHz).

The significant difference of permittivity for urine and saliva samples across the groups stage 1, stage 2, stage 3 and normal subjects were figured out using SPSS statistical analysis software. Graphs of the mean of dielectric parameters for all groups were depicted using excel.

According to the results obtained from the research statistical analysis output, which are represented graphically and summarized in tables, it can be concluded that permittivity of urine of patients with different stages of breast cancer has a potential for staging of breast cancer. The significant difference derived from the output of urine samples for all parameters including dielectric constant, loss factor and loss tangent can be considered as a starting for more research in the staging research using microwave technique. However in this study, All the groups could be classified at the microwave frequency mentioned in table 4.4. The primary attractive point is the ability to use of urine as biomarker due to ease of its collection in sufficient amounts noninvasively. However, using saliva samples there was no significant difference observed in all parameters over all the frequency range considered. There are still a lot of research studies to be conducted before making generalization and achieving non invasive, inexpensive, and accurate staging.

Today, as the research in the breast cancer field tends toward using microwaves potential in detecting and staging of the disease; the future trend is tending toward finding the thresholds of permittivity of Urine and saliva in differentiating breast Cancer. This research will also attempt to find a non invasive method, fast and accurate to distinguish the carcinoma of the breast.

5.2 Future Work

As prostate cancer is the most common cancer in men after lung and bronchus, future plans tend to detect prostate cancer using permittivity of urine as an attempt to introduce a non invasive method for detection of prostate cancer. Moreover, the research will try to differentiate between different stages of prostate carcinoma and classify different types of prostate carcinoma based on finding the significant difference in permittivity across the groups. The significant difference across the groups will be extracted by the application of statistical methods offered by SPSS.

References

(2006) Basics of Measuring the Dielectric Properties of Materials, Application Note.

(2009) what do you need to know about breast cancer, in: N. C. institute (Ed.), National institute of health, Rockville.

(2011) 85070E Dielectric Probe Kit, 200 MHz to 50 GHz, Technical overview: Agilent.

Atoum MF H.H., Shoter A, Al-Raheem SN, Al Muhrib TK. (2010) TNM staging and classification (familaial and non familial) of breast cancer in Jordanian females. Indian Journak of Cancer 47:194-198.

Boulevard J., Brook O. (2010) Magnetic resonance imaging (MRI)-Breast, Radiological society of north America.

Brem F.R., Katherine H.M., Zawistowski G. (2006) Approaches to improving breast cancer diagnosis using a high resolution: breast specific camera. Physica medica 21:17-19.

Chaudhary S.S., Mishra R.K., Arvind Swarup, Thomas J.M. (1984) Dielectric properties of normal and malignant human breast tissue at radiowave and microwaves frequencies. Indian J. Biochem. Biophys 21:76-79.

Chauveau N., Hamzaoui L., Rochaix P., Rigaud B., Voigt J.J., Morucci J.P. (1999) Ex vivo discrimination between normal and pathological tissues in human breast surgical biopsies using bioimpedance spectroscopy. Ann NY Acad Sci 873:42-50.

Choi J.W., Cho J., Lee Y., Yim J., Kang B., Oh K.K., Jung W.H., Kim H.J., Cheon C., Lee H.-D., Kwon Y. (2004) Microwave detection of metastasized breast cancer cells in the lymph node. Potential application for sentinel lymphadenectomy. Breast Cancer Research and Treatment 86:107-115.

Demartini W., Lehman C., Partridge S. (2008) Breast MRI for cancer detection and characterization. Academic Radiology 15:408-416.

Elsdon M., Leach M., SergeiSkobelev, Smith D. (2007) Microwave holographic imaging of breast cancer, IEEE International Symposium on Microwave, Antenna, Propagation, and EMC Technologies For Wireless Communications. pp. 966-969.

Fricke H., Morse S. (1926) The electric capacity of tumors of the breast. Journal of Cancer Research 16:310-376.

Gabriel C., Gabriel S., Corthout E. (1996) The dielectric properties of biological tissues: I. Literature survey. Phys. Med. Biol. 41:2231-2249.

Gabriel C. G.S., Corthout E. (1996) The dielectric properties of biological tissues: I. Literature survey. Phys. Med. Biol. 41:2231-2249.

Gibbins D., Klemm M., Craddock I.J., Leendertz J.A., Preece A., Benjamin R. (2010) A comparison of a wide-slot and a stacked patch antenna for the purpose of breast cancer detection. IEEE transactions on antennas and propagation 58:665-673.

Jochelson M.S., Morris E.A. (2011) An imaging approach to high-risk screening for breast cancer. Seminars in roentgenology 46:68-75.

Joines W.T., Dhenxing Y.Z., Jirtle R.L. (1994) The measured electrical properties of normal and malignant human tissues from 50 to 900 MHz. Med. Phys. 21:547-550.

Jossinet J. (1996) Variability of impedivity in normal and pathological breast tissue. . J.Med Biol Eng Comput 34:346-350.

Jossinet J. (1998) The impedivity of freshly excised human breast tissue. Physiol Meas 19:61-75.

Jossinet J., Schmitt M. (1999) A review of parameters for the bioelectrical characterization of breast tissue. Ann NY Acad Sci 873:30-41.

Kalogerakos K., Sofoudis C., Baltayiannis N. (2008) Early Breast Cancer: A review. Cancer Therapy 6:463-473.

Kao H.P., Cardoso R., Shwedyk E. (1999) Correlation of Permittivity and Water Content During Cerebral Edema. IEEE Transactions on biomedical engineering 46:1121-1128.

Kearney J.A., Murray M. (2010) Breast cancer screening ecommendation; is mammography the only answer? The journal of midwifery and women's health 54:393-400.

Kopans P.D. (2006) Breast Imaging Lippincott Williams & Wilkins.

Krag N.D. (1999) The sentinel node for staging breast cancer: Current review. Breast cancer 6:233-236.

Lockey E., Anderson A.J., Maclagan N.F. (1956) Urine and serum mucoproteins in cancer and other diseases. Br J Cancer 10:209-221.

Morimoto T., Kimura S., Konishi Y., Kinouchi Y., Iritani T., Mitsuyama N., Komaki K., Monden Y. (1990) Measurement of the electrical bioimpedance of breast tumors. Eur Surg Res 22:86-92.

Morimoto T., Kimura S., Konishi Y., Komaki K., Uyama T., Monden Y., Kinouchi Y., Iritani T. (1993) A study of the electrical bio-impedance of tumors. J Invest Surg 6:25-32.

Neves B. (1996) Permittivity/Dielectric Constant: Do the Math.

Qiao G., Duan W., Chatwin C., Sinclair A., Wang W. (2010) Electrical properties of breast cancer cells from impedance measurement of cell suspensions. . Journal of Physics: conference series 224.

Roberts E.J., Cook F.H. (1952) Microwaves in medical and biological research. British Journal of Applied Physics 3:33-40.

Singh B., Smith C.W., Hughes R. (1979) In vivo dielectric spectrometer Med. Biol. Eng. Comput. 17.

Smith R.S., Foster R.K. (1985) Dielectric properties of low-water-content tissues. Phys. Med. Biol. 30:965-973.

Stang J.P. (2008) A 3D active microwave imaging system for breast cancer screening, Department of electrical and computer engineering, Duke University. pp. 157.

Suroweic A.J., Stuchly S.S., Barr J.R., Swarup A. (1988) Dielectric Properties of Breast Carcinoma and the Surrounding Tissues. IEEE Transactions On Biomedical Engineering 35:257-263.

Swarup A., Stuchly S.S., Surowiec A.J. (1991) Dielectric properties of mouse MCA1 fibrosarcoma at different stages of development. Bioelectromagnetics 12:1-8.

Tyna A.H., Sian E.L. (2004) Technology review: The use of electrical impedance scanning in the detection of breast cancer. . Breast Cancer Res. 6:69-74.

Whitman G.J., Sheppard D.G., Phelps M.J., Gonzales B.N. (2006) Breast cancer staging. Seminars in roentgenology 41:91-104.

APPENDIX

App.1: Summary of the SPSS output for the dielectric constant of urine where a significant difference was found across the groups.

			Multiple Comparisons		
Dependent Variable	(I) VAR00001	(J) VAR00001	Mean Difference (I-J)	Std. Error	Sig.
1209400000	normal	stage2	9.5931238*	3.35E+00	0.047
1409300000	normal	stage2	9.7326286*	3.21E+00	0.033
1609200000	normal	stage2	9.7489536*	3.16E+00	0.029
2009000000	normal	stage2	8.7547619*	3.07E+00	0.048
4607700000	stage1	stage2	7.8181226*	2.75E+00	0.048
4807600000	stage1	stage2	8.0045845*	2.73E+00	0.04
5007500000	stage1	stage2	8.1814952*	2.76E+00	0.038
5207400000	stage1	stage2	8.3874143*	2.78E+00	0.034
5407300000	stage1	stage2	8.4211310*	2.73E+00	0.03
5607200000	stage1	stage2	8.6529321*	2.77E+00	0.028
5607200000	normal	stage2	8.8955155*	3.12E+00	0.048
5807100000	stage1	stage2	8.8301929*	2.73E+00	0.022
6007000000	stage1	stage2	9.0089131*	2.70E+00	0.017
6206900000	stage1	stage2	9.2420679*	2.74E+00	0.016
6206900000	normal	stage2	8.7285595*	3.08E+00	0.049
6406800000	stage1	stage2	9.3442929*	2.68E+00	0.013
6606700000	stage1	stage2	9.3895226*	2.61E+00	0.01
6606700000	normal	stage2	8.3649976*	2.94E+00	0.048
6806600000	stage1	stage2	9.5724893*	2.62E+00	0.009
6806600000	normal	stage2	8.7739976*	2.96E+00	0.038
7006500000	stage1	stage2	9.4981583*	2.57E+00	0.008
7006500000	normal	stage2	8.2766667*	2.89E+00	0.047
7206400000	stage1	stage2	9.5540619*	2.60E+00	0.008
7206400000	normal	stage2	8.5642952*	2.92E+00	0.041
7406300000	stage1	stage2	9.6590083*	2.64E+00	0.009
7406300000	normal	stage2	8.9678167*	2.97E+00	0.034
7606200000	stage1	stage2	9.5237583*	2.56E+00	0.008
7606200000	normal	stage2	8.2862833*	2.89E+00	0.046
7806100000	stage1	stage2	9.6739083*	2.58E+00	0.007
7806100000	normal	stage2	9.0736333*	2.91E+00	0.028
8006000000	stage1	stage2	9.6942440*	2.56E+00	0.007
8006000000	normal	stage2	9.1194774*	2.89E+00	0.025
8205900000	stage1	stage2	9.5908750*	2.46E+00	0.005
8205900000	normal	stage2	8.2828167*	2.77E+00	0.036
8405800000	stage1	stage2	9.8619060*	2.55E+00	0.006
8405800000	normal	stage2	9.5852226*	2.88E+00	0.018

8605700000	stage2	stage1	-9.7811036*	2.45E+00	0.004
8605700000	stage2	stage3	-7.4943186*	2.57E+00	0.042
8605700000	stage2	normal	-9.0241452*	2.76E+00	0.02
8805600000	stage2	stage1	-9.7664048*	2.38E+00	0.003
8805600000	stage2	stage3	-7.7562881*	2.51E+00	0.029
8805600000	stage2	normal	-8.3547798*	2.68E+00	0.028
9005500000	stage2	stage1	-10.0490262*	2.53E+00	0.004
9005500000	stage2	stage3	-7.8739295*	2.66E+00	0.038
9005500000	stage2	normal	-9.9153595*	2.85E+00	0.013
9205400000	stage2	stage1	-9.7806500*	2.34E+00	0.003
9205400000	stage2	stage3	-7.8775833*	2.47E+00	0.024
9205400000	stage2	normal	-8.6003500*	2.64E+00	0.021
9405300000	stage2	stage1	-9.9364298*	2.36E+00	0.003
9405300000	stage2	stage3	-7.8483881*	2.48E+00	0.025
9405300000	stage2	normal	-8.3793881*	2.65E+00	0.026
9605200000	stage2	stage1	-10.0097452*	2.42E+00	0.003
9605200000	stage2	stage3	-7.6195719*	2.54E+00	0.036
9605200000	stage2	normal	-9.5275702*	2.72E+00	0.012
9805100000	stage2	stage1	-9.6729107*	2.35E+00	0.003
9805100000	stage2	stage3	-7.3129690*	2.47E+00	0.038
9805100000	stage2	normal	-7.9530607*	2.64E+00	0.035
10005000000	stage2	stage1	-9.8917560*	2.39E+00	0.003
10005000000	stage2	stage3	-7.2181376*	2.51E+00	0.045
10005000000	stage2	normal	-8.2680643*	2.69E+00	0.03
10204900000	stage2	stage1	-9.7195310*	2.35E+00	0.003
10204900000	stage2	normal	-8.6338393*	2.65E+00	0.021
10404800000	stage1	stage2	9.5560083*	2.40E+00	0.004
10604700000	stage1	stage2	9.7166988*	2.37E+00	0.003
10604700000	normal	stage2	7.9114238*	2.67E+00	0.038
10804600000	stage1	stage2	9.4755500*	2.28E+00	0.003
10804600000	normal	stage2	7.8824167*	2.57E+00	0.031
11004500000	stage2	stage1	-9.4711369*	2.29E+00	0.003
11004500000	stage2	stage3	-7.1177986*	2.41E+00	0.038
11004500000	stage2	normal	-7.2994702*	2.58E+00	0.049
11204400000	stage2	stage1	-9.5503619*	2.22E+00	0.002
11204400000	stage2	stage3	-7.3625819*	2.33E+00	0.025
11204400000	stage2	normal	-7.8987702*	2.50E+00	0.025
11404300000	stage2	stage1	-9.4374988*	2.14E+00	0.002
11404300000	stage2	stage3	-7.5086938*	2.25E+00	0.018
11404300000	stage2	normal	-7.9038655*	2.41E+00	0.02
11604200000	stage2	stage1	-9.3359345*	2.13E+00	0.002
11604200000	stage2	stage3	-7.9044962*	2.24E+00	0.012
11604200000	stage2	normal	-7.8522012*	2.40E+00	0.02
11804100000	stage2	stage1	-9.3607393*	2.13E+00	0.002
11804100000	stage2	stage3	-8.1535810*	2.25E+00	0.009
11804100000	stage2	normal	-8.7007060*	2.40E+00	0.01

12004000000	stage2	stage1	-9.2760417*	2.10E+00	0.002
12004000000	stage2	stage3	-8.1632867*	2.22E+00	0.008
12004000000	stage2	normal	-8.7596583*	2.37E+00	0.008
12203900000	stage2	stage1	-8.8580940*	2.16E+00	0.003
12203900000	stage2	stage3	-8.2360390*	2.27E+00	0.009
12203900000	stage2	normal	-8.7529107*	2.43E+00	0.01
12403800000	stage2	stage1	-8.9106631*	2.17E+00	0.003
12403800000	stage2	stage3	-8.1022948*	2.28E+00	0.011
12403800000	stage2	normal	-9.5774548*	2.44E+00	0.005
12603700000	stage2	stage1	-8.4834917*	2.22E+00	0.006
12603700000	stage2	stage3	-7.8058667*	2.34E+00	0.018
12603700000	stage2	normal	-9.1225250*	2.51E+00	0.009
12803600000	stage2	stage1	-7.9164202*	2.40E+00	0.019
12803600000	stage2	stage3	-7.6033219*	2.52E+00	0.034
12803600000	stage2	normal	-8.4971286*	2.70E+00	0.026
13003500000	stage2	stage1	-8.0342429*	2.36E+00	0.015
13003500000	stage2	stage3	-7.3954362*	2.49E+00	0.037
13003500000	stage2	normal	-8.8571512*	2.66E+00	0.018
14202900000	stage2	stage3	-7.4417748*	2.55E+00	0.042
14402800000	stage2	stage3	-7.3293133*	2.57E+00	0.048
14602700000	stage2	stage3	-7.9630371*	2.43E+00	0.02
14802600000	stage2	stage3	-7.5590252*	2.43E+00	0.028
15002500000	stage2	stage3	-7.2630533*	2.46E+00	0.039
15202400000	stage2	stage3	-7.4435533*	2.59E+00	0.045

App. 2: Summary of the SPSS output for the loss factor of urine where a significant difference was found across the groups.

Dependent Variable	(I) VAR00001	(J) VAR00001	Mean Difference (I-J)	Std. Error	Sig.
4.1E+08	normal	stage1	71.0725533*	1.84E+01	0.005
4.1E+08	normal	stage2	83.0599724*	1.78E+01	0.001
4.1E+08	normal	stage3	112.8751433*	1.92E+01	0
6.1E+08	normal	stage1	46.5256767*	1.23E+01	0.006
6.1E+08	normal	stage2	55.0067552*	1.19E+01	0.001
6.1E+08	normal	stage3	75.0154767*	1.28E+01	0
8.1E+08	normal	stage1	35.5310567*	9.32E+00	0.006
8.1E+08	normal	stage2	41.9287019*	9.01E+00	0.001
8.1E+08	normal	stage3	57.0962000*	9.74E+00	0
1.01E+09	normal	stage1	28.0866967*	7.47E+00	0.007
1.01E+09	normal	stage2	33.6177514*	7.22E+00	0.001
1.01E+09	normal	stage3	46.2474167*	7.80E+00	0
1.21E+09	stage1	stage3	15.7309267*	5.19E+00	0.032
1.21E+09	normal	stage1	24.1332433*	5.19E+00	0.001
1.21E+09	normal	stage2	31.9124267*	5.02E+00	0
1.21E+09	normal	stage3	39.8641700*	5.42E+00	0
1.41E+09	stage1	stage3	13.5771467*	4.54E+00	0.035
1.41E+09	normal	stage1	21.0078000*	4.54E+00	0.001
1.41E+09	normal	stage2	28.3607143*	4.39E+00	0
1.41E+09	normal	stage3	34.5849467*	4.75E+00	0
1.61E+09	stage1	stage3	12.3101683*	4.11E+00	0.034
1.61E+09	normal	stage1	18.7316783*	4.11E+00	0.001
1.61E+09	normal	stage2	25.2261248*	3.97E+00	0
1.61E+09	normal	stage3	31.0418467*	4.29E+00	0
1.81E+09	stage1	stage3	11.4317500*	3.71E+00	0.029
1.81E+09	normal	stage1	17.2801200*	3.71E+00	0.001
1.81E+09	normal	stage2	23.5674652*	3.59E+00	0
1.81E+09	normal	stage3	28.7118700*	3.88E+00	0
2.01E+09	stage1	stage3	9.9906083*	3.33E+00	0.034
2.01E+09	normal	stage1	15.5209117*	3.33E+00	0.001
2.01E+09	normal	stage2	21.4866438*	3.22E+00	0
2.01E+09	normal	stage3	25.5115200*	3.47E+00	0
2.21E+09	stage1	stage3	9.1622150*	3.02E+00	0.032
2.21E+09	normal	stage1	14.7704350*	3.02E+00	0.001
2.21E+09	normal	stage2	20.3951957*	2.92E+00	0
2.21E+09	normal	stage3	23.9326500*	3.16E+00	0
2.41E+09	stage1	stage3	8.7723450*	2.85E+00	0.029
2.41E+09	normal	stage1	13.7032083*	2.85E+00	0.001
2.41E+09	normal	stage2	19.2986857*	2.75E+00	0
2.41E+09	normal	stage3	22.4755533*	2.97E+00	0
2.61E+09	stage1	stage3	7.8593483*	2.65E+00	0.036
2.61E+09	normal	stage1	12.5855050*	2.65E+00	0.001
2.61E+09	normal	stage2	18.1037252*	2.56E+00	0

2.61E+09	normal	stage3	20.4448533*	2.77E+00	0
2.81E+09	stage1	stage3	7.2159433*	2.50E+00	0.043
2.81E+09	normal	stage1	12.1166567*	2.50E+00	0.001
2.81E+09	normal	stage2	17.6379852*	2.41E+00	0
2.81E+09	normal	stage3	19.3326000*	2.61E+00	0
3.01E+09	stage1	stage3	6.7517850*	2.40E+00	0.05
3.01E+09	normal	stage1	11.2531783*	2.40E+00	0.001
3.01E+09	normal	stage2	16.7130581*	2.32E+00	0
3.01E+09	normal	stage3	18.0049633*	2.51E+00	0
3.21E+09	normal	stage1	10.8514850*	2.33E+00	0.001
3.21E+09	normal	stage2	16.3032576*	2.26E+00	0
3.21E+09	normal	stage3	17.1830000*	2.44E+00	0
3.41E+09	normal	stage1	10.4423017*	2.24E+00	0.001
3.41E+09	normal	stage2	15.8986529*	2.16E+00	0
3.41E+09	normal	stage3	16.3297533*	2.34E+00	0
3.61E+09	stage1	stage2	5.5279310*	1.90E+00	0.041
3.61E+09	normal	stage1	9.6241000*	2.06E+00	0.001
3.61E+09	normal	stage2	15.1520310*	2.00E+00	0
3.61E+09	normal	stage3	15.2604000*	2.16E+00	0
3.81E+09	stage1	stage2	5.7154048*	1.85E+00	0.028
3.81E+09	normal	stage1	9.1345633*	2.01E+00	0.001
3.81E+09	normal	stage2	14.8499681*	1.95E+00	0
3.81E+09	normal	stage3	14.6371533*	2.10E+00	0
4.01E+09	stage1	stage2	5.8940190*	1.74E+00	0.015
4.01E+09	normal	stage1	8.4153367*	1.90E+00	0.001
4.01E+09	normal	stage2	14.3093557*	1.84E+00	0
4.01E+09	normal	stage3	13.9732200*	1.98E+00	0
4.21E+09	stage1	stage2	6.0788643*	1.67E+00	0.009
4.21E+09	normal	stage1	7.6666033*	1.82E+00	0.002
4.21E+09	normal	stage2	13.7454676*	1.76E+00	0
4.21E+09	normal	stage3	13.2850567*	1.90E+00	0
4.41E+09	stage1	stage2	6.4167036*	1.70E+00	0.006
4.41E+09	normal	stage1	7.3657417*	1.84E+00	0.004
4.41E+09	normal	stage2	13.7824452*	1.78E+00	0
4.41E+09	normal	stage3	13.1868700*	1.93E+00	0
4.61E+09	stage1	stage2	6.4947226*	1.60E+00	0.003
4.61E+09	normal	stage1	6.8270783*	1.74E+00	0.005
4.61E+09	normal	stage2	13.3218010*	1.68E+00	0
4.61E+09	normal	stage3	12.6841567*	1.82E+00	0
4.81E+09	stage1	stage2	6.7596810*	1.62E+00	0.003
4.81E+09	normal	stage1	6.5205567*	1.76E+00	0.008
4.81E+09	normal	stage2	13.2802376*	1.70E+00	0
4.81E+09	normal	stage3	12.4800133*	1.84E+00	0
5.01E+09	stage1	stage2	7.0344952*	1.70E+00	0.003
5.01E+09	normal	stage1	6.5584200*	1.85E+00	0.011
5.01E+09	normal	stage2	13.5929152*	1.79E+00	0

5.01E+09	normal	stage3	12.6244833*	1.93E+00	0
5.21E+09	stage1	stage2	7.2517821*	1.67E+00	0.002
5.21E+09	normal	stage1	5.9772883*	1.82E+00	0.019
5.21E+09	normal	stage2	13.2290705*	1.76E+00	0
5.21E+09	normal	stage3	12.0360633*	1.90E+00	0
5.41E+09	stage1	stage2	7.6126512*	1.83E+00	0.003
5.41E+09	normal	stage1	6.0298450*	2.00E+00	0.033
5.41E+09	normal	stage2	13.6424962*	1.93E+00	0
5.41E+09	normal	stage3	12.1075133*	2.08E+00	0
5.61E+09	stage1	stage2	7.8247190*	1.91E+00	0.003
5.61E+09	normal	stage1	6.1170033*	2.08E+00	0.039
5.61E+09	normal	stage2	13.9417224*	2.01E+00	0
5.61E+09	normal	stage3	12.0192933*	2.17E+00	0
5.81E+09	stage1	stage2	8.0024012*	1.88E+00	0.002
5.81E+09	normal	stage2	13.4976395*	1.98E+00	0
5.81E+09	normal	stage3	11.1872567*	2.14E+00	0
6.01E+09	stage1	stage2	8.4527536*	2.17E+00	0.005
6.01E+09	normal	stage2	14.3505119*	2.28E+00	0
6.01E+09	normal	stage3	11.6018367*	2.46E+00	0.001
6.21E+09	stage1	stage2	8.7034476*	2.10E+00	0.003
6.21E+09	normal	stage2	14.0568176*	2.21E+00	0
6.21E+09	normal	stage3	11.1048467*	2.39E+00	0.001
6.41E+09	stage1	stage2	9.0919452*	2.14E+00	0.002
6.41E+09	normal	stage2	13.8990186*	2.26E+00	0
6.41E+09	normal	stage3	10.6690267*	2.44E+00	0.002
6.61E+09	stage1	stage2	9.5509048*	2.37E+00	0.004
6.61E+09	normal	stage2	14.8141548*	2.49E+00	0
6.61E+09	normal	stage3	11.2472700*	2.69E+00	0.003
6.81E+09	stage1	stage2	9.7693202*	2.19E+00	0.001
6.81E+09	normal	stage2	14.0327586*	2.30E+00	0
6.81E+09	normal	stage3	9.9814567*	2.48E+00	0.004
7.01E+09	stage1	stage2	10.2124310*	2.31E+00	0.002
7.01E+09	normal	stage2	14.3969943*	2.43E+00	0
7.01E+09	normal	stage3	9.6901767*	2.62E+00	0.008
7.21E+09	stage1	stage2	10.5539655*	2.38E+00	0.001
7.21E+09	normal	stage2	15.0570171*	2.50E+00	0
7.21E+09	normal	stage3	10.2146667*	2.70E+00	0.006
7.41E+09	stage1	stage2	10.7689726*	2.24E+00	0.001
7.41E+09	normal	stage2	14.0976210*	2.35E+00	0
7.41E+09	normal	stage3	9.1665267*	2.54E+00	0.009
7.61E+09	stage1	stage2	11.1814440*	2.38E+00	0.001
7.61E+09	normal	stage2	15.1163390*	2.50E+00	0
7.61E+09	normal	stage3	10.1648867*	2.70E+00	0.007
7.81E+09	stage1	stage2	11.4253762*	2.41E+00	0.001
7.81E+09	normal	stage2	15.3698462*	2.53E+00	0
7.81E+09	normal	stage3	10.4568600*	2.74E+00	0.006

8.01E+09	stage1	stage2	11.6851429*	2.36E+00	0
8.01E+09	normal	stage2	14.5352329*	2.48E+00	0
8.01E+09	normal	stage3	9.4908667*	2.68E+00	0.011
8.21E+09	stage1	stage2	12.0828988*	2.55E+00	0.001
8.21E+09	normal	stage2	16.0497538*	2.68E+00	0
8.21E+09	normal	stage3	10.7677700*	2.90E+00	0.007
8.41E+09	stage1	stage2	12.2982310*	2.58E+00	0.001
8.41E+09	normal	stage2	15.7474610*	2.71E+00	0
8.41E+09	normal	stage3	10.2742800*	2.93E+00	0.012
8.61E+09	stage1	stage2	12.6298845*	2.58E+00	0.001
8.61E+09	normal	stage2	15.3049062*	2.72E+00	0
8.61E+09	normal	stage3	9.3504900*	2.94E+00	0.023
8.81E+09	stage1	stage2	13.0155857*	2.81E+00	0.001
8.81E+09	normal	stage2	16.8194724*	2.95E+00	0
8.81E+09	normal	stage3	10.4008267*	3.19E+00	0.02
9.01E+09	stage1	stage2	13.4082024*	2.95E+00	0.001
9.01E+09	normal	stage2	16.3540824*	3.11E+00	0
9.01E+09	normal	stage3	9.4634367*	3.36E+00	0.049
9.21E+09	stage1	stage2	13.6597060*	2.91E+00	0.001
9.21E+09	normal	stage2	16.0586510*	3.06E+00	0
9.41E+09	stage1	stage2	14.1356333*	3.17E+00	0.001
9.41E+09	normal	stage2	17.3115900*	3.34E+00	0
9.61E+09	stage1	stage2	14.4996810*	3.37E+00	0.002
9.61E+09	normal	stage2	17.0488343*	3.55E+00	0.001
9.81E+09	stage1	stage2	14.7824250*	3.15E+00	0.001
9.81E+09	normal	stage2	16.3214600*	3.32E+00	0.001
1E+10	stage1	stage2	15.3528548*	3.49E+00	0.002
1E+10	normal	stage2	17.7771681*	3.68E+00	0.001
1.02E+10	stage1	stage2	15.4902940*	3.41E+00	0.001
1.02E+10	normal	stage2	17.1539257*	3.58E+00	0.001
1.04E+10	stage1	stage2	15.8672655*	3.24E+00	0.001
1.04E+10	normal	stage2	16.4894771*	3.41E+00	0.001
1.06E+10	stage1	stage2	16.4167679*	3.55E+00	0.001
1.06E+10	normal	stage2	18.0757795*	3.73E+00	0.001
1.08E+10	stage1	stage2	16.3846548*	3.30E+00	0
1.08E+10	normal	stage2	16.7265681*	3.48E+00	0.001
1.1E+10	stage1	stage2	16.9759345*	3.42E+00	0
1.1E+10	normal	stage2	16.7772995*	3.60E+00	0.001
1.12E+10	stage1	stage2	17.4682429*	3.62E+00	0.001
1.12E+10	normal	stage2	17.9786395*	3.81E+00	0.001
1.14E+10	stage1	stage2	17.5242369*	3.49E+00	0
1.14E+10	normal	stage2	16.4439486*	3.67E+00	0.001
1.16E+10	stage1	stage2	18.3743821*	3.83E+00	0.001
1.16E+10	normal	stage2	17.4123405*	4.03E+00	0.002
1.18E+10	stage1	stage2	18.7390262*	3.97E+00	0.001
1.18E+10	normal	stage2	18.1179429*	4.18E+00	0.002

1.2E+10	stage1	stage2	18.9626536*	3.94E+00	0.001
1.2E+10	normal	stage2	17.0386586*	4.14E+00	0.003
1.22E+10	stage1	stage2	19.9762560*	4.49E+00	0.001
1.22E+10	normal	stage2	18.9106343*	4.73E+00	0.004
1.24E+10	stage1	stage2	19.9807952*	4.50E+00	0.001
1.24E+10	normal	stage2	19.1035586*	4.74E+00	0.004
1.26E+10	stage1	stage2	20.4852988*	4.59E+00	0.001
1.26E+10	normal	stage2	18.9918005*	4.83E+00	0.005
1.28E+10	stage1	stage2	20.9248238*	5.04E+00	0.003
1.28E+10	normal	stage2	21.1983805*	5.30E+00	0.004
1.3E+10	stage1	stage2	21.0226190*	4.78E+00	0.002
1.3E+10	normal	stage2	20.5925024*	5.03E+00	0.003
1.32E+10	stage1	stage2	21.1632583*	4.72E+00	0.001
1.32E+10	normal	stage2	20.8462133*	4.97E+00	0.003
1.34E+10	stage1	stage2	21.2311405*	4.72E+00	0.001
1.34E+10	normal	stage2	22.1243871*	4.97E+00	0.001
1.36E+10	stage1	stage2	21.3484798*	4.47E+00	0.001
1.36E+10	normal	stage2	20.8592948*	4.70E+00	0.001
1.38E+10	stage1	stage2	21.2462524*	4.34E+00	0.001
1.38E+10	normal	stage2	21.2480224*	4.57E+00	0.001
1.4E+10	stage1	stage2	21.3347881*	4.29E+00	0
1.4E+10	normal	stage2	21.4869348*	4.51E+00	0.001
1.42E+10	stage1	stage2	21.4672357*	4.19E+00	0
1.42E+10	normal	stage2	20.1265024*	4.41E+00	0.001
1.44E+10	stage1	stage2	21.5853250*	4.19E+00	0
1.44E+10	stage2	stage3	-12.5049100*	4.41E+00	0.048
1.44E+10	normal	stage2	20.7851633*	4.41E+00	0.001
1.46E+10	stage1	stage2	21.9754988*	4.24E+00	0
1.46E+10	stage2	stage1	-21.9754988*	4.24E+00	0
1.46E+10	stage2	stage3	-12.5831205*	4.46E+00	0.049
1.46E+10	stage3	stage1	-9.3923783	4.61E+00	0.21
1.46E+10	normal	stage2	20.2988538*	4.46E+00	0.001
1.48E+10	stage1	stage2	22.3764083*	4.31E+00	0
1.48E+10	stage2	stage1	-22.3764083*	4.31E+00	0
1.48E+10	stage2	stage3	-12.9620767*	4.54E+00	0.046
1.48E+10	stage3	stage1	-9.4143317	4.69E+00	0.221
1.48E+10	normal	stage2	19.7357567*	4.54E+00	0.002
1.5E+10	stage1	stage2	22.6898619*	4.53E+00	0
1.5E+10	stage2	stage1	-22.6898619*	4.53E+00	0
1.5E+10	stage2	stage3	-13.5228119*	4.77E+00	0.048
1.5E+10	normal	stage2	20.9974186*	4.77E+00	0.002
1.52E+10	stage1	stage2	23.3953940*	4.81E+00	0.001
1.52E+10	normal	stage2	21.3005157*	5.06E+00	0.002
1.54E+10	stage1	stage2	23.9407321*	5.00E+00	0.001
1.54E+10	normal	stage2	22.1118371*	5.26E+00	0.002
1.56E+10	stage1	stage2	24.4586524*	5.40E+00	0.001

1.56E+10	normal	stage2	24.4776724*	5.68E+00	0.002
1.58E+10	stage1	stage2	24.7610393*	5.45E+00	0.001
1.58E+10	normal	stage2	24.8077443*	5.74E+00	0.002
1.6E+10	stage1	stage2	25.1299702*	5.27E+00	0.001
1.6E+10	normal	stage2	25.4543486*	5.55E+00	0.001
1.62E+10	stage1	stage2	25.1701036*	5.22E+00	0.001
1.62E+10	normal	stage2	26.3649852*	5.50E+00	0.001
1.64E+10	stage1	stage2	25.1527821*	4.98E+00	0
1.64E+10	normal	stage2	25.4542938*	5.24E+00	0.001
1.66E+10	stage1	stage2	24.9283607*	4.66E+00	0
1.66E+10	stage2	stage3	-13.9675657*	4.91E+00	0.047
1.66E+10	normal	stage2	24.7342090*	4.91E+00	0
1.68E+10	stage1	stage2	24.8596726*	4.62E+00	0
1.68E+10	stage2	stage3	-13.9280510*	4.87E+00	0.045
1.68E+10		normal	-24.4902943*	4.87E+00	0
1.68E+10	normal	stage2	24.4902943*	4.87E+00	0
1.7E+10	stage1	stage2	24.7955774*	4.50E+00	0
1.7E+10	stage2	stage3	-13.5147124*	4.74E+00	0.046
1.7E+10	normal	stage2	22.5692224*	4.74E+00	0.001
1.72E+10	stage1	stage2	24.4946667*	4.37E+00	0
1.72E+10	stage2	stage3	-14.0476900*	4.60E+00	0.031
1.72E+10	normal	stage2	22.1277067*	4.60E+00	0.001
1.74E+10	stage1	stage2	24.5846857*	4.40E+00	0
1.74E+10	stage2	stage3	-14.2477257*	4.63E+00	0.029
1.74E+10	normal	stage2	21.6142424*	4.63E+00	0.001
1.76E+10	stage1	stage2	24.5962631*	4.33E+00	0
1.76E+10	stage2	stage3	-14.6008748*	4.56E+00	0.022
1.76E+10	normal	stage2	21.2087281*	4.56E+00	0.001
1.78E+10	stage1	stage2	24.4549179*	4.28E+00	0
1.78E+10	stage2	stage3	-15.7182829*	4.50E+00	0.012
1.78E+10	normal	stage2	22.1828729*	4.50E+00	0
1.8E+10	stage1	stage2	24.7210571*	4.31E+00	0
1.8E+10	stage2	stage3	-15.9299438*	4.53E+00	0.011
1.8E+10	normal	stage2	23.3532505*	4.53E+00	0
1.82E+10	stage1	stage2	24.4743000*	4.25E+00	0
1.82E+10	stage2	stage3	-16.1509400*	4.47E+00	0.009
1.82E+10	normal	stage2	23.7892400*	4.47E+00	0
1.84E+10	stage1	stage2	24.7073881*	4.51E+00	0
1.84E+10	stage2	stage3	-17.0441214*	4.75E+00	0.01
1.84E+10	normal	stage2	26.7999814*	4.75E+00	0
1.86E+10	stage1	stage2	24.8058667*	4.68E+00	0
1.86E+10	stage2	stage3	-16.7183600*	4.92E+00	0.015
1.86E+10	normal	stage2	27.9101000*	4.92E+00	0
1.88E+10	stage1	stage2	24.4712726*	4.58E+00	0
1.88E+10	stage2	stage3	-16.6229243*	4.82E+00	0.013
1.88E+10	normal	stage2	27.5279976*	4.82E+00	0

1.9E+10	stage1	stage2	24.4081833*	4.72E+00	0
1.9E+10	stage2	stage3	-17.0986200*	4.97E+00	0.013
1.9E+10	normal	stage2	28.8956267*	4.97E+00	0
1.92E+10	stage1	stage2	24.3628619*	4.62E+00	0
1.92E+10	stage2	stage3	-16.4869152*	4.87E+00	0.015
1.92E+10	normal	stage2	27.2573652*	4.87E+00	0
1.94E+10	stage1	stage2	24.2082321*	4.67E+00	0
1.94E+10	stage2	stage3	-16.4526671*	4.92E+00	0.016
1.94E+10	normal	stage2	26.6497205*	4.92E+00	0
1.96E+10	stage1	stage2	24.1298917*	4.45E+00	0
1.96E+10	stage2	stage3	-16.9228700*	4.69E+00	0.009
1.96E+10	normal	stage2	25.5763567*	4.69E+00	0
1.98E+10	stage1	stage2	24.0925690*	4.47E+00	0
1.98E+10	stage2	stage3	-16.1847490*	4.70E+00	0.013
1.98E+10	normal	stage2	24.2673490*	4.70E+00	0
2E+10	stage1	stage2	24.0039048*	4.31E+00	0
2E+10	stage2	stage3	-16.4352781*	4.54E+00	0.009
2E+10	normal	stage2	23.3034548*	4.54E+00	0

App. 3: Summary of the SPSS output for the loss tangent of urine where a significant difference was found across the groups.

Dependent Variable	(I) VAR00001	(J) VAR00001	Mean Difference (I-J)	Std. Error	Sig.
4.1E+08	normal	stage1	71.0725533*	1.84E+01	0.005
4.1E+08	normal	stage2	83.0599724*	1.78E+01	0.001
4.1E+08	normal	stage3	112.8751433*	1.92E+01	0
6.1E+08	normal	stage1	46.5256767*	1.23E+01	0.006
6.1E+08	normal	stage2	55.0067552*	1.19E+01	0.001
6.1E+08	normal	stage3	75.0154767*	1.28E+01	0
8.1E+08	normal	stage1	35.5310567*	9.32E+00	0.006
8.1E+08	normal	stage2	41.9287019*	9.01E+00	0.001
8.1E+08	normal	stage3	57.0962000*	9.74E+00	0
1.01E+09	normal	stage1	28.0866967*	7.47E+00	0.007
1.01E+09	normal	stage2	33.6177514*	7.22E+00	0.001
1.01E+09	normal	stage3	46.2474167*	7.80E+00	0
1.21E+09	stage1	stage3	15.7309267*	5.19E+00	0.032
1.21E+09	normal	stage1	24.1332433*	5.19E+00	0.001
1.21E+09	normal	stage2	31.9124267*	5.02E+00	0
1.21E+09	normal	stage3	39.8641700*	5.42E+00	0
1.41E+09	stage1	stage3	13.5771467*	4.54E+00	0.035
1.41E+09	normal	stage1	21.0078000*	4.54E+00	0.001
1.41E+09	normal	stage2	28.3607143*	4.39E+00	0
1.41E+09	normal	stage3	34.5849467*	4.75E+00	0
1.61E+09	stage1	stage3	12.3101683*	4.11E+00	0.034
1.61E+09	normal	stage1	18.7316783*	4.11E+00	0.001
1.61E+09	normal	stage2	25.2261248*	3.97E+00	0
1.61E+09	normal	stage3	31.0418467*	4.29E+00	0
1.81E+09	stage1	stage3	11.4317500*	3.71E+00	0.029
1.81E+09	normal	stage1	17.2801200*	3.71E+00	0.001
1.81E+09	normal	stage2	23.5674652*	3.59E+00	0
1.81E+09	normal	stage3	28.7118700*	3.88E+00	0
2.01E+09	stage1	stage3	9.9906083*	3.33E+00	0.034
2.01E+09	normal	stage1	15.5209117*	3.33E+00	0.001
2.01E+09	normal	stage2	21.4866438*	3.22E+00	0
2.01E+09	normal	stage3	25.5115200*	3.47E+00	0
2.21E+09	stage1	stage3	9.1622150*	3.02E+00	0.032
2.21E+09	normal	stage1	14.7704350*	3.02E+00	0.001
2.21E+09	normal	stage2	20.3951957*	2.92E+00	0
2.21E+09	normal	stage3	23.9326500*	3.16E+00	0
2.41E+09	stage1	stage3	8.7723450*	2.85E+00	0.029
2.41E+09	normal	stage1	13.7032083*	2.85E+00	0.001
2.41E+09	normal	stage2	19.2986857*	2.75E+00	0
2.41E+09	normal	stage3	22.4755533*	2.97E+00	0
2.61E+09	stage1	stage3	7.8593483*	2.65E+00	0.036
2.61E+09	normal	stage1	12.5855050*	2.65E+00	0.001
2.61E+09	normal	stage2	18.1037252*	2.56E+00	0

2.61E+09	normal	stage3	20.4448533*	2.77E+00	0
2.81E+09	stage1	stage3	7.2159433*	2.50E+00	0.043
2.81E+09	normal	stage1	12.1166567*	2.50E+00	0.001
2.81E+09	normal	stage2	17.6379852*	2.41E+00	0
2.81E+09	normal	stage3	19.3326000*	2.61E+00	0
3.01E+09	stage1	stage3	6.7517850*	2.40E+00	0.05
3.01E+09	normal	stage1	11.2531783*	2.40E+00	0.001
3.01E+09	normal	stage2	16.7130581*	2.32E+00	0
3.01E+09	normal	stage3	18.0049633*	2.51E+00	0
3.21E+09	normal	stage1	10.8514850*	2.33E+00	0.001
3.21E+09	normal	stage2	16.3032576*	2.26E+00	0
3.21E+09	normal	stage3	17.1830000*	2.44E+00	0
3.41E+09	normal	stage1	10.4423017*	2.24E+00	0.001
3.41E+09	normal	stage2	15.8986529*	2.16E+00	0
3.41E+09	normal	stage3	16.3297533*	2.34E+00	0
3.61E+09	stage1	stage2	5.5279310*	1.90E+00	0.041
3.61E+09	normal	stage1	9.6241000*	2.06E+00	0.001
3.61E+09	normal	stage2	15.1520310*	2.00E+00	0
3.61E+09	normal	stage3	15.2604000*	2.16E+00	0
3.81E+09	stage1	stage2	5.7154048*	1.85E+00	0.028
3.81E+09	normal	stage1	9.1345633*	2.01E+00	0.001
3.81E+09	normal	stage2	14.8499681*	1.95E+00	0
3.81E+09	normal	stage3	14.6371533*	2.10E+00	0
4.01E+09	stage1	stage2	5.8940190*	1.74E+00	0.015
4.01E+09	normal	stage1	8.4153367*	1.90E+00	0.001
4.01E+09	normal	stage2	14.3093557*	1.84E+00	0
4.01E+09	normal	stage3	13.9732200*	1.98E+00	0
4.21E+09	stage1	stage2	6.0788643*	1.67E+00	0.009
4.21E+09	normal	stage1	7.6666033*	1.82E+00	0.002
4.21E+09	normal	stage2	13.7454676*	1.76E+00	0
4.21E+09	normal	stage3	13.2850567*	1.90E+00	0
4.41E+09	stage1	stage2	6.4167036*	1.70E+00	0.006
4.41E+09	normal	stage1	7.3657417*	1.84E+00	0.004
4.41E+09	normal	stage2	13.7824452*	1.78E+00	0
4.41E+09	normal	stage3	13.1868700*	1.93E+00	0
4.61E+09	stage1	stage2	6.4947226*	1.60E+00	0.003
4.61E+09	normal	stage1	6.8270783*	1.74E+00	0.005
4.61E+09	normal	stage2	13.3218010*	1.68E+00	0
4.61E+09	normal	stage3	12.6841567*	1.82E+00	0
4.81E+09	stage1	stage2	6.7596810*	1.62E+00	0.003
4.81E+09	normal	stage1	6.5205567*	1.76E+00	0.008
4.81E+09	normal	stage2	13.2802376*	1.70E+00	0
4.81E+09	normal	stage3	12.4800133*	1.84E+00	0
5.01E+09	stage1	stage2	7.0344952*	1.70E+00	0.003
5.01E+09	normal	stage1	6.5584200*	1.85E+00	0.011
5.01E+09	normal	stage2	13.5929152*	1.79E+00	0

5.01E+09	normal	stage3	12.6244833*	1.93E+00	0
5.21E+09	stage1	stage2	7.2517821*	1.67E+00	0.002
5.21E+09	normal	stage1	5.9772883*	1.82E+00	0.019
5.21E+09	normal	stage2	13.2290705*	1.76E+00	0
5.21E+09	normal	stage3	12.0360633*	1.90E+00	0
5.41E+09	stage1	stage2	7.6126512*	1.83E+00	0.003
5.41E+09	normal	stage1	6.0298450*	2.00E+00	0.033
5.41E+09	normal	stage2	13.6424962*	1.93E+00	0
5.41E+09	normal	stage3	12.1075133*	2.08E+00	0
5.61E+09	stage1	stage2	7.8247190*	1.91E+00	0.003
5.61E+09	normal	stage1	6.1170033*	2.08E+00	0.039
5.61E+09	normal	stage2	13.9417224*	2.01E+00	0
5.61E+09	normal	stage3	12.0192933*	2.17E+00	0
5.81E+09	stage1	stage2	8.0024012*	1.88E+00	0.002
5.81E+09	normal	stage2	13.4976395*	1.98E+00	0
5.81E+09	normal	stage3	11.1872567*	2.14E+00	0
6.01E+09	stage1	stage2	8.4527536*	2.17E+00	0.005
6.01E+09	normal	stage2	14.3505119*	2.28E+00	0
6.01E+09	normal	stage3	11.6018367*	2.46E+00	0.001
6.21E+09	stage1	stage2	8.7034476*	2.10E+00	0.003
6.21E+09	normal	stage2	14.0568176*	2.21E+00	0
6.21E+09	normal	stage3	11.1048467*	2.39E+00	0.001
6.41E+09	stage1	stage2	9.0919452*	2.14E+00	0.002
6.41E+09	normal	stage2	13.8990186*	2.26E+00	0
6.41E+09	normal	stage3	10.6690267*	2.44E+00	0.002
6.61E+09	stage1	stage2	9.5509048*	2.37E+00	0.004
6.61E+09	normal	stage2	14.8141548*	2.49E+00	0
6.61E+09	normal	stage3	11.2472700*	2.69E+00	0.003
6.81E+09	stage1	stage2	9.7693202*	2.19E+00	0.001
6.81E+09	normal	stage2	14.0327586*	2.30E+00	0
6.81E+09	normal	stage3	9.9814567*	2.48E+00	0.004
7.01E+09	stage1	stage2	10.2124310*	2.31E+00	0.002
7.01E+09	normal	stage2	14.3969943*	2.43E+00	0
7.01E+09	normal	stage3	9.6901767*	2.62E+00	0.008
7.21E+09	stage1	stage2	10.5539655*	2.38E+00	0.001
7.21E+09	normal	stage2	15.0570171*	2.50E+00	0
7.21E+09	normal	stage3	10.2146667*	2.70E+00	0.006
7.41E+09	stage1	stage2	10.7689726*	2.24E+00	0.001
7.41E+09	normal	stage2	14.0976210*	2.35E+00	0
7.41E+09	normal	stage3	9.1665267*	2.54E+00	0.009
7.61E+09	stage1	stage2	11.1814440*	2.38E+00	0.001
7.61E+09	normal	stage2	15.1163390*	2.50E+00	0
7.61E+09	normal	stage3	10.1648867*	2.70E+00	0.007
7.81E+09	stage1	stage2	11.4253762*	2.41E+00	0.001
7.81E+09	normal	stage2	15.3698462*	2.53E+00	0
7.81E+09	normal	stage3	10.4568600*	2.74E+00	0.006

8.01E+09	stage1	stage2	11.6851429*	2.36E+00	0
8.01E+09	normal	stage2	14.5352329*	2.48E+00	0
8.01E+09	normal	stage3	9.4908667*	2.68E+00	0.011
8.21E+09	stage1	stage2	12.0828988*	2.55E+00	0.001
8.21E+09	normal	stage2	16.0497538*	2.68E+00	0
8.21E+09	normal	stage3	10.7677700*	2.90E+00	0.007
8.41E+09	stage1	stage2	12.2982310*	2.58E+00	0.001
8.41E+09	normal	stage2	15.7474610*	2.71E+00	0
8.41E+09	normal	stage3	10.2742800*	2.93E+00	0.012
8.61E+09	stage1	stage2	12.6298845*	2.58E+00	0.001
8.61E+09	normal	stage2	15.3049062*	2.72E+00	0
8.61E+09	normal	stage3	9.3504900*	2.94E+00	0.023
8.81E+09	stage1	stage2	13.0155857*	2.81E+00	0.001
8.81E+09	normal	stage2	16.8194724*	2.95E+00	0
8.81E+09	normal	stage3	10.4008267*	3.19E+00	0.02
9.01E+09	stage1	stage2	13.4082024*	2.95E+00	0.001
9.01E+09	normal	stage2	16.3540824*	3.11E+00	0
9.01E+09	normal	stage3	9.4634367*	3.36E+00	0.049
9.21E+09	stage1	stage2	13.6597060*	2.91E+00	0.001
9.21E+09	normal	stage2	16.0586510*	3.06E+00	0
9.41E+09	stage1	stage2	14.1356333*	3.17E+00	0.001
9.41E+09	normal	stage2	17.3115900*	3.34E+00	0
9.61E+09	stage1	stage2	14.4996810*	3.37E+00	0.002
9.61E+09	normal	stage2	17.0488343*	3.55E+00	0.001
9.81E+09	stage1	stage2	14.7824250*	3.15E+00	0.001
9.81E+09	normal	stage2	16.3214600*	3.32E+00	0.001
1E+10	stage1	stage2	15.3528548*	3.49E+00	0.002
1E+10	normal	stage2	17.7771681*	3.68E+00	0.001
1.02E+10	stage1	stage2	15.4902940*	3.41E+00	0.001
1.02E+10	normal	stage2	17.1539257*	3.58E+00	0.001
1.04E+10	stage1	stage2	15.8672655*	3.24E+00	0.001
1.04E+10	normal	stage2	16.4894771*	3.41E+00	0.001
1.06E+10	stage1	stage2	16.4167679*	3.55E+00	0.001
1.06E+10	normal	stage2	18.0757795*	3.73E+00	0.001
1.08E+10	stage1	stage2	16.3846548*	3.30E+00	0
1.08E+10	normal	stage2	16.7265681*	3.48E+00	0.001
1.1E+10	stage1	stage2	16.9759345*	3.42E+00	0
1.1E+10	normal	stage2	16.7772995*	3.60E+00	0.001
1.12E+10	stage1	stage2	17.4682429*	3.62E+00	0.001
1.12E+10	normal	stage2	17.9786395*	3.81E+00	0.001
1.14E+10	stage1	stage2	17.5242369*	3.49E+00	0
1.14E+10	normal	stage2	16.4439486*	3.67E+00	0.001
1.16E+10	stage1	stage2	18.3743821*	3.83E+00	0.001
1.16E+10	normal	stage2	17.4123405*	4.03E+00	0.002
1.18E+10	stage1	stage2	18.7390262*	3.97E+00	0.001
1.18E+10	normal	stage2	18.1179429*	4.18E+00	0.002

1.2E+10	stage1	stage2	18.9626536*	3.94E+00	0.001
1.2E+10	normal	stage2	17.0386586*	4.14E+00	0.003
1.22E+10	stage1	stage2	19.9762560*	4.49E+00	0.001
1.22E+10	normal	stage2	18.9106343*	4.73E+00	0.004
1.24E+10	stage1	stage2	19.9807952*	4.50E+00	0.001
1.24E+10	normal	stage2	19.1035586*	4.74E+00	0.004
1.26E+10	stage1	stage2	20.4852988*	4.59E+00	0.001
1.26E+10	normal	stage2	18.9918005*	4.83E+00	0.005
1.28E+10	stage1	stage2	20.9248238*	5.04E+00	0.003
1.28E+10	normal	stage2	21.1983805*	5.30E+00	0.004
1.3E+10	stage1	stage2	21.0226190*	4.78E+00	0.002
1.3E+10	normal	stage2	20.5925024*	5.03E+00	0.003
1.32E+10	stage1	stage2	21.1632583*	4.72E+00	0.001
1.32E+10	normal	stage2	20.8462133*	4.97E+00	0.003
1.34E+10	stage1	stage2	21.2311405*	4.72E+00	0.001
1.34E+10	normal	stage2	22.1243871*	4.97E+00	0.001
1.36E+10	stage1	stage2	21.3484798*	4.47E+00	0.001
1.36E+10	normal	stage2	20.8592948*	4.70E+00	0.001
1.38E+10	stage1	stage2	21.2462524*	4.34E+00	0.001
1.38E+10	normal	stage2	21.2480224*	4.57E+00	0.001
1.4E+10	stage1	stage2	21.3347881*	4.29E+00	0
1.4E+10	normal	stage2	21.4869348*	4.51E+00	0.001
1.42E+10	stage1	stage2	21.4672357*	4.19E+00	0
1.42E+10	normal	stage2	20.1265024*	4.41E+00	0.001
1.44E+10	stage1	stage2	21.5853250*	4.19E+00	0
1.44E+10	stage2	stage3	-12.5049100*	4.41E+00	0.048
1.44E+10	normal	stage2	20.7851633*	4.41E+00	0.001
1.46E+10	stage1	stage2	21.9754988*	4.24E+00	0
1.46E+10	stage2	stage1	-21.9754988*	4.24E+00	0
1.46E+10	stage2	stage3	-12.5831205*	4.46E+00	0.049
1.46E+10	stage3	stage1	-9.3923783	4.61E+00	0.21
1.46E+10	normal	stage2	20.2988538*	4.46E+00	0.001
1.48E+10	stage1	stage2	22.3764083*	4.31E+00	0
1.48E+10	stage2	stage1	-22.3764083*	4.31E+00	0
1.48E+10	stage2	stage3	-12.9620767*	4.54E+00	0.046
1.48E+10	stage3	stage1	-9.4143317	4.69E+00	0.221
1.48E+10	normal	stage2	19.7357567*	4.54E+00	0.002
1.5E+10	stage1	stage2	22.6898619*	4.53E+00	0
1.5E+10	stage2	stage1	-22.6898619*	4.53E+00	0
1.5E+10	stage2	stage3	-13.5228119*	4.77E+00	0.048
1.5E+10	normal	stage2	20.9974186*	4.77E+00	0.002
1.52E+10	stage1	stage2	23.3953940*	4.81E+00	0.001
1.52E+10	normal	stage2	21.3005157*	5.06E+00	0.002
1.54E+10	stage1	stage2	23.9407321*	5.00E+00	0.001
1.54E+10	normal	stage2	22.1118371*	5.26E+00	0.002
1.56E+10	stage1	stage2	24.4586524*	5.40E+00	0.001

1.56E+10	normal	stage2	24.4776724*	5.68E+00	0.002
1.58E+10	stage1	stage2	24.7610393*	5.45E+00	0.001
1.58E+10	normal	stage2	24.8077443*	5.74E+00	0.002
1.6E+10	stage1	stage2	25.1299702*	5.27E+00	0.001
1.6E+10	normal	stage2	25.4543486*	5.55E+00	0.001
1.62E+10	stage1	stage2	25.1701036*	5.22E+00	0.001
1.62E+10	normal	stage2	26.3649852*	5.50E+00	0.001
1.64E+10	stage1	stage2	25.1527821*	4.98E+00	0
1.64E+10	normal	stage2	25.4542938*	5.24E+00	0.001
1.66E+10	stage1	stage2	24.9283607*	4.66E+00	0
1.66E+10	stage2	stage3	-13.9675657*	4.91E+00	0.047
1.66E+10	normal	stage2	24.7342090*	4.91E+00	0
1.68E+10	stage1	stage2	24.8596726*	4.62E+00	0
1.68E+10	stage2	stage3	-13.9280510*	4.87E+00	0.045
1.68E+10	normal	stage2	24.4902943*	4.87E+00	0
1.7E+10	stage1	stage2	24.7955774*	4.50E+00	0
1.7E+10	stage2	stage3	-13.5147124*	4.74E+00	0.046
1.7E+10	normal	stage2	22.5692224*	4.74E+00	0.001
1.72E+10	stage1	stage2	24.4946667*	4.37E+00	0
1.72E+10	stage2	stage3	-14.0476900*	4.60E+00	0.031
1.72E+10	normal	stage2	22.1277067*	4.60E+00	0.001
1.74E+10	stage1	stage2	24.5846857*	4.40E+00	0
1.74E+10	stage2	stage3	-14.2477257*	4.63E+00	0.029
1.74E+10	normal	stage2	21.6142424*	4.63E+00	0.001
1.76E+10	stage1	stage2	24.5962631*	4.33E+00	0
1.76E+10	stage2	stage3	-14.6008748*	4.56E+00	0.022
1.76E+10	normal	stage2	21.2087281*	4.56E+00	0.001
1.78E+10	stage1	stage2	24.4549179*	4.28E+00	0
1.78E+10	stage2	stage3	-15.7182829*	4.50E+00	0.012
1.78E+10	normal	stage2	22.1828729*	4.50E+00	0
1.8E+10	stage1	stage2	24.7210571*	4.31E+00	0
1.8E+10	stage2	stage3	-15.9299438*	4.53E+00	0.011
1.8E+10	normal	stage2	23.3532505*	4.53E+00	0
1.82E+10	stage1	stage2	24.4743000*	4.25E+00	0
1.82E+10	stage2	stage3	-16.1509400*	4.47E+00	0.009
1.82E+10	normal	stage2	23.7892400*	4.47E+00	0
1.84E+10	stage1	stage2	24.7073881*	4.51E+00	0
1.84E+10	stage2	stage3	-17.0441214*	4.75E+00	0.01
1.84E+10	normal	stage2	26.7999814*	4.75E+00	0
1.86E+10	stage1	stage2	24.8058667*	4.68E+00	0
1.86E+10	stage2	stage3	-16.7183600*	4.92E+00	0.015
1.86E+10	normal	stage2	27.9101000*	4.92E+00	0
1.88E+10	stage1	stage2	24.4712726*	4.58E+00	0
1.88E+10	stage2	stage3	-16.6229243*	4.82E+00	0.013
1.88E+10	normal	stage2	27.5279976*	4.82E+00	0
1.9E+10	stage1	stage2	24.4081833*	4.72E+00	0

1.9E+10	stage2	stage3	-17.0986200*	4.97E+00	0.013
1.9E+10	normal	stage2	28.8956267*	4.97E+00	0
1.92E+10	stage1	stage2	24.3628619*	4.62E+00	0
1.92E+10	stage2	stage3	-16.4869152*	4.87E+00	0.015
1.92E+10	normal	stage2	27.2573652*	4.87E+00	0
1.94E+10	stage1	stage2	24.2082321*	4.67E+00	0
1.94E+10	stage2	stage3	-16.4526671*	4.92E+00	0.016
1.94E+10	normal	stage2	26.6497205*	4.92E+00	0
1.96E+10	stage1	stage2	24.1298917*	4.45E+00	0
1.96E+10	stage2	stage3	-16.9228700*	4.69E+00	0.009
1.96E+10	normal	stage2	25.5763567*	4.69E+00	0
1.98E+10	stage1	stage2	24.0925690*	4.47E+00	0
1.98E+10	stage2	stage3	-16.1847490*	4.70E+00	0.013
1.98E+10	normal	stage2	24.2673490*	4.70E+00	0
2E+10	stage1	stage2	24.0039048*	4.31E+00	0
2E+10	stage2	stage3	-16.4352781*	4.54E+00	0.009
2E+10	normal	stage2	23.3034548*	4.54E+00	0