BREAST CANCER, MEDICAL IMAGING, AND CANCER GENETICS

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A new genetic concept regarding the causes and prevention strategies of cancer is presented

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Abstract

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Keywords: Breast cancer; Medical imaging; Mammography; CT; Ultrasound; MRI; Genetics; Y-DNA haplogroups

Breast cancer is the most common cancer type in the United Kingdom. Many women with breast cancer do not show any noticeable symptoms in their early stages, hence regular breast screening is important. In this research focus is on medical imaging and its role in breast cancer screening, diagnosis, and treatment monitoring. Around 10% of all cancers are caused by inherited gene mutations which may cause cancer to run in families. Though, majority of cancer cases (up to 90%) are caused by acquired gene mutations which may also appear to run in families when family members share a particular environment or exposure. Genetic testing is conducted in this research on a number of participants to investigate the cancer cases found among their families. The findings of this research show that significant improvements have taken place in the emergence of hybrid imaging modalities used for breast imaging, through the fusion of different imaging techniques. The findings also provide evidence that similar to cancers caused by inherited gene mutations, cancers caused by non-inherited gene mutations may also appear to run in families when family members share certain environments and exposures or lifestyle behaviours. As a result, a new genetic concept of cancer essential to understand and control the disease is presented in this work which links between the human population origins and migrations, environmental factors and gene mutations, and the development of cancer. Furthermore, a number of cancer prevention strategies are recommended in this study to prevent people from getting the disease.

Acknowledgements

In the name of Allah, the Beneficent, the Merciful

All praise is due to Allah. Prayers and peace be upon our Prophet, Mohammed, his family and companions. This is by the grace of Allah, and everything I have is out of His mercy alone. Thereafter, I would like to express my sincere gratitude to my research supervisor, Dr Mansour Youseffi, for all his advice and immense knowledge that allowed this work. I could not have imagined a better supervisor and mentor for my research.

And certainly, did We create man from an extract of clay. Then We placed him as a sperm-drop in a firm lodging. Then We made the sperm-drop into a clinging clot, and We made the clot into a lump [of flesh], and We made [from] the lump, bones, and We covered the bones with flesh; then We developed him into another creation. So blessed is Allah, the best of creators. Then indeed, after that you are to die. Then indeed you, on the Day of Resurrection, will be resurrected.

The Noble Quran: 23:12-16

O mankind, indeed, We have created you from male and female and made you peoples and tribes that you may know one another. Indeed, the most noble of you in the sight of Allah is the most righteous of you. Indeed, Allah is Knowing and Acquainted.

The Noble Quran: 49:13

Dedication

To my late parents, Hameed Rasheed, and Sophia Kareem, who taught me to read and write when I was a child before starting school and instilled in me values and the first lessons of knowledge and wisdom. *‘’And say: My Lord, have mercy upon them as they raised me up when I was little’’.*

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AIs- aromatase inhibitors

AKF- acute kidney failure

ALND- axillary lymph node dissection

AI- artificial intelligence

ATM- ataxia telangiectasia mutated

BARD1- brca1 associated ring domain 1

BCS- breast-conserving surgery

BI-RADS- breast imaging reporting and database systems

BRCA1- breast cancer gene 1

BRCA2- breast cancer gene 2

BRIP1- brca1 interacting protein c-terminal helicase 1

BSE- breast self-examination

BSP- breast screening programme

C+- contrast-enhanced

CAD- computer-aided detection

CAT- computerised axial tomography

CBE- clinical breast examination

CBs- cannabinoids

CC- craniocaudal

CDH1- cadherin-1

CHEK2- checkpoint kinase 2

CIS- carcinoma in situ

COSS-96- cooperative osteosarcoma study group 96

CS- chondrosarcoma

CXR- chest x-ray

DBT- digital breast tomosynthesis

DCIS- ductal carcinoma in situ

DD- dose-dense

DIBH- deep inspiration breath hold

DNA- deoxyribonucleic acid

EAC- external auditory canal

ER+- oestrogen receptor-positive

FatSat- fat-saturated

FDA- food and drug administration

FDG- fluorodeoxyglucose

FFDM- full-field digital mammography

FSE- fast spin echo

FTDNA- family tree dna

GP- general practitioner

G3- grade 3

HER2- human epidermal growth factor receptor 2

HRT- hormone replacement therapy

IBC- inflammatory breast cancer

ICB- immune checkpoint blockade

IDC- invasive ductal carcinoma

ILC- invasive lobular carcinoma

KSA- kingdom of saudi arabia

LCIS- lobular carcinoma in situ

MBI- molecular breast imaging

MDT- multidisciplinary team

ME- middle ear

MLO- mediolateral oblique

MpBC- metaplastic breast cancer

MRCA- most recent common ancestor

MRE11A- meiotic recombination 11 homolog a

NAC- neoadjuvant chemotherapy

NBN- nibrin

NHS- national health services

NIHR- national institute for health research

NSC- national screening committee

PA- posteroanterior

PALB2- partner and localiser of brca2

pH- power of hydrogen

PMS2- mismatch repair endonuclease

PPB- pleuropulmonary blastoma

PTEN- phosphatase and tensin homolog

QOL- quality of life

RT- radiation therapy

SCC- squamous cell carcinoma

SERMs- selective oestrogen receptor modulators

SFOV- scan field of view

SLNB- sentinel lymph node biopsy

SNP- single nucleotide polymorphism

STK11- serine/threonine kinase 11

STR- short tandem repeat

T1W- t1-weighted

TNBC- triple-negative breast cancer

TNM- tumour node metastasis

TP53- tumour protein 53

TSE- turbo spin echo

ZW- zamzam water

CHAPTER 1

INTRODUCTION

1.1 Background

According to the National Health Service (NHS), breast cancer is the most common type of cancer in the UK affecting mainly women aged 50 and above, however it may affect younger women [1]. Breast cancer is related to the uncontrolled growth of the breast cells and usually the disease is identified with the red appearance and swelling of the breast. However, many breast cancer patients do not have any noticeable symptoms in the early stages of the disease. The common causes of breast cancer are due to gene mutations responsible for the normal healthy growth of the breast cells. For the breasts to function healthy, the old and damaged cells are continuously replaced by healthy cells, however any changes in this process due to gene mutations, it may eventually lead to the out-of-control growth of the breast cells, which may lead to the formation of tumours. Gene mutations can be inherited (hereditary) or acquired (non-hereditary). Inherited gene mutations can be passed on from generation to generation, and a gene mutation that is linked to cancer may cause cancer to run in families. Only 5–10% of all cancers are thought to be hereditary [2] [3]. Women from families with a history of breast cancer are at a higher risk of developing the disease. The common hereditary breast cancers are linked to mutations in breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) [4]. BRCA1 and BRCA2 genes' function is to repair any breast cell damage and to keep the normal growth of the breasts. These mutated genes can be passed from parents (including relatives from both sides) to children. Whereas acquired gene mutations occur sometime during the lifetime of a person and can be caused by environmental factors or certain lifestyles. About 90–95% of all cancer cases are caused by acquired gene mutations and they tend to occur later in life compared to similar inherited cancer types [2] [3]. However, non-inherited genetic cancers may also appear to run in families when they have a shared environment or lifestyle behaviours [5] [6]. The stages of breast cancer are the number 0 and the Roman numerals I, II, III, and IV. Stage 0 describes non-invasive breast cancer, which means cancer has not completely developed or spread into the surrounding areas of the breast, while stage IV is invasive, i.e., cancer has extended to other parts of the body [7]. Medical imaging tests such as

mammography, in combination with clinical breast examination (CBE) and breast self-examination (BSE), contribute to the early detection of breast cancer before any symptoms appear in women who look healthy and are not suspected of having breast cancer. However, if any areas of concern on mammography are detected, breast ultrasound imaging (USI), breast magnetic resonance imaging (MRI), in addition to newer breast imaging tests such as molecular breast imaging (MBI) are recommended. A biopsy i.e., a sample of breast cells is taken from the patient and evaluated, is usually performed if a breast abnormality showed up, to determine whether or not breast cancer is present and also to find out if the disease has spread outside the breast (metastasis). Accurate breast cancer diagnosis, and staging i.e., the degree of tumour spread, are used to guide treatment options and decisions for which several different imaging modalities are commonly used such as chest X-rays (CXR), computed tomography (CT) scan, bone scans, positron emission tomography (PET) scans or MRI scans. PET scan is often combined with CT scan which is known as a PET/CT scan, to produce more detailed images and provide more accurate diagnoses [8]. There are various treatment choices available for treating breast cancer, all depend on the type and stage of each case. The list of the main breast cancer treatments available include, radiotherapy (RT), surgery, hormone replacement therapy (HRT), chemotherapy and biological therapy (targeted therapy). Radiotherapy and surgical treatments are local treatments, i.e., the breast tumour is treated with no damage to other parts of the body. On the other hand, HRT, chemotherapy, and targeted therapy, are systematic therapies, i.e., the drugs that are used to treat breast cancer can reach all the parts of the body. Breast cancer patients often have one or a combination of these treatments depending on diagnosis and staging. The more the cancer has spread, the more treatment will likely be needed. A multidisciplinary team (MDT) which is a team of healthcare professionals and specialists who work together, is usually appointed to provide the best patient care and treatment [9]. Mammography, ultrasound, PET scan, CT scan as well as breast MRI, play a vital role in breast cancer treatment response monitoring. Furthermore, monitoring tests are also used to check for any recurrence signs in women who have had treatment for breast cancer. This study has focused on the following medical imaging modalities; X-ray, CT scan,

mammography, ultrasound imaging, MRI, radionuclide imaging, PET scan, PET scan combined with CT scan, PET scan combined with MRI, single-photon emission computed tomography (SPECT), and SPECT scan combined with CT scan. The main aim of this work is to present the role of the different medical imaging techniques used for breast cancer screening, diagnosis, and treatment in breast cancer patients, also, to identify the role of these modalities in the early detection of breast cancer recurrence in breast cancer survivors. Genetic testing is also conducted in this research to present a new genetic concept regarding the causes of breast cancer and other types of cancer, and it works as a prevention strategy to avoid people from getting cancer. The new genetic concept focuses on studying several types of cancers that look to run in families that are not caused by inherited gene mutations. Therefore, the new concept of cancer is based on the analysis of the test results of genetic samples obtained from several participants in this research who are members of healthy families and families with a long history of different types of cancer including breast cancer. The new genetic concept of cancer links between the human population origins and migrations, environmental factors and gene mutations, and the development of cancer, for which the human Y-Chromosome DNA tests are used to examine Y-Chromosome DNA short tandem repeat (STR) markers on the Y-Chromosome, in addition to the human Y-Chromosome DNA single nucleotide polymorphism (SNP) test to determine each participant's Y-Chromosome DNA haplogroup and investigate their geographic origin and ancient ancestry. There are 20 major human Y-Chromosome DNA haplogroups, and each haplogroup has a site of origin that has natural physical boundaries. Descendants of each human Y-Chromosome DNA haplogroup share a distinct mutation that shapes their physical features and behavioural adaptations for the geographic region of their haplogroup. All the different human body systems such as the respiratory system, the immune system, the integumentary system, etc., of the descendants of each human Y-Chromosome DNA haplogroup are genetically designed exclusively for their haplogroup's site of origin, to enable them to deal with the different environmental pathogens and climate conditions. Therefore, it is essential for descendants of each human Y-Chromosome DNA haplogroup to stay within the geographical zone of their human Y-Chromosome DNA haplogroup, or in case if

they left their site of origin and migrated to other geographic regions that they do not belong to, to keep the environments around them similar to the environments of their site of origin as that may cause gene mutations that may lead to the development of cancer and other unrelated health conditions. Cancer is recognised as a serious disease, and it can come back (recurrent cancer) after treatment. However, according to the new genetic concept of cancer presented in this work, cancer is a preventable illness and therefore, this research has highlighted the available natural cancer prevention strategies to help prevent people from getting the disease.

1.2 Thesis layout

This thesis is composed of ten chapters. The following chapter, chapter 2, is the research methodology which tends to show the comprehensive research design selected for conducting the systematic review of the topics of breast cancer and medical imaging. The design and approach chosen for the data collection and data analysis are justified in this chapter, including framing the research question for breast cancer and medical imaging systematic review, sources and searching, assessment of studies quality, summarising the evidence, and interpretations of findings.

Chapter 3 is the systematic review of the topic of breast cancer. The chapter presents an extensive review through discussing the anatomy of the breast, the stages of breast cancer, the breast cancer risk factors, in addition to the existing breast cancer prevention strategies and breast cancer control. The chapter also discusses the breast cancer symptoms, the types of breast cancer, the incidence of breast cancer in men, the existing breast cancer treatments, as well as the topic of breast cancer recurrence including the available blood tests used to predict breast cancer recurrence. Furthermore, the chapter discusses the complementary and alternative medicine (CAM) use for breast cancer and other types of cancer for cancer patients across the various parts of the world.

Following the understanding of the elements associated with breast cancer in chapter 3, the subsequent chapter 4 of this thesis is the systematic review of the

topic of medical imaging and the role of the various types of the medical imaging techniques used for the diagnosis, treatment and follow-up of breast cancer. The chapter describes medical imaging and all its associated aspects in detail, and it discusses numerous medical imaging techniques that are known to have an effective role in the overall assessment of breast cancer including X-ray (conventional radiography), computed tomography (CT), mammography, ultrasound imaging (USI), magnetic resonance imaging (MRI), radionuclide imaging (RI), positron emission tomography (PET), as well as single-photon emission computed tomography (SPECT). The chapter further examines the medical science reliance on the use of multiple medical imaging techniques for breast cancer diagnosis, treatment, and follow-up to find out whether one individual medical imaging modality can lead to specific outcomes in all the identified areas.

Chapter 5 is about the clinical observation sessions attended at various medical imaging units of several teaching hospitals in the UK and abroad as part of this PhD work. The chapter explains the purpose of attending the clinical sessions such as gaining an insight into the clinical practice experience, obtaining medical images of various cancer cases, attending genetic counselling clinical observation in addition to genetic testing conducted to identify specific gene mutations that are known to cause breast cancer and related types of cancer found among the families investigated in this study. Likewise, genetic testing conducted to identify the human Y-Chromosome DNA haplogroups to investigate various cancer cases found among families of participants in this research work is also presented in chapter 5. The chapter finishes by discussing some cancer cases obtained from the clinical observation sessions.

Chapter 6 introduces the new genetic concept of cancer presented in this research. The chapter starts by discussing the topics of the human Y-Chromosome DNA, the human Y-Chromosome DNA haplogroups, in addition to the human Y-Chromosome DNA testing types and the geographic origins of the human Y-Chromosome DNA haplogroups. The chapter also discusses the natural physical boundaries and the political boundaries. A new definition of race and ethnicity is presented in chapter 6 which gives the actual race and ethnicity

classification through classifying the world's human populations according to the major human Y-Chromosome DNA haplogroups. Likewise, the chapter discusses the genetic test results of the genetic samples obtained from the participant in this study to support the new genetic concept of cancer, in addition to the genetic test results of the genetic testing for cancer risk genes conducted in this work. The chapter finishes by presenting the new genetic concept of cancer proposed in this work through detailed explanation of how acquired gene mutations lead to the development of cancer. The chapter also discusses the topics of the human X-Chromosome recombination in addition to the topic of the male chimerism in females. The chapter discusses and defends the rational as well as the methodological approaches adopted for this study. Likewise, the chapter suggests in-depth prevention strategies to help prevent people from getting cancer.

In chapter 7 detailed clinical case studies conducted in this work are presented to support the novelty added by the current study. The clinical case studies provide in-depth analyses and discussion of the main topics of breast cancer and other types of cancer, medical imaging, in addition to genetic testing conducted in this research. In this chapter, both primary and secondary data findings are analysed for the successful accomplishment of the research objectives.

Chapter 8 provides detailed discussions on the topics of breast cancer, medical imaging, along with concluding remarks. The chapter provides a summary of the key insights gathered about the role of different medical imaging techniques in breast cancer diagnosis, treatment, and follow-up.

Chapter 9 is about conclusions and discussions regarding the newly proposed concept of cancer which links the development of cancer to the human population origins and migrations, and the environmental factors and gene mutations.

Chapter 10 is the final chapter, which is on recommendations and implications.

CHAPTER 2

METHODOLOGY

2.1 Systematic review

To investigate the commonly recognised medical imaging modalities used for the overall assessment of breast cancer, a comprehensive systematic methodology was conducted. The systematic review methodology was chosen as majority of editors of core clinical journals consider that systematic reviews are original research [10]. Medical investigation requires investigators to exercise a great objectivity in selecting scientific studies to carry out a qualitative systematic review. Failure to consider the reliability and validity of the information and data sources extracted from various sources may lead to misguiding findings. A qualitative approach is therefore used for the current review in order to focus on subjective interpretations of the past studies in relation to breast cancer and the various medical imaging techniques used for breast cancer diagnosis, treatment and follow-up. The significance of qualitative research in the field of healthcare is extensively highlighted in the past studies to gain a detailed and richer picture of the research process. The choice of qualitative research is preferred by medical researchers to adopt a range of procedures and approaches to distinguish what things really matter to patients and healthcare professionals in dealing with illnesses and for obtaining positive health outcomes [11]. Due to the fact that information from multiple contexts is necessary to increase the quality of care for patients, systematic review was therefore conducted to investigate breast cancer and the different medical imaging modalities commonly used for the overall assessment of breast cancer. Systematic review was used as a research method to maintain the consistency between research method and research approach. The systematic research method is defined as the type of literature review that aims to collect and analyse existing findings on a specific topic of investigation. The current study has employed the systematic review method with an aim to identify and evaluate the past findings for subsequently drawing on different experiences and good practices regarding different medical imaging modalities and their role in breast cancer screening, diagnosis, and treatment monitoring. The reason behind selecting systematic review was its benefits in accumulating considerable evidence base to conclude the research findings. However, it can be described that the effectiveness of the systematic review methodology is also

reliant on the stepwise process. The current review work on breast cancer and medical imaging was designed using the five steps highlighted below [12]:

2.1.1 Step 1: Framing the research question for systematic review

The first step was to frame the research question in a structural and explicit way for directing the review work. A structured clinical research question is based on the different components of the clinical processes. In other words, a good question is explicit in targeting all the relevant research components. The qualitative research review was directed in a way to target the characteristics and abilities of the different medical imaging techniques in dealing with breast cancer. The research question used for searching studies for the current investigation on breast cancer and medical imaging was which medical imaging technique would be the best in the early diagnosis, treatment, and follow up of breast cancer in women and consequently reducing the rates of complications and mortality. In this research question, the population is women suffering from breast cancer regardless of their age. The method of investigation is the descriptive analysis and the intervention outlined in the research question is the different medical imaging techniques used for breast cancer, moreover the outcome is the reduction in the rates of complications and mortality.

2.1.2 Step 2: Sources and searching to identify relevant work

To find out data sources and identify relevant work, extensive search was required. Clinical systematic review required focusing on multiple resources (online and printed), due to the focus of the research question on various aspects of different medical imaging techniques used for breast cancer. Library and internet search engines were used for accessing books and a range of journals and open-access sources with extensive information from old to new data acquisition, image reconstruction, and image analysis integrated clinical theories, methods, systems, and applications. Inclusion criteria was set for study selection and search was restricted to studies in English language only. The study did not restrict the review inclusion criteria to reviews of randomised controlled trials, but

it was extended for inclusion of other literature reviews as well. The reason behind that is that the nature of the study was to present various aspects of the medical imaging modalities used for the overall assessment of breast cancer. The review did not focus on only female participants or a specific stage of the disease or the lesion type. Likewise, the investigation did not focus on only studies conducted on patients in the UK, but international findings were also included.

2.1.3 Step 3: Assessment of study quality

Assessment of study quality is very important as it is related to all the aspects of the systematic review and the selection of studies is extremely essential to examine their quality before including them in the systematic review. It is significant to understand that such reviews are highly valuable for decision makers of future research recommendations. Systematic reviews are expected to present a logical sequence of the findings with district comparison and contrast along with the evidence needed. The main aim behind this systematic review was to identify whether there is a medical imaging modality that could be used for breast cancer screening, diagnosis, and treatment monitoring simultaneously. The focus was placed on the early detection of lesions or abnormalities because it is typically easier to detect complications with any medical imaging modality when the disease is in later or advanced stages. Moreover, the quality assessment of the studies was used to determine that the selected review is of high quality.

2.1.4 Step 4: The summary of the evidence

The summary of the evidence was gathered from the review of the abstracts of the past studies to get details about the authors, the titles of the studies, the research methods, the results, as well as the analysis and conclusions. However, summarising the evidence from the past investigations and the evidence from the diverse types of studies was not easy. The differences between the results of the studies were therefore investigated for making the summary of the narrative findings. In general, many studies were found focusing on the detection of breast

cancer however, the substantial proportion was focused on the early detection of breast lesions at the time of screening and diagnosis compared with the detection at the time of treatment monitoring.

2.1.5 Step 5: Interpretation of the findings

Systematic review of the past studies required exercising a great caution at the time of making interpretations, due to the fact that the varying nature of the past studies on the various medical imaging techniques used for the overall assessment of breast cancer needed significant considerations. The summary of the findings was therefore, needed to interpret the results to show the association between breast cancer detection and the effectiveness of the various medical imaging modalities. Likewise, the benefits along with the issues associated with the medical imaging techniques all required to be considered to reach towards an adequate conclusion. However, the efforts in searching many databases provided some sort of safeguarding against missing the important relevant studies. Therefore, the evidence summarised in this systematic review is likely to be as good as it will get in future as the current investigation is addressing the findings to answer the existing and future issues. Data findings gathered through the literature review is designed in the context of the physical and mathematical aspects of the medical image formation, analysis and comparison of the technical performance, and evaluation of the health and safety considerations when using these medical imaging modalities. The medical images produced via the different medical imaging techniques investigated in this systematic review play a very important role in examining the capability of these medical imaging modalities in the adequate visualisation of breast lesions as well as breast tissue abnormalities with competence at various stages of the clinical process. Furthermore, it was essential to determine how the findings need to be considered in relation to investigating the strengths and weaknesses of these medical imaging modalities.

CHAPTER 3

BREAST CANCER

3.1 Systematic review of breast cancer

Similar to the other types of cancer, breast cancer has turned out as one of the major public health problems worldwide. Breast cancer is one of the four major cancer types in addition to lung cancer, prostate cancer and colorectal cancer, which drive global trends in the overall incidences of cancer cases [13]. For gaining the right understanding of breast cancer, it is highly necessary to understand the aetiology of the human breast and its formation. The following image **Fig. 1** shows the anatomy of the human female breast essential to understand the different parts of the breast in addition to their functions. Women's breasts are mostly made up of adipose tissue and glandular tissue. Adipose tissue is simply fat, while glandular tissue is the milk producing tissue. Moreover, milk ducts transmit milk made in the glandular tissue to the nipple [14]. Clinical evidence has suggested that breast cancer can affect any part of the breast, including the ducts and tissue [15].

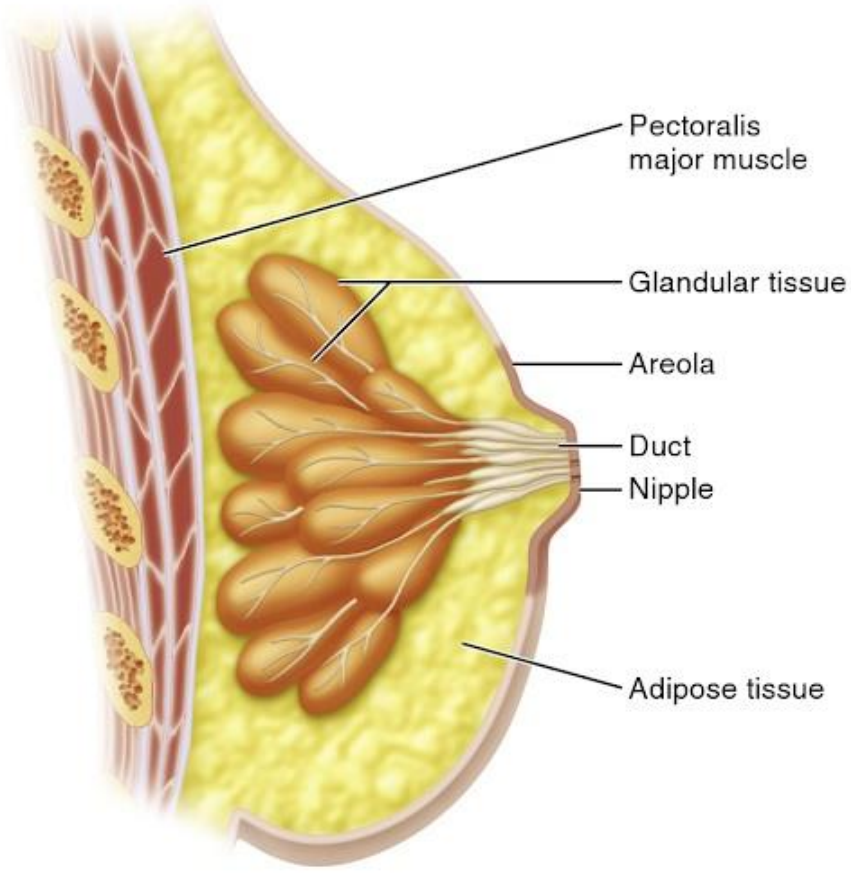

Figure 1 The structure of a mature female breast [14]**.**

Breast cancer is described as a cancer type, in which the breast cells start growing out of control and result in a tumour formation. The severity of the disease is based on its various stages, mainly numbered from stage 0 to IV. Stage IV is the most critical stage, in which the tumour has turned into malignant due to the growth of the cancer cells in the nearby tissues and it has spread to other parts of the body [16]. It can be identified that due to the emergence of novel screening technologies such as mammography, clinicians are able to detect rapidly and early the asymptomatic disease and symptoms associated with it to provide timely intervention to affected women. Breast cancer is one of the life-threatening types of cancers associated with the abnormal development of lumps in the breast. Identification of breast cancer is associated with the red and swelling appearances of the breast due to the uncontrolled growth of breast cells, which is referred to as malignant. Investigations have further highlighted that when left unchecked for an assessment, these malignant cells can turn out into conditions beyond the original tumour, spreading out to other body parts in a process called metastasis [17]. Breast cancer occurs due to changes in mutations of genes responsible for the regulation of growth of breast cells [18]. Such changes affect the functioning of the genes associated with retaining the health of the cells of the breast. The healthy functioning of the breast is associated with the orderly process of cell growth within the breast i.e., automatic, and continuous replacement of old cells by healthy ones. In case there is a change in such orderly process and mutations started turning on and off some of the genes in a cell, this can lead to an uncontrollable division of breast cells. The increased production or overgrowth of cells in the breast eventually leads to the formation of tumours, which can be further categorised into benign or malignant [17].

3.2 Breast cancer stages

The stages of breast cancer are usually numbered as 0, I, II, III and IV. Breast cancer staging depends on the severity of the cancer, i.e., the tumour size and whether the disease has hormone receptors as well as to what extend the cancer has spread to healthy tissues inside the breasts, the nearby lymph nodes, and the other body parts and organs. Stage IA and stage IB are the subdivisions of

stage I. Stage IIA and stage IIB are the subdivisions of stage II. Furthermore, stage IIIA, stage IIIB and stage IIIC are the subdivisions of stage III [7]. The details of all these stages are given below:

3.2.1 Stage 0

Stage 0 is non-invasive breast cancer. In stage 0, cancer cells remain inside the affected area of the breast in the ducts of the breast tissue, without invasion to adjacent breast tissues. Stage 0 cancers are known as carcinoma in situ i.e., cancer remains in the original place.

3.2.2 Stage I

Stage I is invasive breast cancer. However, it is an early stage breast cancer and cancer is contained to only the area where it first started in the breast tissue. Cancer may also be found in the lymph nodes near the breast. Stage I is subdivided into stage IA and stage IB.

3.2.2.1 Stage IA

Stage IA is invasive breast cancer. The tumour size is up to 2 cm in stage IA. Cancer has invaded the adjacent breast tissues but not outside the breast. In stage IA no cancer cells are found in the lymph nodes.

3.2.2.2 Stage IB

Stage IB is invasive breast cancer. In stage IB cancer cells of 0.2 mm to 2 mm in size are found in the axillary lymph nodes or the lymph nodes near the breastbone. A tumour of up to 2 cm in size may also be found in the breast.

3.2.3 Stage II

Stage II is invasive breast cancer. In stage II cancer is bigger in size compared to stage I and it is found in a limited area of breast tissue. Cancer may also be found in the lymph nodes close to the breast. Stage II is subdivided into stage IIA and stage IIB.

3.2.3.1 Stage IIA

Stage IIA is invasive breast cancer. In stage IIA either no tumours are found in the breast, but cancer is found in the axillary lymph nodes. Or a tumour of up to 2 cm in size is found in the breast plus cancer is found in the axillary lymph nodes. Or a tumour of 2 cm to 5 cm in size is found in the breast but no cancer is found in the axillary lymph nodes.

3.2.3.2 Stage IIB

Stage IIB is invasive breast cancer. In stage IIB either a tumour of 2 cm to 5 cm in size is found in the breast in addition to groups of cancer cells of 0.2 mm to 2 mm in size are found in the lymph nodes. Or a tumour of 2 cm to 5 cm in size is found in the breast and cancer has spread to the axillary lymph nodes or the lymph nodes near the breastbone. Or a tumour of bigger than 5 cm in size is found in the breast but no cancer is found in the axillary lymph nodes.

3.2.4 Stage III

Stage III is invasive breast cancer. In stage III cancer is larger in size compared to stage I and stage II, and it has spread furthur into the breast tissue. Cancer is also found in the lymph nodes. Stage III is subdivided into stage IIIA, stage IIIB and stage IIIC.

3.2.4.1 Stage IIIA

Stage IIIA is invasive breast cancer. In stage IIIA, either no tumours are found, or a tumour of any size is found in the breast and cancer has spread to the axillary lymph nodes or the lymph nodes near the breastbone. Or a tumour of bigger than 5 cm in size is found in the breast and groups of cancer cells of 0.2 mm to 2 mm in size are found in the lymph nodes. Or a tumour that is bigger than 5 cm in size is found in the breast and cancer has spread to the axillary lymph nodes or the lymph nodes close to the breastbone.

3.2.4.2 Stage IIIB

Stage IIIB is invasive breast cancer. In stage IIIB, a tumour of any size is found in the breast and cancer has reached the skin of the breast and the chest wall leading to ulcer and swelling. Cancer is also found in the axillary lymph nodes or the lymph nodes near the breastbone.

3.2.4.3 Stage IIIC

Stage IIIC is invasive breast cancer. Either no tumours or a tumour of any size is found in the breast and cancer has reached the skin of the breast and the chest wall leading to ulcer and swelling. Cancer is also found in the axillary lymph nodes, or the lymph nodes below or above the collar bone, or the lymph nodes close to the breastbone.

3.2.5 Stage IV

Stage IV is invasive breast cancer. Breast cancer is described as advanced or metastatic i.e. cancer has spread from its origin to other body parts and organs such as the lungs and the bones in a process called metastasis. Bone metastasis is typically very common in breast cancer patients [7].

3.3 Breast cancer risk factors

Breast cancer has been identified as one of the most prevalent cancer in women worldwide including both the developed as well as the developing countries. However, and according to the World Health Organization (WHO) statistics, breast cancer is mostly referred to as the disease of the developed world, where people get the illness mainly due to environmental factors and lifestyle behaviours. In the United States for example, the highly prevalent rates of breast cancer are seen among the white and black women i.e., the Europeans and the Africans compared to the indigenous people of the continent such as the American Indian and Alaska Native women who have the lowest incidence rate [19]. In addition to race and ethnicity, other risk factors that are linked to breast cancer include obesity, high rates of smoking, high levels of alcohol consumption, reproductive history, and the increased use of hormone replacement therapy among the US women. In comparison, breast cancer incidence rates in Asia are quite low with the breast cancer age-standardized incidence rate (ASR) in Asia (ASR of 29.1/100,000) compared to the US (ASR 92.9/100,000) [20]. Many factors such as the environment, eating habits, as well as early marriage and pregnancy as well as early childbirth and prolonged breastfeeding among women in the Asian countries are examined as the key factor behind the comparatively lower prevalence rate. Other factors such as the trends of less smoking status, less drinking alcohol statues, less use of hormones, and exercise have been recognised as key elements in the Asian countries. Other risk factors that are linked to breast cancer include inheriting certain mutated genes. About up to 10% of breast cancer cases are believed to be directly caused by gene mutations that are hereditary and passed down from generation to generation. The most inherited breast cancers are linked to mutations in the genes, BRCA1 (BReast CAncer gene one) and BRCA2 (BReast CAncer gene two) [21]. Therefore, many factors affect breast cancer occurrence, some of the factors can be changed, while some other factors cannot be changed. For example, factors like obesity, lack of physical activity and drinking alcohol are among the factors that can be modified by choosing a healthy lifestyle. Other factors that cannot be modified, include being woman, age, and genetics. The risk of developing breast cancer

for female gender is 100 times larger than for male gender [22]. Reproductive factors, such as early first menstrual cycle, late menopause, and late age at first childbirth are highlighted as significant causes of breast cancer, additionally, women taking hormone replacement therapy (HRT) and oral contraceptive, are also at higher risk.

3.3.1 Age

The biggest breast cancer risk factor, after being a woman, is the aging process. Around 2 in 3 cases of invasive breast cancer are found amongst patients aged 50 years and older. However, around 1 in 8 cases of invasive breast cancer are found in patients under the age 45 years. The reason behind that is that with the aging process the human body becomes weaker in genetic damage repairing, and consequently there are higher chances for mutations to occur in the body [23] [24].

3.3.2 Family history and genetics

Genetic transmission is recognised as one of the most significant risk factors of breast cancer, and there is a higher risk of developing breast cancer in women who have close relatives diagnosed with the disease. About 5% to 10% of cases of breast cancer are believed to be from abnormal genes passing from parents to children. Such genetic transfers can occur from close blood relatives, including relatives from both the father side and the mother side, and in general about 15% of breast cancer patients have a family member diagnosed with the disease [22]. The common inherited cases of breast cancer are linked to mutations in BRCA1 and BRCA2 genes. Females with a BRCA1 mutation have about 50% to 70% risk of developing breast cancer, while those with a BRCA2 mutation have about 40% to 60% risk of developing the disease by age 70 [4]. BRCA1 and BRCA2 genes produce tumour suppressor proteins which help repairing damaged DNA and keeping the breasts grow normally. Mutations in other genes such as PALB2 (Partner And Localiser of BRCA2) gene are also associated with inherited breast cancers. PALB2 interacts with BRCA1 and BRCA2 at the DNA damage site to

take part in repairing damaged DNA by homologous recombination (HR). PALB2 mutation is recognised for having a high risk of developing breast cancer, estimated at about 35% by age 70 [25]. Other high risk gene mutations include PTEN (phosphatase and tensin homolog deleted on chromosome 10) gene, and TP53 (tumour protein 53) gene. PTEN gene gives instructions for making a tumour suppressor enzyme that is found in almost all body tissues to regulate the normal growth of cells. On the other hand, TP53 gene gives instructions for making a tumour suppressor protein called tumour protein p53 which also regulates the normal growth of cells. Females with a PTEN mutation have the lifetime risk of breast cancer of about 25% to 50%, while those with a TP53 mutation have the risk of getting any type of cancer of up to almost 100% [4]. Moderate to high-risk gene mutations that are also associated with inherited breast cancers include the genes that help repairing damaged DNA such as the ATM (ataxia-telangiectasia mutated) gene and the CDH1 (cadherin 1) gene [4]. Mutations to other genes such as CHEK2 (checkpoint kinase 2) gene are considered as moderate risk breast cancer genes [26]. CHEK2 is a tumour suppressor gene, and it is also involved in repairing damaged DNA. In general, genetic testing is available to determine if a woman has BRCA1, BRCA2 or other gene mutations. In the UK, a referral is usually needed from a GP to a consultant specialist, so as the patient can be seen and treated urgently [27].

3.3.3 Taking oral contraceptives

Taking oral contraceptives (birth control pills) is highly dominant among women worldwide, to prevent pregnancy. Roughly 140 million women globally, use some type of contraceptive pills, with 16 million being in the United States alone [28]. The various formulation types of such medicines also mediate the effects of such oral contraceptives on breast cancer. Clinical investigations have revealed that the use of oral contraceptives such as oestrogen at high dose, ethynodiol diacetate, in addition to other oral contraceptives, has been linked to higher risk of breast cancer, however low dose oestrogen oral contraceptives are not subjected to high risk of breast cancer [29]. Findings have also suggested that the risk of breast cancer associated with the use of hormonal contraceptives is

further dependent on the durations of use. Therefore, the longer women take oral contraceptives, the higher their breast cancer risk. There is a 9% breast cancer risk for women taking contraceptives for less than a year and 38% for women taking contraceptives for 10 years and above [28].

3.3.4 Taking hormone replacement therapy (HRT)

Women take hormone replacement therapy to help them in relieving the common symptoms of the menopause, such as vaginal dryness, mood swings, hot flushes, night sweats and reduced sex drive [30]. Using HRT formulations is also identified as a possible reason for women to be at a higher risk of developing breast cancer [31]. Breast cancer risks are typically greater among women using estrogen–progestin formulations, than those using estrogen-only formulations. High risks of breast cancer are further highlighted to be linked to hormone replacement therapy for estrogen receptor positive breast cancers compared to estrogen receptor negative breast cancers. Women going through hormone replacement therapy are subjected to an increased risk of breast cancer typically within two years of cessation. However, the relationship between HRT and the risks associated with breast cancer are also moderated by other factors such as menopause (mainly using hormone replacement therapy straight away after the menopause time) [32] in addition to a lean body mass and high mammographic breast densities are also linked to a higher breast cancer risk amongst women taking hormone replacement therapy [31].

3.3.5 Pregnancy history

Past studies have highlighted that full-term pregnancies before the age of 30 years decrease the long-term breast cancer risk amongst women. If women did not give birth in early life to their first child, then they are at a higher risk of getting breast cancer, compared to women who had their first child before the age of 30 years [33]. Pregnancy offers a protective effect against breast cancer, through decreasing the lifetime menstrual cycles, as researchers have highlighted that women who had breast cancer had more menstrual cycles before the first full-

term pregnancy [34]. The first full-term pregnancy also stimulates a regular growth of breast cells resulting in fully mature breasts. Typically, breast cells before the first full-term pregnancy are very active and immature, therefore a delay in childbearing, contributes significantly to increasing the rate of breast cancer prevalence [35]. Breast cancer incidence during pregnancy is about 2% to 3% of total cases of breast cancer [36]. However, diagnosis and treatment of pregnant women with breast cancer is a challenging issue, therefore it is highly essential if a woman had any breast lumps during pregnancy to be referred to multidisciplinary professionals.

3.3.6 Race and ethnicity

The effects of race and ethnicity in shaping the disparities in breast cancer are persistently discussed in the clinical investigations. Research studies have diagnosed breast cancer incidences while categorising their research population into local communities, migrant communities, Asians, Blacks, White Europeans, etc. Studies have concluded with evidence that some populations are at higher risk of developing breast cancer in comparison to other women populations. Researchers have investigated various factors in relation to race and ethnicity and the incidence of breast cancer such as environmental, behavioural, biological factors in addition to other factors including social and economic factors, etc., [37] [38] [39]. However, and due to the fact that the race and ethnicity cannot be changed, further discussions and explanations, and a new genetic concept of cancer is presented in chapter 6 of this research work about the wider topic of race and ethnicity, human population origins and migrations, and the development of cancer in addition to suggested cancer protection and prevention strategies to help prevent people from getting acquired gene mutations that may cause the disease.

3.3.7 Breast composition (Density)

Dense breast tissue is not abnormal, and it is very common for women to have dense breasts. However, dense breast tissue is one of the risk factors that put women at higher risk of getting breast cancer and possibly four to six times more likely to get the disease. Dense breasts are not related to the size of the breast, it cannot be self-examined, and it can make it harder to read mammography results compared to women with fatty breasts. However, on a mammogram a way to measure the breast density is by measuring the thickness of the breast tissue [40]. A dense breast has less fatty tissue but more fibrous and glandular tissue, and on a mammogram, fat appears dark, while breast gland tissue looks light. Similar to gland tissue, breast tumours and calcifications look light on mammography, and this can make cancers difficult to be seen as it can merge inside the breast tissue [40]. Therefore, other modalities such as ultrasound imaging is used to aid mammography in screening patients with dense breasts. Breast density assessment is included in the Breast Imaging Reporting and Database Systems (BI-RADS), and it is classified into four categories; A) mostly fatty breast tissue, B) scattered fibroglandular breast tissue, C) heterogeneously dense breast tissue, and D) extremely dense breast tissue [41]. Breast density can also be passed down from mothers with dense breasts to their daughters who are also expected have dense breasts, however other factors can influence breast composition [42].

3.3.8 Drinking alcohol and its effect on breast cancer

Likewise, the use of alcohol is not only associated with the occurrence of breast cancer the first time but also associated with the recurrence of breast cancer in breast cancer patients. Women drinking alcohol have a higher risk of getting breast cancer and the risk is increased by 50% in women who drink excessively about 45 g/day of alcohol [17] [43]. The mechanism behind that is believed to be associated with the alcohol effect on the levels of circulating oestrogen [22]. Drinking alcohol may also put women at higher risk of developing breast cancer through causing damage to DNA in cells [44].

3.4 Breast cancer prevention

Prevention strategies to deal with breast cancer is associated with the existing as well as new emerging risk factors. Based on the range of identified risk factors associated with breast cancer, clinical investigators have highlighted different types of prevention strategies for dealing with the above-mentioned risk factors. Women with a higher risk of breast cancer may benefit from the prevention strategies and treatments that are available to lower the risks of getting the disease. Although different strategies have been developed in the past considering, the primary and secondary preventions in addition to the choices and applicability of an effective breast cancer prevention strategy are dependent on the severity of the disease and the conditions of each case. These preventions are discussed precisely, while keeping the focus on the factors that need to be considered to prevent the occurrence of breast cancer the first time as well as to avoid the prevalence of the subsequent breast cancer [45] [46].

3.4.1 Modification of lifestyle and eating habits

Changing lifestyle and diet is recognised as a recommended prevention strategy to lower the risks of breast cancer in females with a higher risk of developing breast cancer. For all women, practising regular exercises and keeping a nice and healthy body weight is recommended as a dedicated cancer prevention effort. Clinical investigations have presented evidence that eating fruit and vegetables as well as a balanced diet may lower the breast cancer risks [45]. The effect of Mediterranean diet is also investigated for cancer prevention including the significant components of the diet such as balanced ratio of omega 6 as well as omega 3, fibre and fatty acids in addition to antioxidants and polyphenols [46]. Similarly, other studies have established the efficiency of a diet grounded on Mediterranean and wholegrain recipes and philosophies connected with modest physical activities in contributing towards the incidence of additional breast cancer events in women already experiencing breast cancer. Researchers have highlighted that by increasing awareness among women including those affected with breast cancer about the common meals and exercise sessions organised

with healthy lifestyle, the risk of breast cancer can ultimately be reduced by as much as a third [47] [48].

3.4.2 Early pregnancy and breast feeding

A protective factor for breast cancer is by reducing the exposure of breast tissue to oestrogen. During pregnancy oestrogen levels are lower, therefore females have a lower risk of getting breast cancer if they had a full-term pregnancy before the age of 30 years. Likewise, breast-feeding may keep oestrogen levels lower as well. Women who breast-feed for a full year and more have a lower risk of breast cancer [49]. Therefore, having children earlier than later and breast-feeding are recommended options for women to lower their breast cancer risk.

3.4.3 Taking medicines

One of the most common breast cancer prevention strategies is using pharmaceutical drugs and medicines. Evidence from clinical investigations have revealed that tamoxifen and raloxifene (known as selective oestrogen receptor modulators (SERMs)) and anastrozole and exemestane (known as aromatase inhibitors (AIs)) can be used to reduce the breast cancer risk. However, these medications act only to reduce the risk of a specific breast cancer type called oestrogen receptor-positive ((ER)-positive) breast cancer, which accounts for about two-thirds of all cases of breast cancer. Tamoxifen's common side effects, include vaginal discharge, night sweats, hot flashes, and blood clots, while the side effects of raloxifene include, joint and muscle pain, weight gain, vaginal dryness and hot flashes. The aromatase inhibitors' common side effects, include vaginal dryness, hot flashes, fatigue, joint and muscle pain, and headache [50]. However, contrary to the effectiveness of such pharmaceutical drugs in reducing the risk of breast cancer, researchers have also acknowledged the risks associated with the consumption of these medicines, as they are not well tolerated by women. Academic investigators have further highlighted that poor adherence to these medications and clinical trials without looking after their impact on the quality of life of breast cancer patients ultimately raise questions

regarding the effectiveness of pharmaceutical-based treatments [51]. It is highly crucial to evaluate the consequences and effects of using these medications in order to reduce the risk of breast cancer according to the aforementioned risk factors associated with breast cancer. From the examination of the different prevention strategies available across the globe to prevent the risk of breast cancer, it was found that the effectiveness and feasibility of these pharmaceutical prevention strategies vary case-by-case and therefore it cannot be implemented in a generalised and standard way. There is a possibility that women suffering from advanced stages of breast cancer cannot be treated with pharmaceuticals. In such situations, surgery is mainly a considerable prevention strategy for women.

3.4.4 Prevention through surgery

Breast-conserving surgery (BCS) with or without irradiation is also suggested for breast cancer prevention among females diagnosed with early breast cancer. Surgery is helpful in removing the affected areas and tissues permanently. Clinical investigators have confirmed the role of risk-reducing surgery especially in hereditary breast cancer cases [52]. Breast-conserving surgery is also known as lumpectomy, segmental mastectomy, partial mastectomy or quadrantectomy, and it is a type of surgery initiated to remove cancer and to leave as much as possible healthy breast tissues in the body. At present BCS is the benchmark treatment for patients with stages 0, I and II, invasive breast cancers [53]. Other types of prevention surgeries include mastectomy and breast reconstruction. Mastectomy is defined as a preventive strategy to avoid the transfer of breast cancer to other areas of the body. Mastectomy is consisted of the removal of the whole breast and is mainly suggested to patients suffering from a large and widely spread breast cancer or patients suffering from more than one cancer in the breast [17] [54]. In rare cases, clinicians also suggest double mastectomy. Evidence further suggests that patients experiencing mastectomy also prefer going through breast reconstruction surgeries such as implant reconstruction and flap reconstruction. Breast cancer surgery is considered as a significant option for patients while they are not left with any other option [55].

3.5 Breast cancer control

Prevention, early detection, diagnosis and treatment, rehabilitation, and palliative care, are the main steps involved in breast cancer control. Prevention of breast cancer is mostly connected to the control of risk factors leading to the diseases. It is important to highlight that breast cancer is a non-communicable disease and therefore an integrated care and control can result in highly effective and long-term outcomes for patients. Usually, healthcare regulatory participates in increasing public awareness about the need to adopt a lifestyle capable of modifying the risk factors. However, despite the adoption of the risk-reducing measures to achieve the goal of prevention, the effectiveness and feasibility of these prevention strategies vary on a case-by-case basis and therefore it cannot be implemented in a generalised and standard way. There is a possibility that women suffering from advanced stages of breast cancer, cannot be treated with pharmaceuticals and modification of diet and lifestyle. In such situations, surgery is only a considerable prevention strategy [56].

3.6 Breast cancer symptoms

Similar to the categorisation of breast cancer into different stages and types, clinical investigators have also segmented the symptoms of breast cancer according to the invasiveness and non-invasiveness. Occurrence and mortality rates linked to invasive breast cancer are quite high across the globe, where thousands of women die from the disease. A range of symptoms are identified with invasive breast cancer including the presence of a mass or lump in the breast. A lump is more likely to be cancer when it is painless, hard and has uneven edges. Any unusual changes like the following in the breast, may be a symptom of breast cancer; swelling of all or part of the breast, skin dimpling or irritation, nipple and breast pain, nipple retraction, changing appearance of the nipple or breast skin resulting in redness, rash or thickening, any nipple bleeding or discharge other than breast milk [57]. Significant importance is given to invasive breast cancer due to its potential of spreading to the other parts of the

body. The identification of right symptom is highly essential for the identification of the correct breast cancer type.

3.7 Breast cancer types

There are many different breast cancer types, and they may start in various areas of the breast. Each breast cancer type depends on the specific breast cells that are affected, and they are named on the bases of where they form and how far they have spread. There are common breast cancer types, such as ductal carcinoma in situ, and less common breast cancer types, such as Paget's disease of the nipple. In situ (non-invasive), invasive (infiltrating) and metastatic are the terms used to describe the extent of the breast cancer. In some breast cancers one breast tumour can be a combination of more than one type and sometimes the breast cancer cells may not form a tumour or lump in any way. The most widespread types of breast cancers are carcinomas.

3.7.1 Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ, which is also known as intraductal carcinoma, it refers to the incidence of breast cancer when the cancer cells are found inside the ducts of the breast. DCIS is a non-invasive or pre-invasive breast cancer i.e., cancer has not completely developed or spread into the surrounding areas. DCIS is counted as stage 0 breast cancer. In general DCIS has no symptoms or signs, however a breast lump may be found sometimes in the breast or discharge from the nipple [58]. To be noted is that almost all females diagnosed with this early-stage breast cancer can be cured and the chances of a recurrence are less than 30%. However, the majority recurrences occur within 5 to 10 years from the first diagnosis. Furthermore, DCIS accounts for approximately 20% to 25% of all newly detected cases of breast cancer in the United States [59].

3.7.2 Invasive ductal carcinoma (IDC)

Invasive ductal carcinoma, sometimes known as infiltrating ductal carcinoma, it happens when the cancer cells have spread out the ducts of the breast and started invading the tissues. IDC is an invasive breast cancer meaning it can spread into lymph nodes and other parts of the body through the bloodstream and the lymphatic system. IDC initially may have no symptoms but often there is an abnormal area or a new mass or lump in the breast that turns up during a breast self-examination (BSE) or a mammogram screening. IDC is the most common breast cancer type, and it accounts for about 70-80% of all detected breast cancer cases. In the United States about 180,000 of women are diagnosed with IDC each year [60].

3.7.3 Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ also called lobular neoplasia, is non-invasive breast cancer i.e., cancer is confined to the lobules of the breast and has not spread to surrounding fatty tissue or other parts of the body. Women with LCIS have an increased risk of developing an invasive breast cancer later in life in the same or the other breast. In general, LCIS affects more than one lobule and usually it has no symptoms, as it does not cause a lump or changes that can be felt or seen on a mammogram [61], therefore women with LCIS need to take regular mammogram screening and clinical breast examinations. LCIS is typically counted as a risk factor for developing breast cancer, apart from one type of LCIS known as Pleomorphic Breast Cancer (Lobular) which may turn into invasive breast cancer; therefore, surgery is performed to totally remove it [62].

3.7.4 Invasive lobular carcinoma (ILC)

Invasive lobular carcinoma or infiltrating lobular carcinoma, is the second most common form of invasive breast cancer after IDC and it accounts for about 10% of all invasive breast cancers [63]. ILC starts initially in one of the lobules i.e., the milk producing glands of the breast and then the cancer cells spread to other

parts of the breast. ILC usually found in both breasts, but it can also spread to the lymph nodes and other parts of the body. ILC tends to occur later in life from late 50s to early 60s. Like IDC, ILC at first may have no signs but sometimes an abnormal area in the breast turns up during a mammogram screening or there is a thickening in the breast that can be felt.

3.7.5 Inflammatory breast cancer (IBC)

Inflammatory breast cancer is identified as a rare type of breast cancer and it is known for being a very aggressive disease. IBC at diagnosis is either stage III or IV, depending on whether it has spread to surrounding lymph nodes or to other tissues too. IBC in the United States accounts for about 1% to 5% of all cases of breast cancer. IBC grows and spreads very fast with symptoms getting worse within hours or days. The disease generally, develops after the age of 50 and its indications vary from simple to more complex prognosis such as dermal lymphatic invasion. IBC usually starts with the feeling of heaviness or thickness in the breast, and it tends to grow in the form of tissue layers. The cancer cells block the lymph vessels causing the breasts to become inflamed and swell. The symptoms may include breast swelling and redness, breasts get the orange-peel appearance, breasts may feel tender and ache, swelling of lymph nodes, nipple inversion and nipple flattening [64].

3.7.6 Paget's disease of the nipple

Paget's disease of the nipple is a rare type of breast cancer, about 1% to 4% of breast cancer patients have Paget's disease of the nipple. It usually develops after the age of 50 and is recognised by changes occur in the appearance of the nipple and areola. The symptoms of Paget’s disease are itchy, red, scaly, and irritated nipple and areola. The disease first starts from the ducts of the nipple and then spreads to the surface of the nipple and areola. Additionally, patients may notice thickening and scaling of the skin, flattering of the nipple and they may experience some bloody or yellowish discharge from the nipple. There is a strong relationship between DCIS and the prevalence of Paget’s disease and in most

cases, the presence of Paget's disease is the indication of the presence of an early form of cancer. Paget's disease mainly affects one breast, and it is often mistaken for eczema, but eczema generally affects the areola not the nipple [65].

3.7.7 HER2-positive breast cancer

HER2 (human epidermal growth factor receptor 2) gene is responsible for making HER2 proteins, these proteins are receptors located on the cells of the breast and they help in controlling the healthy growth, division, and self-repairing of these breast cells. About 1 out of 5 women with breast cancer are HER2-positive [66]. The cancer cells of this type of breast cancer, have more HER2 proteins and they make the cancer cells to grow and spread very aggressively and more rapidly than the cells that have normal levels of HER2 proteins. HER2 gene amplification occurs when this gene does not work properly and it makes too many copies of itself, this huge number of HER2 genes inform the breast cells to make too many HER2 receptors, which in return causes the breast cells to grow and divide in a way that cannot be controlled. The growth of this type of cancer is relatively faster than the other types of breast cancer. As far as the symptoms of the HER2 breast cancer are concerned, they are like the other types of breast cancer symptoms. The treatment of both early and metastatic HER2-positive breast cancer using anti-HER2 treatment has changed this type of cancer's natural biology and it has further helped in increasing the survival rates of almost 5 years in patients with metastatic HER2-positive breast cancer. The effective interventions have ultimately led towards a pathological complete response by 75% of patients [67].

3.8 Breast cancer treatments

There are various treatment choices available to treat breast cancer, depending on the type and stage of each case. The National health services (NHS) in the United Kingdom, has highlighted the list of the main breast cancer treatments available including surgery, radiotherapy, chemotherapy, hormone therapy and biological therapy (targeted therapy) [9]. Surgery and radiotherapy treatments are

local treatments i.e., tumour is treated with no damage to other body parts. On the other hand, chemotherapy, hormone therapy and biological therapy are systematic treatments i.e., the drugs that are used to treat breast cancers can reach almost all the body parts. Patients may get one or a combination of these treatments. Treatments offered are either for full recovery from the disease or in case of patients with advanced stages of breast cancer, treatments offered as pain relief and better life quality. In most cases, it is upon the personal preferences of the patient as well as their close family members to choose among the different treatment options available. However, the chosen option needs to be compatible with the type of breast cancer, stage of the disease, patient's age as well as their overall health. In general, a multidisciplinary team (MDT) is appointed to provide care and treatment. MDT is a team of healthcare professionals and specialists who work together for each cancer type [9].

3.8.1 Surgery

Surgery is one of the most common types of breast cancer treatments and it is the first treatment that patients usually undergo as their primary treatment modality [68]. There are different types of surgical options available including, breast-conserving surgery (lumpectomy) and total removal of the breast (mastectomy), all depending on the severity of the condition. Breast-conserving surgery (BCS) is the surgery of removing the tumour from the breast while leaving as much healthy breast tissue as possible. BCS is typically chosen for women with early-stage breast cancers, but in most cases, patients will also get radiotherapy treatment. During the surgery, the tumour is removed along with a rim of healthy tissue around it, called margin of resection or the surgical margin, to make sure that all the cancer cells have been removed. The presentation of a precise assessment of resection margins is an important part of a successful local treatment of breast cancer. Likewise, mastectomy is the surgery of removing the entire breast, including all the breast tissue and other nearby healthy tissue and lymph nodes, depending on each patient's specific situation. Mastectomy is either unilateral i.e., one breast is surgically removed, or some patients may get a double (bilateral) mastectomy, which is a risk-reducing surgery in which both

breasts are removed [9]. Side effects associated with the different types of breast cancer surgeries may include discomfort, pain, drowsiness, fatigue, seroma (swelling in the breast or armpit) infection and other problems in the general health of the patient. Patients with surgery to the armpit, may get more discomfort and pain and other complications including dysfunction of the upper limb related to surgeries such as axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). To deal with such side effects associated with such breast cancer surgeries, patients are recommended to go for postoperative physical therapy and post-surgery exercises such as strength and resistance exercises, concentrating on pain and discomfort management [69]. The quality of life (QOL) after breast cancer surgery may also become affected. QOL is usually better in patients following BCS compared to mastectomy. QOL includes social, emotional role functioning, fatigue symptoms, body image, arm symptoms and pain [70].

3.8.2 Chemotherapy

Chemotherapy or chemo is another type of treatment for breast cancer, which involves the use of cytotoxic medication to kill the cancer cells including any cancer cells that have spread to other body parts by metastasis. Anti-cancer drugs are given to patients intravenously through a drip directly into the blood and in some cases, tablets are given as well. Breast cancer patients usually get chemotherapy after surgery to destroy any remaining cancer cells. When chemotherapy is given after surgery, it is known as adjuvant chemotherapy and when it is given before surgery to reduce the size of the tumour so that it could be removed easier, it is called neoadjuvant chemotherapy [71]. Different anti-cancer drugs are used for chemotherapy and in many cases a combination of three drugs is given at once. The choice of drugs and combinations depend on the type and severity of the breast cancer, and the treatment length is dependent on how well the chemotherapy is working and how well the patient can keep up with it along with what side effects they have. The main side effects of chemotherapy include anaemia, infection, fatigue, loss of appetite, vomiting, diarrhoea, hair changes and sore mouth and throat. Breast cancer survivors may

also get long-term side-effects such as impact on fertility, treatment-induced menopause, cardiovascular toxicity, and cognitive impairment [9].

3.8.3 Radiotherapy (RT)

The other important treatment choice for breast cancer patients is radiation therapy. RT uses doses of ionising radiation to kill or control breast cancer cells. Radiotherapy may be offered on its own or in conjunction with surgery or chemotherapy. RT can be used after mastectomy or as a part of breast-conserving surgery to kill any remaining cancer cells around the affected area of the breast, or after mastectomy to minimise the local-regional recurrence risks and to improve long-term breast cancer-specific and overall survival. Radiotherapy is recommended after the patient has recovered from the surgical process and that is open to different options including, breast radiotherapy (which is offered after BCS, in which radiotherapy is delivered to all the remaining breast tissue), chest wall radiotherapy (which is delivered after mastectomy, in which radiation is applied to the chest wall), breast boost (in which a boost of high-dose radiation is applied to the affected area of the breast after surgery) and radiotherapy to the lymph nodes (in which radiation is applied to the armpit and the surrounding area of axilla to kill any cancer cells in the lymph nodes). Similar to surgery and chemotherapy, Radiation therapy is also subject to side effects including skin reactions such as darkening and irritation, pain, fatigue and tiredness, armpit and chest hair loss, breast oedema and lymphoedema [9]. Likewise, modern techniques of radiotherapy such as deep inspiration breath hold (DIBH) is used for breast cancer treatment. Due to the position of the heart in the chest, which is slightly left of the centre, DIBH technique is used in patients with left-sided breast cancer. In DIBH the patient takes a deep breath during radiotherapy and holds their breath at the same time as the radiation is delivered. DIBH is necessary to avoid the patient’s heart from receiving any radiation dose.

3.8.4 Hormone treatment

Breast cancers that are stimulated by the hormones oestrogen or progesterone are called hormone receptor-positive (ER+) breast cancers. Hormone treatment works by lowering the amount of these hormones in the body or by blocking their action. Hormone therapy is either offered before surgery (called primary or neo-adjuvant treatment) to reduce the size of the tumour to make it easier to be removed or it can be given after surgery (called adjuvant treatment) to reduce the risk of breast cancer coming back. Hormone treatment may also be offered as the only breast cancer treatment in patients that have other illnesses such as lung or heart illnesses and that their general health prevents them to have these treatments. However, the effectiveness of hormone treatment is dependent on the stage, age, and the sensitiveness of the breast cancer to the hormones. In case of absence of any sensitivity, hormone treatment will have no effect. Tamoxifen, aromatase inhibitors and ovarian ablation or suppression are the main types of medicines used in hormonal therapy. The side effects of hormone therapy are mainly menopausal symptoms such as hot flushes and sweats, vaginal dryness, and psychological problems such as depressions and mood swings as well as loss of libido or sex drive. Other side effects include nausea, headaches, stiffness, joint pain and fatigue or tiredness [9].

3.8.5 Biological therapy (Targeted therapy)

Biological therapy works by targeting the changes that occur in the cancer cells, the drugs used stop the growth and spread of the cancer cells. Unlike chemotherapy, targeted therapy drugs attack only the cancer cells and sometimes they may work better than chemotherapy. Targeted therapy is the treatment for breast cancers that are HER2-positive [66]. HER2-positive breast cancer has more HER2 proteins, and they make the cancer cells to grow and spread faster than cancer cells with normal levels of HER2 proteins. Biological therapy using medications such as Trastuzumab (Herceptin) and Pertuzumab (Perjeta) are monoclonal antibodies used for the treatment of both early and metastatic HER2-positive breast cancer and they have changed this type of

cancer's natural biology and they have further helped in increasing the survival rates of almost 5 years in patients with metastatic HER2-positive breast cancer. The effective interventions have ultimately led towards a pathological complete response by 75% of patients. The side effects of biological therapy are often mild such as pains, tiredness, fever, nausea, and diarrhoea, but some side effects can be serious heart problems [72]. Likewise, breast cancer immunotherapy is part of biologic therapy, and it uses the patient's immune system as a treatment for breast cancer. Breast cancer immunotherapy is a type of systemic treatments used for breast cancer and is developing rapidly as several studies recently have demonstrated improved outcomes in treating some types of breast cancer. Immune Checkpoint Blockade (ICB) is the most investigated form of breast cancer immunotherapy. ICB is used as monotherapy or in combination with chemotherapy to improve treatment responses. Immunotherapy has shown helpful results for some patients, but it may cause severe side effects. Therefore, more research needs to be done to make advances in breast cancer treatment. The U.S. Food and Drug Administration (FDA) have approved several immunotherapy medicines to treat breast cancer such as Atezolizumab (Tecentriq) [73] which was granted accelerated approval. Tecentriq is used in combination with the chemotherapy drug Albumin-Bound Paclitaxel (Nab-paclitaxel or Abraxane) to treat triple-negative breast cancers. Triple-negative breast cancer is oestrogen-receptor-negative, progesterone-receptor-negative, and HER2-negative breast cancer. Triple-negative breast cancers are more aggressive than hormone-receptor-positive or HER2-positive breast cancers [74].

3.9 Breast cancer recurrence

Breast cancer is recognised as one of the life-threatening diseases as it can come back after treatment at any time, even decades after the occurrence and treatment of the original tumour. When breast cancer can come back it is known as recurrence and it depends on whether it is a local recurrence i.e., in the treated breasts or distant recurrence i.e., in other parts of the body such as lymph nodes, bones, liver, lungs and brain [68]. The incidence of breast cancer recurrence has various factors, such as the type of treatment, stressful life events,

sociodemographic factors, and other physical and pathological factors. In discussing the psychological factors, along with the medical factors, it is highly necessary to investigate the prognostic association, such as severe life stressors to identify the recurrence. Prevalence of breast cancer may also differ in young patients from older adult women. Gender-based differences are also considered significant in clinical investigations, indicating that the incidence of breast cancer can be different in the population of men and women. Clinical researchers have therefore highlighted that the recurrence of breast cancer should be considered on a case-by-case basis. However, improvements in systematic therapy have lowered breast cancer recurrence rates [68].

3.10 Blood marker test

Blood marker tests are used to predict breast cancer recurrence after treatment. However, blood marker tests are also performed before treatment to determine if cancer has spread to other parts of the body. Furthermore, blood marker tests performed during treatment are used to find out if the disease is responding to treatments. CA125 marker test can be used to indicate the recurrence of breast cancer, while CEA (carcinoembryonic antigen) marker test can be used to find out if breast cancer has spread to other parts of the body (metastasis). Moreover, circulating tumour cells marker test may be used to signal that breast cancer is growing into the blood stream, when there is high circulating tumour cell counts [75].

3.11 Prevalence of breast cancer in young women population

Young women are considered as one of the most vulnerable population groups affected by breast cancer. About 6.6% of the cases of breast cancer are diagnosed in the women under 40 years old [76] [77]. Age is an independent prognostic factor, indicating young woman experience more aggressive subtypes of breast cancer such as triple-negative or HER2-positive breast cancers. It is also important to highlight that young woman are subjected to experience advanced stages of breast cancer due to different factors such as delayed

diagnosis. Consequently, such breast cancer cases perhaps transformed into local or regional recurrences and distant metastases. Regardless of the independence of the age factor, the prevailing breast cancer in the young women population can further be categorised differently in different parts of the world such as in Europe, North America, Africa, Asia and other countries. In similar context, investigating the prevalence of breast cancer rates in young women from selected countries such as Italy 0.6%, France 0.59%, UK 0.5%, Lebanon 0.45% and U.S.A. 0.45% as the five top countries having higher cumulative risk of breast cancer prevalence [76]. Among the most influencing factors, affecting the prevailing breast cancer in young women include the long-term use of oral contraceptives, the mass index, and the higher animal fat diet consumption. Findings have also highlighted that obesity is associated with both pre and postmenopausal breast cancer risks. Despite their intensity on the incidence of breast cancer, studies have highlighted that these factors are modifiable relative to the set of non-modifiable factors such as family history and gene mutations. Similarly, the significance of adverse pathological factors cannot be undermined [78]. Furthermore, survival rates in the younger women population are shown to be worse in comparison to the older women age population [79] [80].

3.12 Breast cancer and pregnancy

Pregnancy-associated breast cancers are also identified as highly critical in the younger population group. Young pregnant women with oestrogen receptor-negative tumours and high-grade tumours are expected to have a lower prognosis [81]. Evidence has suggested that it may be difficult to diagnose breast cancer in the pregnant or lactating women and in the case of the presence of a breast lump during pregnancy, the case is referred to multidisciplinary professionals [80]. Studies have further shown that diagnosis and treatment of pregnant young women with breast cancer becomes a challenging issue for the clinicians because several effective imaging techniques such as bone scanning, pelvic x-ray and computed tomography scan, and treatment procedures cannot be applied on such population. Pregnancy-associated breast cancers are every so often misunderstood as only the ones which are diagnosed during the

pregnancy term of nine months whereas it also includes breast cancers diagnosed in the first postpartum year. Investigators have suggested that delay in childbearing is contributing significantly to increasing breast cancer in the young women population [82]. In general, clinical professionals decide about the therapeutic strategies for determining the tumour biology, tumour stage, gestational age and other socio-demographic factors affecting decisions regarding each case.

3.13 Breast cancer in men

Additionally, for better understanding of breast cancer incidences in the women population, analysis of male breast cancer is also significant. Statistics have shown that male breast cancer is very rare and only less than 1% of all breast cancer types is likely to develop in men [83]. Researchers have highlighted the risk factors, biology, diagnosis, treatment, and survivorship of breast cancer in men. Researchers have indicated that the most considerable risk factors responsible for breast cancer in men include BRCA2 mutations, age, circumstances capable of modifying the oestrogen/androgen ratio, in addition to radiation [84]. Symptoms of breast cancer in men include a breast lump, armpit swollen glands, inverted nipple, sore nipple, and nipple discharge [85]. Researchers have further highlighted that the differences in the disease biology in the male gender do not face any effect on the diagnostic approaches and treatments chosen to deal with the cases meaning that both male as well as female gender are diagnosed with the employment of same diagnostic approaches and treatments, one of the reasons behind which is the lack of research in the male gender [84]. Researchers have highlighted that breast cancer in males is subjected to survival issues associated with the sexual and hormonal side effects associated with the endocrine therapies. The variations in the rates of cancer among men linked with variations in behavioural risk factors as well as using screening services in addition to getting exposed to infections that are cancer-causing. Researchers have also highlighted the strategies used to control cancer, such as using vaccinations, screening programmes, exercises

and controlling body weight in addition to controlling smoking and drinking alcohol [86].

3.14 Complementary and alternative medicine (CAM) use for cancer

Complementary and alternative medicine (CAM) is either used to complement the standard cancer therapies given to cancer patients to help them cope with the symptoms and side effects and to improve their quality of life (QOL) such as the patient's emotional, social, and physical wellbeing including pain as the most important distress among cancer patients, or to directly fight cancer as an alternative to conventional cancer treatments. The common practices of many complementary and alternative treatments emphasise on good nutrition and prophylaxis, and it is therefore believed that CAM works by boosting the natural immunity of the body to kill the cancer cells, however more scientific research is needed to find out that improvements in cancer patient's health are real and due to the complementary and alternative therapies used i.e., not as a result of other treatments, and also to present scientific evidence that these treatments are safe to use and do not interact with conventional cancer therapies.

3.14.1 Introduction

The terms complementary medicine and alternative medicine are often used together and usually in one sentence as: complementary and alternative medicine (CAM). However, complementary medicine, also known as integrative medicine, refers to treatments used side by side standard cancer treatments of surgery, chemotherapy, and radiotherapy. Complementary medicine is mainly used to help cancer patients feel better with the side effects and symptoms of conventional therapies. On the other hand, alternative medicine refers to nonstandard treatments used instead of conventional medical therapies. Many different research studies have presented scientific evidence that CAM can encourage better overall health for cancer patients, it can strengthen the immune defences of the body, and aid cancer patients manage the symptoms and side effects of the standard cancer treatments. In this review, clinically successful

evidence regarding CAM treatments given to patients with cancer, including results of a number of medical research studies, are looked at to get a clearer idea on CAM used in different parts of the world to help people with cancer. The following CAM treatments are discussed in this review article; CBD, ZW, Graviola, Origanum vulgare, TCM, and Paris Polyphylla. This review is a summary of the overall use of some CAM treatments against different types of cancers and using CAM as a supportive and palliative care especially in decreasing the side effects of conventional cancer therapies and to improve the QOL. However, more research is needed on the topic of CAM so that it is effectively and safely used to treat and help people with cancer.

3.14.2 Types of complementary and alternative medicine (CAM)

Various CAM therapies are used worldwide to treat cancer. The following is evidence-based information about CAM used for cancer such as Cannabidiol (CBD), Zamzam Water (ZW), Graviola, Origanum Vulgare, Traditional Chinese Medicine (TCM), and Paris Polyphylla. Researchers have highlighted that complementary medicines can help cancer patients feel better when used along with standard cancer treatments, for instance CBD has proved beneficial for improving a variety of symptoms (such as pain and nausea) in cancer patients. Likewise, some alternative therapies such as TCM are approved to be used in China to treat various cancer tumours. Similarly, the side effects of conventional treatments and dissatisfaction are also highlighted to be among the push factors to use CAM, while pull factors, on the other hand, included the positive aspects associated with CAM, such as the expectation of fewer side effects, stronger immunity, and better QOL.

3.14.2.1 Cannabidiol

Cannabidiol (CBD) is a non-intoxicating chemical that comes from the cannabis sativa plant. Cannabidiol is a cannabinoid (CB) found in cannabis and it is non-psychoactive. Therefore, CBD has been used for pain relief and other tumour associated symptoms with no mind-altering effects. CBD is one of many different

cannabinoids and the two main cannabinoids, delta-9-tetrahydrocannabinol (d-9-THC) and cannabidiol [87] [88]. Cannabidiol is known to have a wide range of health benefits such as treating pain, anxiety, depression, epilepsy, anti-inflammatory [89] [90] as well as possessing anticancer activities [91]. CBD works by binding to the cannabinoid receptors such as cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) in the body and it can help regulating the endocannabinoid system (ECS). ECS is a molecular system that regulates and balances various processes in the body to maintain the homeostasis of the body such as helping the immune system when to attack and destroy foreign substances in the body in addition to other body processes including appetite, memory, metabolism, pain, and sleep, etc [92] [91]. CBDs are used in cancer patients to kill cancer cells and prevent cancer cell migration and kill tumours [91]. CBDs have shown antitumour potentials and provided relief for tumour-associated symptoms as well as being active against oestrogen receptor-positive and oestrogen-resistant breast cancer cells. Furthermore, CBDs have been used to manage patients with advanced breast cancer stages and to be effective in tumour progression deceleration in breast cancer patients at earlier stages.

3.14.2.2 Graviola (Soursop)

Graviola, also known as soursop, is the fruit of a small evergreen tree that is broadleaf, and flowering called Annona muricata. Annona muricata is found in the African and Latin American rainforests and known for being used by people as an important source of food and medicine. Graviola has a flavour of a combination of apple and strawberry, and is usually used in making candy, juice, and sorbet. Graviola is also known to have medicinal benefits such as treating viral and parasitic infections as well as arthritis and rheumatism [93] [94]. Graviola extracts can also help treat other medical conditions such as slowing the cancer spread and making conventional cancer treatments work better. Graviola is known for having antitumor and antioxidant properties and can help treat cancer. Graviola extracts have shown anticancer effects and it can kill some types of cancer cells that are usually resistant to some drugs of chemotherapy [95] [96].

3.14.2.3 Origanum vulgare

Origanum vulgare or oregano is one of the herbs in the mint family Lamiaceae found in the Mediterranean, Eurasia, and other parts of the world. Oregano is an invasive plant with a pink flower that has a potent flavour and is used in a variety of cuisines, and it is linked to health benefits. Oregano is known to have antibacterial properties, and it is effective against many organisms such as E. coli, Salmonella enteric, and Clostridium difficile [97]. Oregano oil is a natural anti-inflammatory herb, and it has pain-relieving properties, and commonly used as a medication for cold sores, sore throats, nasal congestion, muscle pain and joint pain [98] and to reduce lower backache. Oregano is also high in antioxidants that help prevent cell damage and cancer and help kill cancer cells. Oregano has shown anti-tumour effects in cancer models [99] and chemo preventive and therapeutic effects to modulate the growth and metastasis of cancer [100].

3.14.2.4 Zamzam Water

Zamzam is the name of a well located in the sacred mosque in the city of Mecca, Saudi Arabia. The water that is taken from the well is known as Zamzam Water (ZW) and it is sacred to Muslims. ZW has a distinct taste, and it is colourless and odourless. ZW is rich in a variety of minerals, and it is naturally alkaline [101] with an average pH of 8.0 [102]. Studies have confirmed that ZW is pathogen-free causing no microbial growth [103] and also the quality and components of ZW remain relatively unchanged for years [102]. ZW is consumed by many people on daily basis especially in the cities of Mecca and Medina as a blessing and for its health benefits. According to Islamic sources, the prophet of Islam, Mohammed (peace be upon him) used to drink ZW and he used to say that ZW is a blessing, and it is food that satisfies and a cure for the sick and it is for whatever purpose for which it is drunk. In general, ZW may have cytotoxic effects [104] and may work as an anticancer agent to naturally treat cancer with no side effects [105] [103]. The right methodology of using ZW to treat cancer and other illnesses is simply by drinking it, and it is recommended when drinking ZW pausing to take a breath three times and drinking one’s fill. ZW is absorbed by the stomach and the

intestines and passed to the bloodstream to circulate all the way through the body in the form of body fluids. It is important to make sure that a genuine ZW is used i.e., as it is obtained from the well in Mecca without changing it before use. If ZW is modified in any way for example if its pH is adjusted to a pH different than normal, it will have less effect on cancer cells [104]. Furthermore, ZW will totally lose its effectiveness when it is diluted and its pH is adjusted to a different pH than its normal pH, in addition to other changes. In a journal article published in 2019 [106], the authors showed that in their experiment, cancer cell growth was increased by ZW treatment and that ZW treatment suppressed the effect of chemotherapeutic agents, etc. in the same paper, the authors stated that the methods they followed were “ZW and DW were buffered using PBS and the pH was adjusted to 7.4. For the treatment, ZW and DW were diluted to 50% with RPMI medium (10% FBS)”. Therefore, when ZW is changed through dilution or pH change and other changes, then it is not ZW anymore but a different substance. And so, when a sample of ZW used in a study that is a modified version of ZW, then the study is invalid, and the results are simply inaccurate and therefore it cannot be claimed that ZW causes harm to cancer and that it interferes with chemotherapy. ZW is free from the holy mosques in Mecca and Medina under the management of the local governments. However, ZW is also sold in shops and sometimes online which cannot be guaranteed if it is a real sample of ZW, therefore it is possible that ZW obtained from shops and online is a modified version of ZW and so it is either contaminated or poisonous [107].

3.14.2.5 Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine (TCM) including a variety of forms of herbal medicine has been used for many years in China and other parts of the world for treating various health problems such as heart and circulatory diseases, mental health disorders for example depression and anxiety, in addition to respiratory diseases, etc. TCM is also approved in China to be used as alternative therapies to treat different types of cancer [108]. Chinese Herbal Medicine (CHM) is used to help reduce side effects associated with chemotherapy, prevent cancer recurrence, enhance the body’s immune system, as well as improving the QOL

of cancer patients [109] [110]. The importance of CHM lays in its effectiveness in treating tumours with minimum side effects and low toxicity [111] [112].

3.14.2.6 Paris Polyphylla

Paris Polyphylla, also known as Multi-leaf Paris, is a flowering plant that grows up to 90 cm and produces flowers with green leaves that may reach up to 30 cm wide. Paris Polyphylla is a TCM herb that has a bitter taste, and its components are commonly used in China and other places in Asia to treat various forms of cancer and other illnesses such as infectious diseases and traumatic injuries [113]. Paris Polyphylla is known to have cytotoxic activities as well as antimicrobial, anticancer and it could reduce tumour growth [114] [115] [116].

CHAPTER 4

MEDICAL IMAGING

4.1 Systematic review of medical imaging

Following the understanding of the elements associated with breast cancer in the previous chapter, this chapter describes the topic of medical imaging and its associated aspects for the better understanding of the research audience. Medical imaging is the visualisation of the inside of the human body using different techniques and it is mainly conducted for an effective clinical examination of a specific disease [117]. Researchers have discussed various imaging modalities and processes that have been heavily in use for the diagnostic and treatment purposes and the improvement of the public health. In general, medical imaging can reduce unnecessary courses of action and the right use of medical imaging can result in the avoidance of some surgical procedures [118]. Various imaging modalities are used for diagnostic and treatment purposes and among the widely used imaging techniques are x-ray and ultrasound imaging (USI). Imaging for medical purposes is very effective and even if medical and clinical judgements are sufficient for analysing a disease, its severity and determining the correct treatment, yet the use of diagnostic imaging techniques cannot be overlooked or suppressed. Medical imaging plays an effective role in the timely confirmation, correct assessment, and documentation of many complex diseases, including breast cancer. Medical imaging has an important role in dealing with breast cancer screening, diagnosis, and treatment monitoring. Past studies have reported significant evidence that mammography has an effective role in the diagnosis of breast cancer, and it is considered as the gold standard [119]. Other imaging techniques used for breast cancer are ultrasound imaging and magnetic resonance imaging (MRI). Medical imaging plays a vital role in the detection of metastatic lesions even before the appearance of the symptoms. Timely detection and diagnosis of breast cancer is very essential for controlling the rising rate of breast cancer occurrence and the underlying factors leading to such rise. The effective follow-up of breast cancer survivors is also very important to avoid the recurrence of the disease [120]. However, like diagnosis, treatment and follow-up stages of breast cancer are still under investigation by medical researchers in the context of breast cancer and the role of medical imaging techniques. This systematic review was therefore intended to add to the

available literature through the presentation of an integrated view of the role of different types of medical imaging techniques in the simultaneous diagnosis, treatment and follow-up of breast cancer. This investigation has attempted to find out whether an individual modality can lead to specific outcomes in the overall assessment of breast cancer. This study has further examined the medical science reliance on the use of multiple modalities for breast cancer diagnosis, treatment and follow-up. Based on the discussed research context, the main aim of this systematic review is to investigate the role of medical imaging in breast cancer diagnosis, treatment and follow-up. For achieving the stated aim successfully, the current investigation has the following research objectives.

- To examine a range of medical imaging techniques through the qualitative systematic review.
- To investigate physical and mathematical aspects of image formation of these imaging techniques.
- To analyse and compare the technical performance of various imaging modalities and to evaluate the health and safety considerations in using these imaging modalities.

4.2 Medical imaging techniques

A range of medical imaging techniques has been developed for improving the outcomes of body imaging in the field of healthcare and medicine. Among these medical imaging modalities, there are various medical imaging techniques used for breast cancer screening, diagnosis, and treatment monitoring. Academic literature has identified that several current medical imaging techniques used for breast imaging principally employ the low energy and low-resolution approaches. Consequences of which are quite harsh leading to harmful effects. Studies have reported that regular use of medical imaging techniques sometimes can result in false-positive outcomes of imaging, further leading towards overtreatment and unnecessary and invasive follow-up testing [121]. Academic literature has also shown that some of the medical imaging techniques are ultimately leading

towards the development of the non-invasive methods for the tumour location and for improving the efficiency and effectiveness of the drug development programs [122]. Despite these negative sides of medical imaging techniques, past researchers have hoped and contributing too in the effective evaluation and adjustment of treatment protocols in the real-time situations to assist in the effective reorganization of the cancer drug development process [123] [124]. The academic literature given in this chapter tends to offer details of the different medical imaging techniques used for breast cancer overall assessment at different stages of the medical process. The medical imaging techniques discussed in this systematic review include, X-ray, Computed Tomography (CT), Mammography, Ultrasound Imaging (USI), Magnetic Resonance Imaging (MRI), Radionuclide Imaging, Positron Emission Tomography (PET), PET scan combined with CT scan, PET scan combined with MRI, Single-Photon Emission Computed Tomography (SPECT), SPECT scan combined with CT scan.

4.2.1 X-ray (Conventional radiography)

X-ray is the most conventional medical imaging technique used for many years for different functions [125]. Clinicians have been using X-rays for diagnosis, monitoring, and treatment of various medical conditions. X-rays are a type of electromagnetic radiation with very high energy and short wavelengths, and it can pass through the human body as well as many other objects [126]. X-rays can produce clear images of the human body from inside. Medical X-ray is used for generating images to show up abnormalities in bones and other structures and certain tissues inside the human body such as breast tissues. The significance of X-rays has been heavily addressed in the past studies with respect to the detection of early-stage breast cancers. Many of researchers have recognised X-rays as a primary imaging modality highly feasible for breast cancer diagnosis [125]. An X-ray machine produces short bursts of X-rays, as X-rays travel through the body, they also travel through a detector on the other side of the body, the detector then forms an image [127]. In the X-rays, images are produced using electromagnetic waves with wavelengths within the range of wavelength from 0.01 to 10 nanometres (nm) [128]. Electromagnetic waves capture images source

of tissues and can weigh the information to computer devices attached to the X-ray machine. The technique has had a remarkable penetrating ability, which makes it useful for the magical radiography. X-rays have played a significant role in breast cancer screening as an important imaging modality that is highly feasible for breast cancer diagnosis [129]. Chest X-rays are also used to monitor how the disease is responding to treatments and to monitor other conditions like if there is pneumonia or inflammation in the lungs [130]. Medical X-rays are safe when it is used with care and in general the lowest amount of radiation, necessary to get the required results, is used. A contrast medium is used in contrast X-rays to show blood vessels and other fluid filled and hollow structures that do not usually show up on X-ray. X-rays are categorised into hard and soft X-rays based on the levels of photon energies. High photon energies have short wavelength and great penetrating power are known as hard X-rays. On the other hand, soft X-rays are lower energy with longer wavelength and less penetrating power [131]. Hard X-rays are usually used in medical X-rays imaging. Contrary to the past practices, clinicians in the present era have started using X-rays as an integrated part of other medical imaging techniques such as mammography. At the start of the 20th century, X-rays were identified as highly effective medical imaging techniques used for the treatment of breast cancer especially in the surgical removal of breast tumours. However, the technology needed to refine itself to give improved contrasts due to the low density of breast tissues and the weak absorption of standard energy X-rays and the fact that diagnosis of breast cancer lesions is highly challenging for clinicians with the conventional X-rays methods being only able to capture straight images without any dimensional views. However, modern X-ray images have resolved this concern by presenting two-dimensional as well as three-dimensional views of the various human body parts [132]. An X-ray is a painless and quick test used to examine the bones and the teeth, the chest, and the abdomen. Chest X-rays are reported to be the most commonly used medical imaging in the emergency departments [126]. On X-rays, bones and dense tissue show up as white, muscles and fat show up as shades of grey and the air shows up as black. The most common views of the chest X-ray are posteroanterior (PA) view and lateral view. The anatomy of the chest is well demonstrated in the PA view. PA view of the chest examines the bony thoracic cavity, the heart and the

lungs, the great vessels and the mediastinum. PA and lateral chest X-ray are the standard chest examination and are usually read together. However, lateral chest X-ray is more difficult to interpret [133]. Lateral chest X-ray is taken from the side of the patient, and it similarly gives valuable information on the bony thoracic cavity, the heart, the lungs, the pericardium, the pleura, the mediastinum and the upper abdomen. The following image **Fig. 2** is the normal chest X-ray (CXR) of a young woman in the PA view demonstrating normal shape as well as size of the chest (thoracic) wall and the contents of the thorax [134].

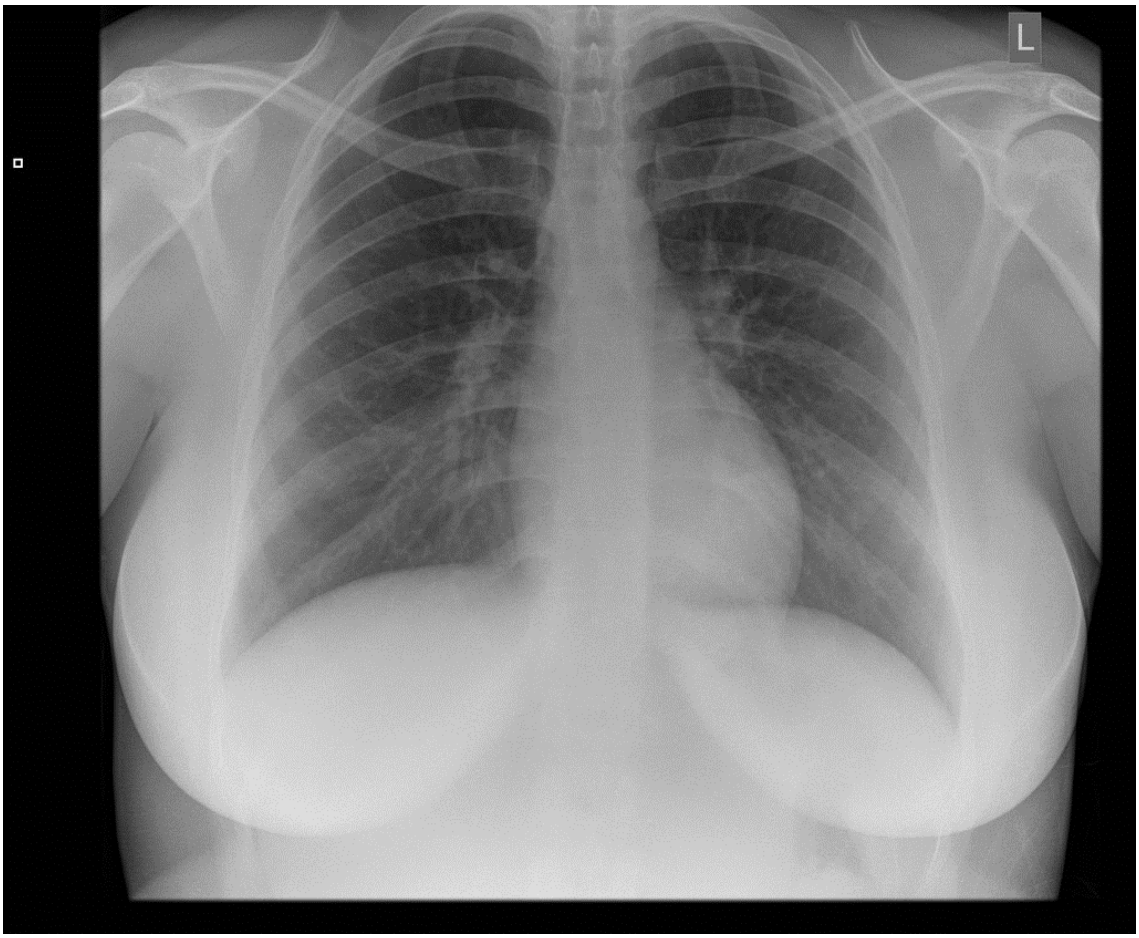

Figure 2 Normal chest X-ray (CXR) of a 23-year-old female in posteroanterior (PA) view [134]**.**

4.2.2 Mammography (Mammogram)

Mammography is recognised as the gold standard imaging method used for breast cancer detection [119]. Mammography is a simple X-ray examination of the human breast, and it refers to the specific type of X-ray imaging which produces images based on the low dose of X-ray system specifically designed for the creation of detailed images of the human breast. Mammography is performed on a specific X-ray machine through which each breast is X-rayed separately. During the mammography examination, the breast is positioned on a parallel plate and compressed firmly but gently with a plastic puddle. Mammography functions by evening out the breast thickness. The technique also helps in reducing X-ray distribution. The image processing protocol of basic mammography is based on the 2D views of the breast [135]. The following image **Fig. 3** shows annotated mammograms of a normal breast [136].

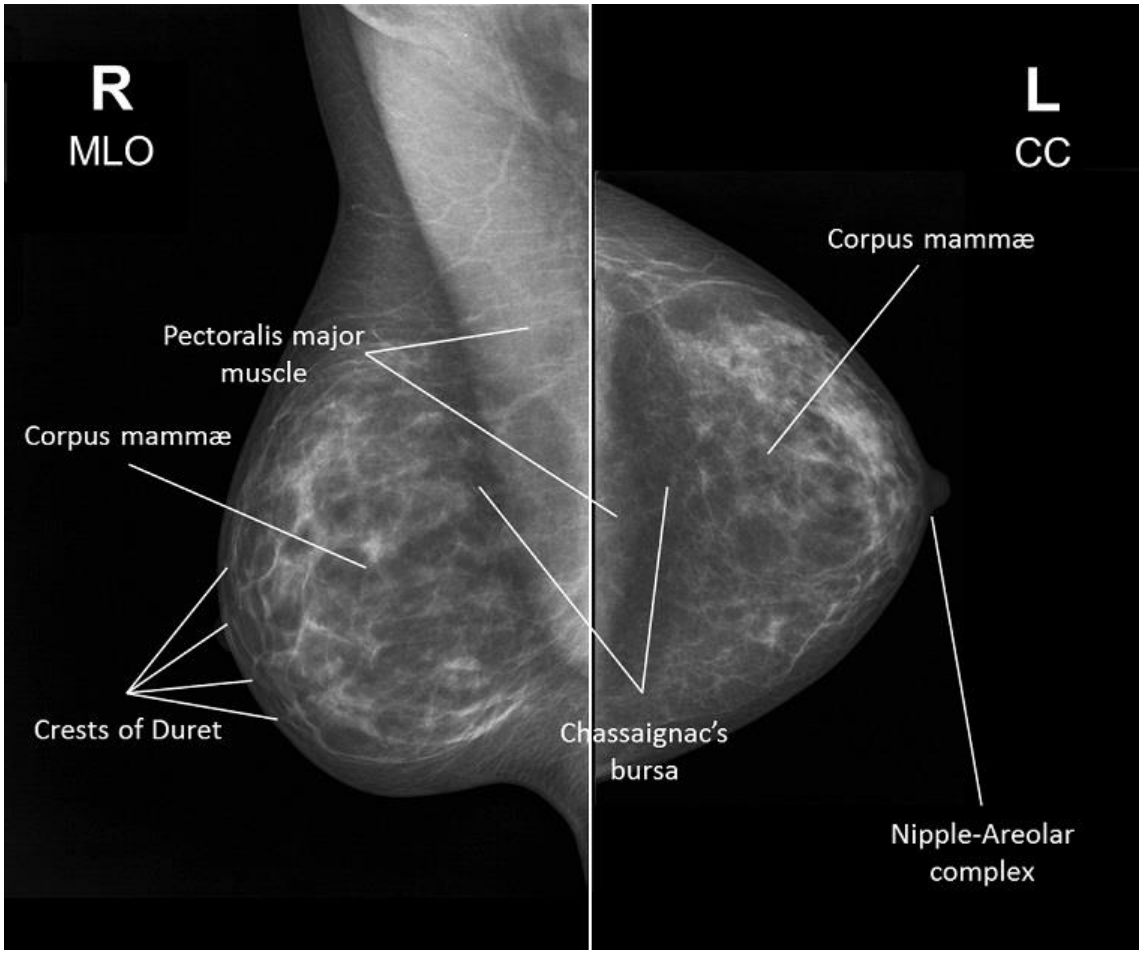

Figure 3 Labelled normal mammograms [136]**.**

In a routine screening mammography two X-rays are taken at different angles, head to foot (craniocaudal (CC)) view and angled side (mediolateral oblique (MLO)) view [137]. CC view and MLO view are the standard views on mammograms. The importance of using mammograms is that it can detect breast cancer in women with or without signs and symptoms of the disease. Mammograms can spot cancers that are too small to be seen or felt. However, basic digital mammography is not identified as a useful tool for the determination of benign and malignant tumours with high-level certainty. For this reason, false-negative (when a mammogram looks normal whereas cancer is present) and false-positive (when a mammogram looks abnormal whereas no cancer is present) results may occur using mammography. In order to deal with such complicatedness, advanced medical imaging techniques have been developed such as the following three recent advances in mammography:

- Digital mammography or full-field digital mammography (FFDM).
- Computer-assisted diagnosis or computer-aided detection (CAD).
- Breast tomosynthesis or digital breast tomosynthesis (DBT), also known as three-dimensional (3D) mammography.

However, other advanced medical imaging techniques have also been developed and used besides mammography for the overall assessment of breast cancer.

4.2.3 Computed tomography (CT)

Computed Tomography (CT) which is also known as computerised tomography or computerised axial tomography (CAT) is a medical imaging technique that uses X-rays to obtain medical images. A CT scanner has an X-ray source and a detector as well as a flat motorised bed for patients to lie on. The flat bed passes through a large rotating ring of the scanner. The ring does not surround the whole body, but a small section of the body as the patient passes through it. When the CT scan rotates, the X-ray source and the detector both rotate, and a series of X-ray pictures of the body are taken from different angles. A computer is then used to put the pictures together to produce a detailed 3D image [138]. A contrast

medium which is a special dye is given to the patient to assist improve the image quality. CT scan plays an important role in breast cancer diagnosis, treatment and monitoring including examination of the tumour size during and after treatment. The contrast medium of the CT scans of the chest can show up the tissues and blood vessels around the breast cancer which helps to see if the tumour can be removed by surgery [139]. The following image **Fig. 4** shows the CT image of the normal chest appearance (axial lung window) of a 35-year-old woman [140].

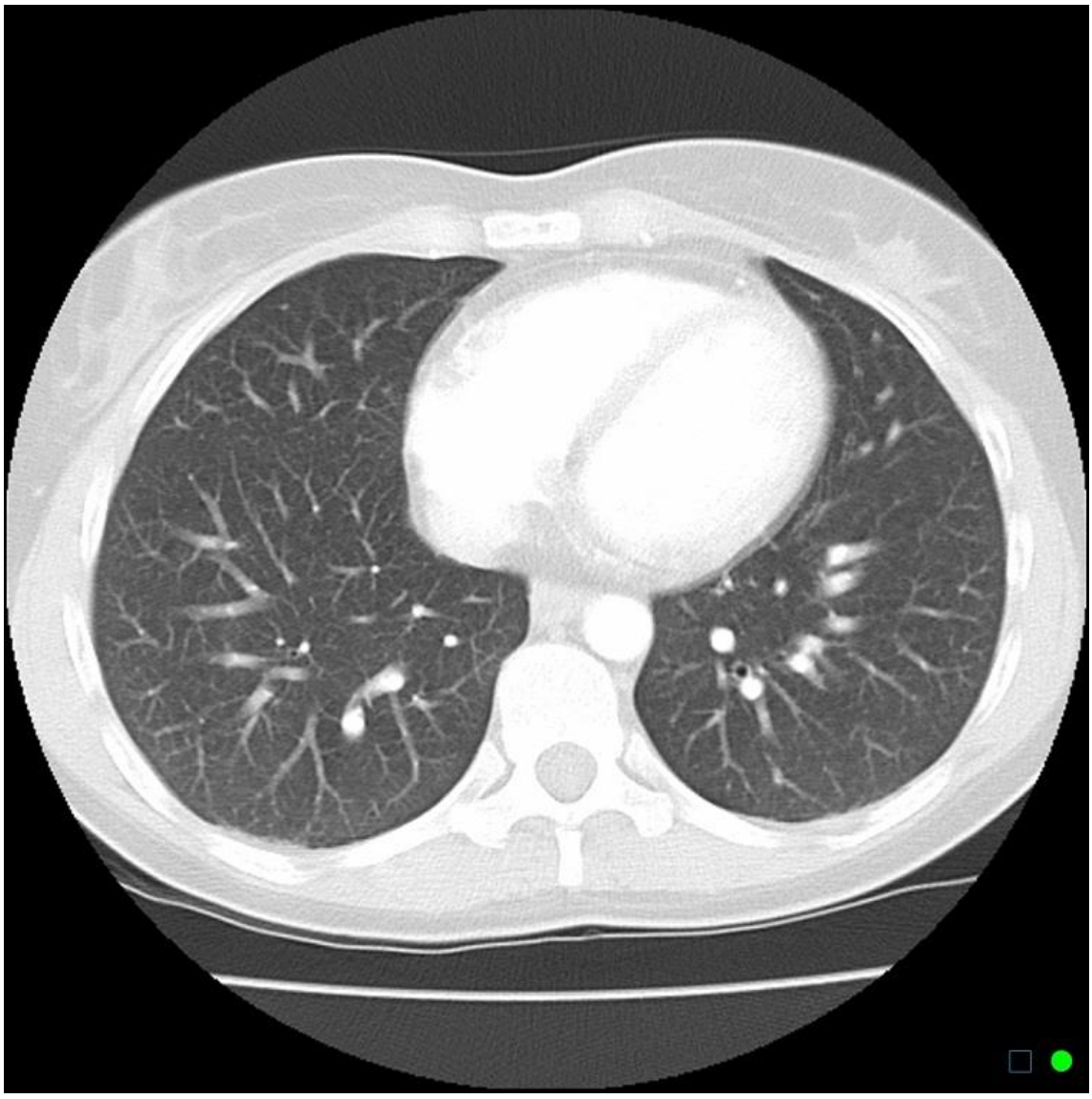

Figure 4 Normal chest on CT (lung window) in a 35-year-old female [140].

4.2.4 Ultrasound imaging (USI)

Ultrasound imaging (USI) which is also known as sonogram is identified as one of the most used medical imaging techniques worldwide due to its immense qualities of detection and characterisation of all breast abnormalities. Past studies have highlighted the emerging role of ultrasound imaging for the effective clinical diagnosis of breast cancer. USI scan generates images of the inside of the human body using high frequency sound waves [135]. The novel developments in ultrasound analysis such as highly sensitive colour Doppler and power Doppler ultrasound machines which have further raised the level of ultrasound significance for clinicians as well as patients. Such techniques are capable of detecting the flow inside solid masses through the provision of high-resolution images. USI is widely used in the evaluation of the breast in breast cancer patients, and it is often used after an abnormality is spotted on a screening mammography or when a lump is felt during breast self-examination (BSE) or clinical breast examination. To be noted is that BSE or clinical breast examinations do not provide a definitive diagnosis of breast abnormalities. Likewise, breast ultrasound imaging can generate medical images of the parts of the breast that cannot be seen on a screening mammogram. Importantly, breast ultrasound imaging is also able to find out if a breast lump is a solid mass or a fluid filled cyst [41]. USI has a small handheld device known as ultrasound probe which is placed on the breast and moved over. The probe gives off high frequency unheard sound waves. The sound waves generate echoes when they bounce off the inside of the breast. The probe then picks up the echoes and turns them into a moving image displayed on a monitor at the same time as the scan is conducted. Ultrasound imaging is also used in breast ultrasound guided biopsy which is a type of biopsy that uses real time ultrasound images to visualise abnormalities and lumps in the breast, while a thin needle is inserted into the lump. The tissue removed from the lump is later analysed [141]. The normal scanning technique for breast ultrasound uses the radial and anti-radial scanning planes. Scanning starts at the nipple and radiates out. A clock face or quadrant is used for location description, and for each breast there is a separate clock. The nipple is in the centre of the clock for both breasts as shown in **Fig. 5** [142]**.**

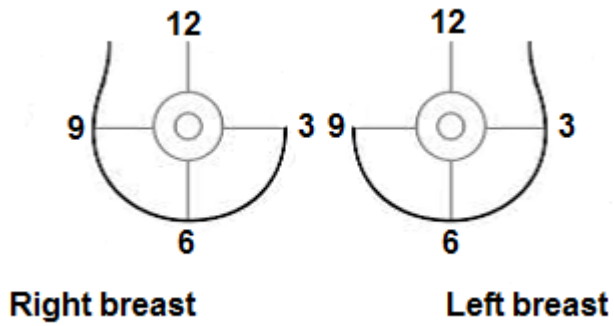

Figure 5 Radial and anti-radial scanning planes [142]**.**

The following image **Fig. 6** is the normal ultrasound image of the right breast of a 50-year-old female with no history of masses or clinical issues [143].

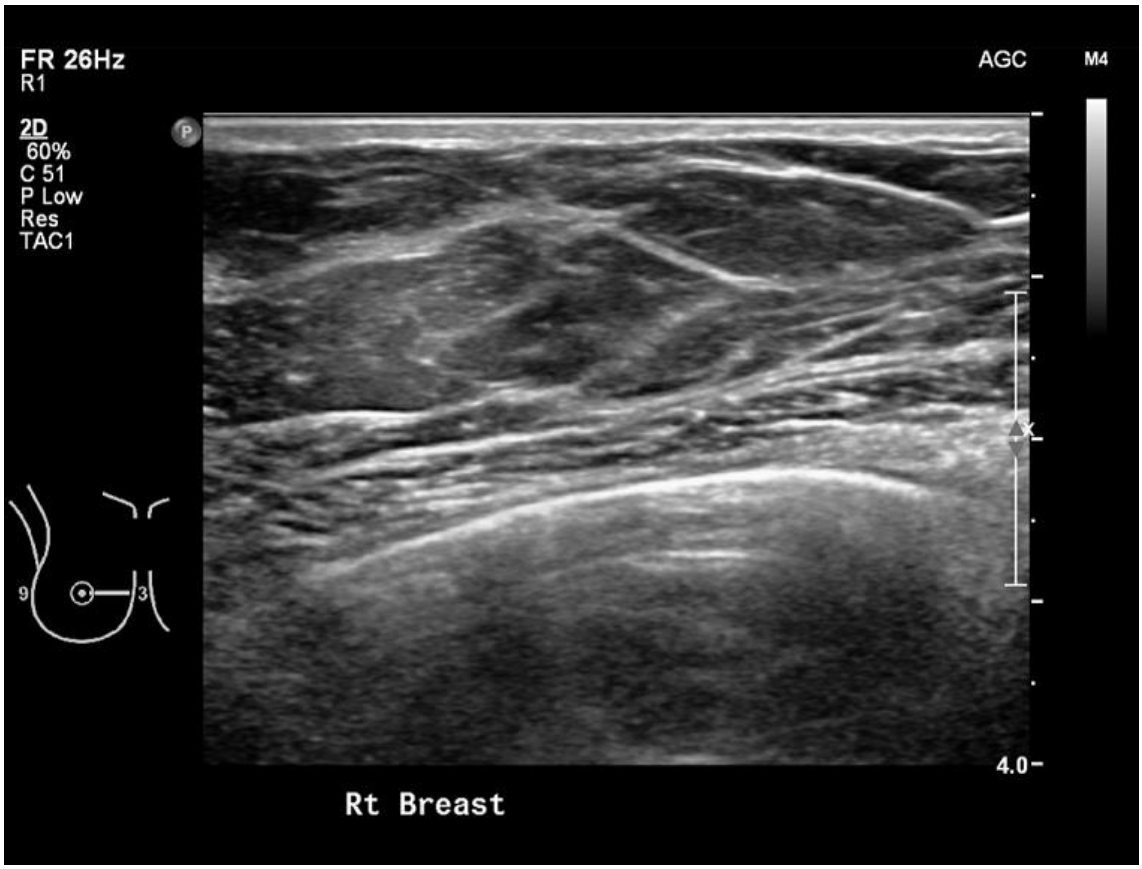

Figure 6 Normal breast ultrasound of the right breast at 3:00 o'clock [143]

Ultrasound imaging is also reliant on the measurement of the tissue elasticity. The technique is helpful in measuring the elasticity of the breast tissues through

an extended form of tissue to provide important diagnostic information that can be used to reduce the number of benign breast biopsies [144]. Automated whole breast ultrasound techniques have been developed for the acquisition of high-quality images in 3D form. This has made ultrasound as unique as the other 3D imaging techniques. The data obtained from the 3D ultrasound screening helps in good interpretation at the right time to give the opportunity to reduce the recall rate, sensitivity, specificity, and positive predictive value essential when dealing with large volume datasets [145]. Clinicians typically need visual qualitative assessment for analysing the imaging performance and for the comparison of the data gathered through different ultrasound imaging probes and modalities and that the information gathered through ultrasound imaging is gathered using the high-level protocol with the ultrasound technique's protocols being based on complete and open research and development systems. Researchers have identified that when ultrasound imaging is used with other modalities such as mammography can result in the detection of multifocal breast tumours as the capability of ultrasound modality in detecting additional cancers is vital for understanding the overall medical condition [146]. The common USI transducer frequencies are approximately between 2.0 to 15.0 megahertz, with 7.5 MHz being typically used for breast ultrasound examination [147]. Likewise, the variety of transducers in different shapes and sizes also help in dealing with the timely diagnosis of the lesion in different types of patients such as pregnant women, men, older patients and others. Ultrasound screening is quite easy to use, and it is a less expensive imaging technique compared to other imaging techniques. The clear imaging of all the breast tissues obtained via ultrasound imaging further makes it a complementary imaging technique with a high level of spatial resolution and real-time imaging useful for the effective detection of breast lesions as well as monitoring of patients [148]. On the contrary, the disadvantages of using ultrasound imaging technique cannot be undermined while assessing this medical imaging modality. Past studies have shown that ultrasound waves can easily be disrupted by air or gas and only for this reason an ideal imaging technique for the air-filled bowel or organs is not possible through the ultrasound technique. Therefore, past studies have identified the challenges associated with the removal of speckle noise in order to retain the significant image

characteristics. However, the modern ultrasound equipment is helpful in dealing with the issues of image quality and diagnostic values in the real-time. The ultrasound technique is recognised as one of the vital technique in the academic literature used for the detection of the breast lesions. The way ultrasound images are generated needs to be assessed in more detail in relation to other imaging modalities such as magnetic resonance imaging (MRI). In the understanding of MRI images, it is extremely necessary to look after the interaction of the beam with the matter, their modes of operating, beam shape and digital processing. The use of ultrasound imaging in the detection of breast cancer at different stages of screening, however, requires further analysis of its mathematical properties and its technical aspects. The properties need to be assessed for the effectiveness of modalities individually as well as collectively.

4.2.5 Magnetic resonance imaging (MRI)

Medical imaging resonance (MRI) is also identified as a highly exceptional medical imaging technique, which is very useful in the timely detection of breast cancer. MRI has been treated as both conventional and modern approach, which is clinically useful for the provision of the volumetric three-dimensional anatomical information as well as physiological information [119]. Magnetic resonance imaging (MRI) uses radio waves and a powerful magnetic field to generate very detailed cross-sectional images of the inside of almost any part of the body. MRI is indicative of the increased vascular density and vascular permeability changes occurring in affected breasts. Past studies have reported up to 100% sensitivity for MRI in detecting invasive cancers [149] [150]. MRI scan is a painless and one of the safest available medical procedures [151]. The MRI scanner has a large tube that has strong magnets inside. The MRI machine used for breast screening is known as MRI with dedicated breast coils. During the scan, the patient lies face down on a flat table inside the MRI tube, with the breasts hanging down into an opening in the flat table. MRI is used as a supplemental tool with mammogram or sonogram in breast cancer screening in young women with dense breast tissue, high risk individuals and those who carry BRCA mutations [152]. MRI is used in patients with breast cancer to help measure the tumour size and to find if

there are other tumours in the breast. MRI can sometimes tell if a tumour is malignant (cancer) or benign (not cancer). Other advantages of using MRI for medical imaging include its non-ionising nature, which helps in the identification of multiple focal cancers easily, even in situations where the cancer is associated with the chest wall. MRI has also been used for assessing cancer recurrence in women who have undergone lumpectomy and it can be used by clinicians for making detailed observations of breast implants and ruptures [119]. MRI can show up soft tissues very clearly, however Gadolinium (Dotarem) contrast (dye) injection is used for MRI scans to detect the pathology of the lesions and to assess their biological features [22]. Gadolinium is a clear colourless fluid that makes the images clearer to show the tissue details and it is injected intravenously before or during the scan. The MRI scan results can help in diagnosing conditions, treatment plans and assessing the effectiveness of the previous treatments [151]. Like every other medical imaging technique, the use of MRI is also associated with some image acquisition. Typical breast imaging protocol in MRI modality can be categorised into four stages. In the first stage scout images are obtained in (~1 minute) and are used for localisation purposes. The second stage is pre-contrast (~5-7 minutes) T1-weighted no-fat suppression and T2-weighted with fat suppression are measured, in addition to high resolution 3D T1-weighted fat suppressed gradient-echo sequence. The third stage is of post-contrast in which 3 to 5 volume acquisitions are obtained in (~10 minutes). When such images are obtained, the pre-contrast and post-contrast images are compared and must have identical parameters for allowing subtraction. The last stage of image acquisition is analysis of subtraction of pre-contrast and post-contrast images for the identical image parameters with an aim to identify enhanced lesions. The enhancement patterns are used for making the evaluation of the dynamic contrast. Analysis is further carried out through the maximum intensity projection (MIP). Studies have highlighted that there is a need to have a set of contrast-enhanced pulse sequence at different phases for acquiring identical images [153] [154]. The following image **Fig. 7** shows the axial T1-weighted (T1W) MRI image of a 25-year-old woman with discharge from the left nipple, suggesting intraductal papilloma (small benign tumour that has formed in the left milk duct in the breast) [155].

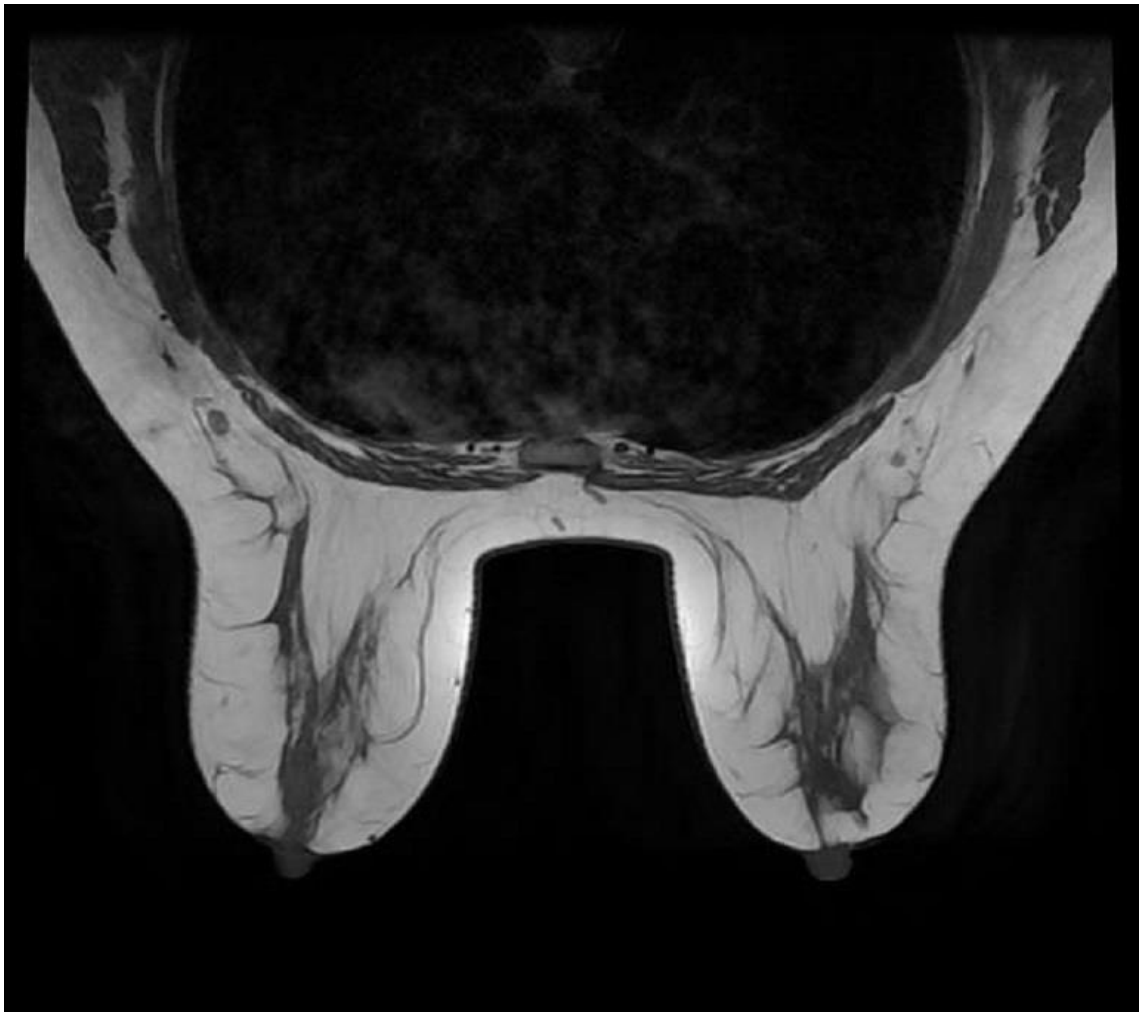

Figure 7 Axial T1-weighted MRI image demonstrating left breast intraductal papilloma in a 25-year-old woman with discharge from the left nipple [155]**.**

Researchers have also identified the risks and limitations associated with MRI protocols for provision of effective MRI scanning. Although the MRI process itself is painless it may involve certain aspects, yet it may lead to higher levels of discomfort for patients. These protocols include three key steps focusing on screening procedures, information to subjects upon termination of the session, and the provision of disposable earplugs or ear protection against the loss of hearing. MRI has been heavily investigated for its safety and biological effects due to the exposure of patients to electromagnetic fields under this medical imaging technique. The biological effects and safety in using MRI has been addressed in the past studies and mentioned that unnecessary examinations

need to be avoided for reducing the risk levels and employing precautionary principles have further been suggested [156] [157]. The following image **Fig. 8** is the axial T2-weighted (T2W) fat-saturated (FatSat) MRI image of the same patient in **Fig. 7** that has left breast intraductal papilloma showing up to 90% to 100% accuracy.

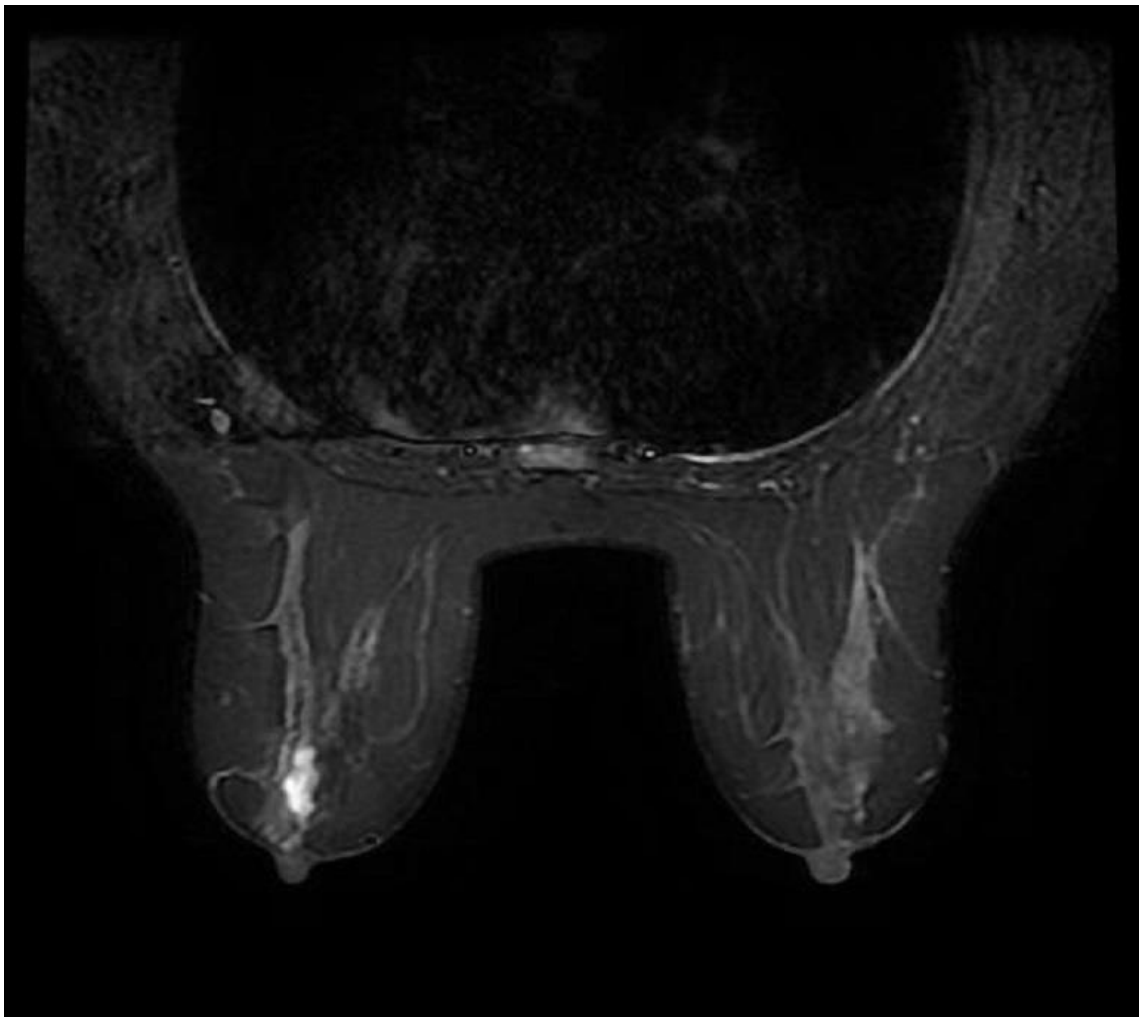

Figure 8 Left breast intraductal papilloma MRI (axial T2 fat sat) image of the same patient in **Fig. 7** [155]

4.2.6 Radionuclide imaging

Radionuclide imaging or nuclear medicine scanning is a medical imaging technique used to visualise the inside of the body by using a small amount of radioactive chemicals called radiotracers that are injected into the body [158].

The radiotracers accumulate in the body, and they give off energy in the form of gamma rays. Gamma cameras are then used to detect this energy and generate detailed images. Radionuclide imaging is a very effective diagnostic technique as it can show the structure and the physiological function of different parts of the body. Researchers have identified the effectiveness of radionuclide imaging techniques in visualising the lesion sites as well as the reflection of specific biological and functional imaging features of the lesions. The features of these lesions include metabolic activities, the status of receptors, as well as perfusion, etc. [159] Radionuclide-based methods are identified as molecular imaging modalities which have potentials in the detection and characterisation of breast lesions. Such techniques have enhanced the ability of the clinical procedures for gene expression, protein expression as well as for investigating the cellular biochemistry [160]. Researchers have emphasised on the role of nuclear medicine in monitoring the therapy response, the progression of the disease, as well as recurrence of the cancer [161]. Moreover, clinicians have investigated the use of radionuclide imaging techniques with other modalities such as MRI or CT to produce hybrid imaging modalities to increase the resolution and sensitivity of this specific medical imaging technique vital to increase the diagnostic confidence. The radionuclide imaging techniques used for breast cancer include various forms of nuclear medicine scans such as positron emission mammography (PEM), breast-specific gamma imaging, and scintimammography which is also called nuclear medicine breast imaging or molecular breast imaging (MBI). MBI is not a screening tool for breast cancer but a supplemental investigative tool to investigate a breast abnormality detected on mammography. During the exam, the radioactive tracer (technetium-99m (Tc-99m) sestamibi) is given to the patient intravenously [162]. Imaging must start immediately after the radioactive tracer injection, and it takes about 40 minutes. A special gamma camera is used to scan the breast from several angles. The radioactive tracer used is taken up more by the cancer cells than the normal breast tissue. MBI can help in reducing unnecessary procedures and it is defined as an appropriate imaging modality in patients with dense breast tissue [158]. Past studies have highlighted that MBI is superior to normal screening mammography in detecting breast tumours by up to 3 times in patients with dense breast tissue [129].

However, MBI is an expensive imaging modality, with the procedure taking longer times, in addition to higher radiation doses. Past studies have confirmed the role of nuclear medicine in breast cancer assessment and that radionuclide imaging is efficient in highlighting the risk of complications with cardio functions and the assessment of cardiotoxicity resulting from chemotherapy and chemoradiotherapy in breast cancer patients [163]. Evidence is also present for the effectiveness of this imaging technique for the axillary sentinel lymph node (SLN) detection in breast cancer [164].

4.2.6.1 Positron emission tomography (PET)

Positron emission tomography scan is a nuclear medicine scanning technique that uses radioactive tracers to show the activity of the tissues and organs inside the body [50]. PET scan can detect cancer cells and tissues before they show up on other imaging techniques. PET scan is useful for evaluating breast cancer in patients diagnosed with the disease, it can also determine how far the disease has spread to the other parts of the body and how well the disease is responding to treatments. In most PET scans the radioactive tracer used is known as fluorodeoxyglucose (FDG). FDG is glucose with one oxygen atom replaced by a fluorine-18 (^{18}F). Fluorine-18 (^{18}F) is a radioactive isotope of fluorine, and it is an important source of positrons. The chemical activity of the cancer cells is higher than healthy cells because cancer cells grow at a faster rate, therefore cancer cells take up more of the FDG tracer than normal tissue. The FDG tracer settles in the cancer cells and releases positrons that can be detected by the PET scan. During the procedure, the radioactive tracer is given to the patient through an intravenous injection and then the patient lies still on a flatbed that is moved into the large circular scanner. A special camera is then used to scan the body to produce detailed 3D images [8]. In general, a PET scan scans the whole body which can help to see if cancer has spread to the other parts of the body. The PET scan used for breast imaging is known as positron emission mammography (PEM). The positron detecting plates are like the compression system used in mammography, however PEM scan does not require compression. During the scan, the breast is placed gently, and two small movable flat detectors are used

by the PEM cameras. The flat detectors are pressed against the breast directly [50]. PEM has demonstrated a better sensitivity particularly for small lesions detection [17]. Hybrid imaging has been introduced to combine PET with CT or with MRI into one single machine. When radionuclide imaging is combined with CT or MRI, special views are produced due to image fusion [8]. The image fusion shows information from two different scans on one image allowing more accurate information. The following image **Fig. 9** is the axial PET/CT fusion image of a 35-year-old lactating woman with lymphoma (swollen lymph nodes and lumps). The image shows normal physiological Fluorine-18 (^{18}F) FDG uptake in both lactating breasts [165].

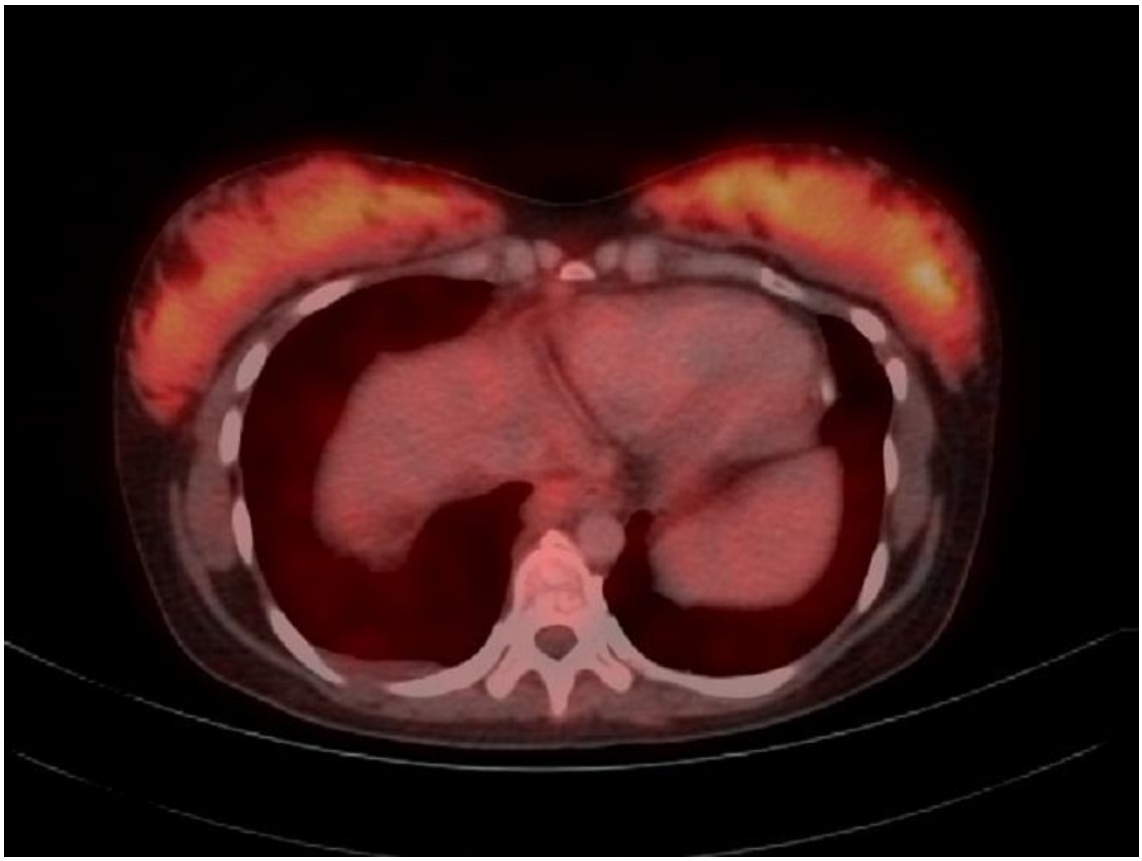

Figure 9 Axial Fluorine-18 (^{18}F) FDG PET/CT fusion image [165]

To be noted is that the process of producing breast milk (lactation) for pregnant or women giving birth, is normal. Hormones signal the mammary glands to produce milk. For staging workup of lymphoma, Fluorine-18 (^{18}F) FDG PET-CT was performed in this patient. Hybrid imaging machines can provide more precise

diagnoses than the two imaging techniques carried out separately. PET scans measure the function of the body tissues and organs to help evaluating how well they are functioning. The following image **Fig. 10** is the axial contrast-enhanced CT in the portal venous phase of the same patient in **Fig. 9** [165]. To be noted is that in the portal venous phase the contrast agent is mostly in the veins.

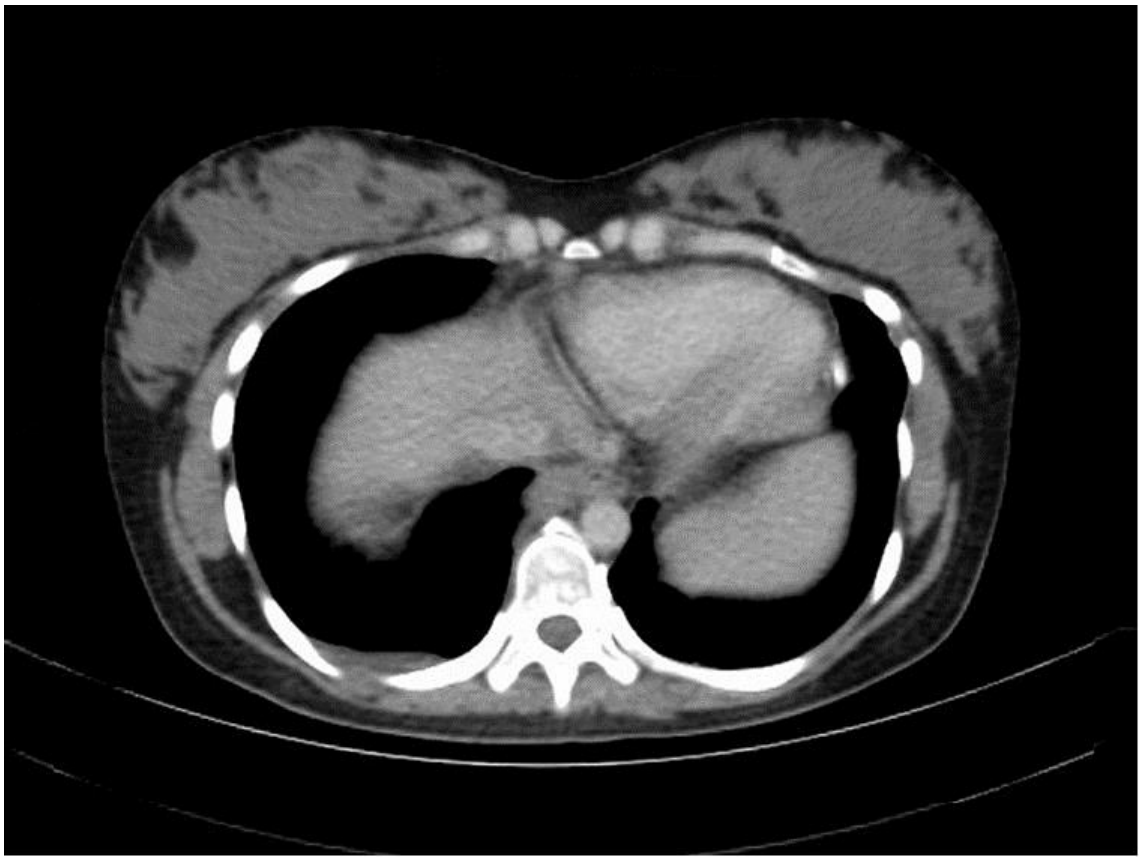

Figure 10 Axial contrast-enhanced CT in the portal venous phase [165]**.**

While CT scans provide excellent anatomical information. A PET/CT scan can reveal information about both the function and the structure of the body tissues and organs during one single scanning session. The registered images can be viewed through a focused colour display for any cross-sectional view [166]. In breast cancer imaging PET/CT scans are carried out to detect the disease and used as part of staging to check for metastasis of the cancer to other areas of the body. PET/CT is also used to assess the treatment effectiveness besides breast cancer recurrence after treatment. Likewise, PET/MRI hybrid imaging combines metabolic information of the body tissues and organs provided by PET scanning

and excellent soft tissue contrast provided by MRI. The excellent soft tissue contrast provided by MRI is very important as PET imaging on its own provides little anatomical information with low spatial resolution which makes it difficult to localise the lesion and give the correct evaluation of the spread of the disease to the surrounding tissues. PET/MRI can also provide an improved differentiation of malignant and benign breast tumours [167].

4.2.6.2 Single-photon emission computed tomography (SPECT)

Single-photon emission computed tomography (SPECT) is a radionuclide imaging technique that uses a radioactive tracer to generate pictures of the body's internal structures and organs. The radioactive tracer is given to the patient intravenously, usually 20 minutes or more before the scan [168]. The body tissues that are more active will take up the radioactive substance more than the normal tissues. The SPECT scanner is a large circular machine, during the scan, the patient lies on a table inside the machine. A special camera that rotates around the body is used to produce 3D images. These images can show colours of the body parts that have absorbed less of the radioactive substance and the body parts that have absorbed more. SPECT scan provides functional information of the selective absorption of the injected radioactive tracer by the cancer cells. This information helps to find tumours that are missed on other imaging techniques. However, with the images produced by SPECT it is hard to measure the precise location of the tracer uptake as these images do not provide enough anatomical framework. Therefore, SPECT scanner has been combined with CT scanner in one single scanning device to produce hybrid SPECT/CT scanners, as CT scan can offer precise anatomical information [169]. SPECT/CT as a combined image can provide information in more detail, it allows more accurate identification of lesions by combining the functional information provided by radionuclide imaging SPECT and the anatomical information provided by CT. In patients with breast cancer, SPECT/CT is used for the diagnosis, staging and follow-up of the disease, due to the increased diagnostic specificity and sensitivity of the radionuclide imaging SPECT and the anatomical information provided by CT [170].

4.2.7 Medical image analysis

The role of medical image analysis has been significantly identified by medical researchers to identify the effectiveness of these technologies in helping clinicians for the effective risk assessment of cancer, detecting tumours, diagnosis, and treatments of the different types of cancer. Researchers have highlighted that medical image analysis is able to conduct quantitative image analysis of breast cancer. Their ability to analyse breast images has been explained through the range of characteristics such as morphological attributes, textural attributes, and kinetic attributes. Breast image analysis techniques help in segmenting, future extracting, classified designing, biomechanical modelling, registering images along with the attribute of correcting motions [171]. Examination of the effectiveness of medical image analysis techniques has further substantiated the ability of these techniques and has assisted clinicians with effective medical image registration and fusion processes. Medical image analysis techniques are also used for the diagnosis and the subsequent follow-up stages in order to optimise the decision-making process about appropriate therapies needed for dealing with patients' conditions. These techniques have been identified as helpful for making the fusion of different imaging modalities by combining main characteristics of each of modality. However, clinical researchers have confirmed the need to carry out trials-based studies in order to confirm the effectiveness of the medical image analysis techniques for dealing with breast cancer patients experiencing different stages [172].

4.2.8 DICOM standard and Merge PACS

Digital Imaging and Communications in Medicine (DICOM) is the international standard protocol used for managing and transmitting medical images and related information exchanged between medical imaging modalities from various healthcare centres and computers to be used in healthcare, research and education. With DICOM, high resolution digital images generated by DICOM-compliant modalities (such as CT, MRI, and USI) are integrated into a Picture Archiving and Communication System (PACS) imaging system (such as Merge PACS). Merge PACS is used for processing, reading, reporting, and displaying

medical images and it is used in this work for presenting the medical images of the discussed cancer cases obtained from the various hospitals attended during this research program [173] [174].

4.2.9 Medical image quality

The following table (**Table 1**) shows the spatial resolution of the medical images obtained via the medical imaging modalities discussed in this research.

Table 1. Spatial resolution

Medical imaging modality	Spatial resolution
X-ray	High
Computed tomography (CT)	Very high
Mammography	High
Ultrasound imaging (USI)	Very high
Magnetic resonance imaging (MRI)	High
Radionuclide imaging (PET, SPECT)	Low

Spatial resolution refers to the pixel numbers used for the construction of the digital images. The quality of the digital images is determined by the spatial resolution with the ability to distinguish between two adjacent objects. Spatial resolution in digital imaging depends on the size of the pixels used. Large pixels are unable to distinguish between two adjacent objects in comparison to small size pixels. Digital images composed of more pixels are higher spatial resolution images of the same dimension and imaging part [175].

4.2.10 Artificial intelligence (AI) and breast cancer imaging

Medical imaging modalities such as mammography can help detect breast cancer especially in women who do not have any signs and symptoms of the disease. However, past studies have highlighted that false-negative and false-positive

results may occur using basic digital mammography [176]. In order to solve such breast imaging issues, advanced medical imaging techniques were developed such as full-field digital mammography (FFDM), computer-aided detection (CAD, and digital breast tomosynthesis (DBT) for better visualisation of the breast tissue. The following images **Fig. 11** are the unilateral mammograms of a middle-aged woman with invasive breast cancer in the right breast demonstrating digital breast tomosynthesis being added to standard mammography.

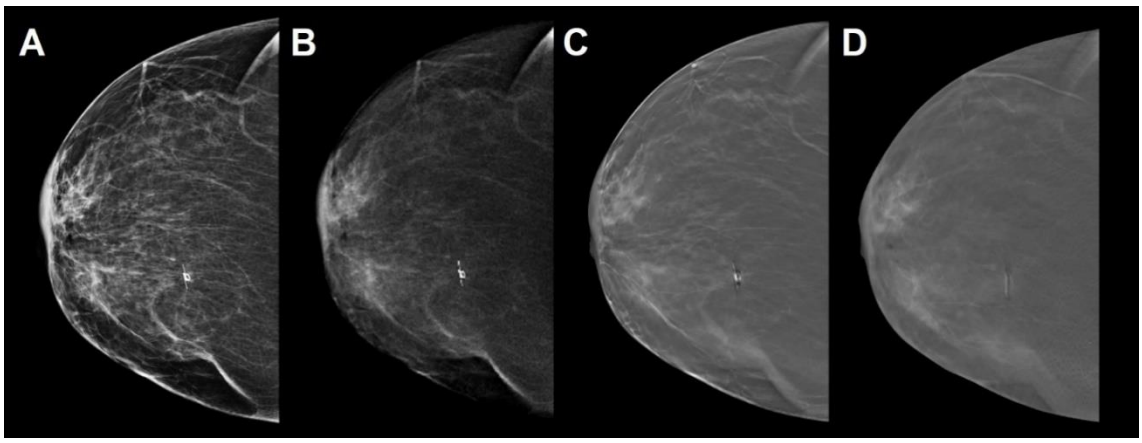

Figure 11 Unilateral mammograms of a middle-aged woman with invasive breast cancer in the right breast (A) Right 2D mammogram craniocaudal (CC) view. (B), (C) and (D) RCC breast tomosynthesis images (different slices).

Though, these advanced techniques still had false results [177] [178]. Additionally, while medical images are read by radiologists or those reporting images, it is possible that they misread medical images and fail to diagnose medical conditions or cancers which may have serious consequences on patients. Various factors such as radiologist's lack of knowledge and other human errors including errors of overreading may contribute to missed diagnoses [179]. The use of artificial intelligence (AI) in medical diagnostics particularly in medical imaging such as breast cancer imaging can significantly improve the patient quality of care and help minimise misdiagnoses and achieve high accuracy [180] [181]. A standard mammogram is performed in combination with tomosynthesis to produce 3D images and it was approved to be optionally used in the NHS breast screening programme (BSP). NHS mammographers require certain

trainings before using digital breast tomosynthesis in the clinic. Radiologists and those reporting images are also required to take trainings before they start reporting digital breast tomosynthesis images. DBT as well as FFDM and CAD allow improved breast visualisation, however these techniques still suffer from the high number of false positive results per analysed image. Moreover, medical images taken via these advanced techniques may also miss tumours that are present in patients due to human errors and cancers may not be visible to radiologists as a result of many factors including tiredness or loss of concentration [179]. In the last few years, scientific studies have concentrated on the application of AI in the field of breast cancer imaging. Artificial intelligence (AI) in breast cancer imaging by the use of machine learning algorithms to detect changes in breast mammograms with less missed tumours is developed to help radiologists in breast cancer screening programmes through various ways including replacing at least one of the mammography readers. AI can offer many advantages due to the fact that it is a computer image recognition, and it does not get tired or lose concentration. The AI use within the NHS BSP is currently under discussion by the UK National Screening Committee (UK NSC). Researchers in the UK have already secured funding from the government through the AI in Health and Care Award in partnership with the National Institute for Health Research (NIHR) and NHSX to test and evaluate the use of AI for breast cancer screening in NHS hospitals [182]. Past studies have reported that the use of AI in the detection of breast cancer showed improved diagnostic performance in comparison with radiologists as human readers, as well as substantial improvements in the performance of the readers when assisted by AI [180] [181]. According to the UK NSC review on the use of AI for image analysis in breast cancer screening, the current breast screening pathway in the UK is explained as in the following image **Fig. 12** [183].

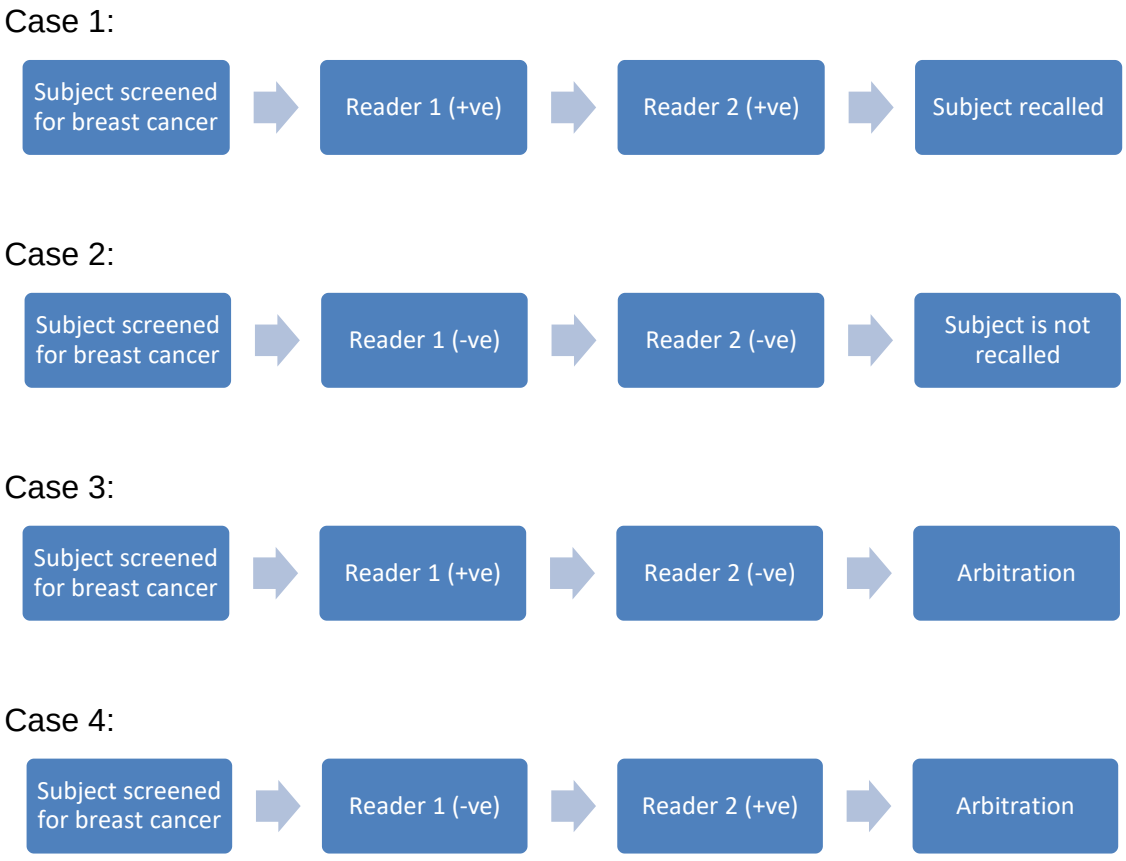

Figure 12. The current breast screening pathway in the UK. Case 1 when the subject tests positive by both readers, she is recalled for further tests. Case 2 when the subject tests negative by both readers, she is not recalled for further tests. Case 3 and 4 when the subject tests positive by either reader 1 or reader 2, arbitration is employed.

According to the UK NSC it is explained that AI is proposed to be used in the current breast screening pathway as the following:

- To be used as a pre-screening tool removing clear normal cases.
- To completely replace reader 1 and reader 2.
- To replace reader 2.
- To aid decision-making for one or both readers.

Likewise, more research is needed to provide evidence and approve each proposed AI use in the current breast screening pathway. To be noted is that researchers in the UK have secured funding from the government to do more research on the application of AI in breast cancer screening within the NHS. However, this work proposes that the application of AI strongly needs to be used as an assistive tool in medical imaging, not to totally replace human readers and radiologists with focus on gradual transformation considering all risk areas that may be caused by AI.

CHAPTER 5

CLINICAL OBSERVATION

5.1 Clinical observation sessions attended as part of this research

One of the main objectives of this research was to be placed at hospitals to attend clinical observation sessions for different medical imaging techniques used in cancer detection and diagnosis and also to obtain a number of medical images of breast cancer and other types of cancer. Different cases were allocated from different hospitals in the UK and abroad. The clinical sessions were very useful to gain an insight into clinical practice experience within medical imaging units of large teaching hospitals. The clinical experience was mainly based on observation, where, during the clinical sessions, radiographers were observed at work. All the sessions were fully supervised with full support which was given all the time. The sessions were completed as part of the imaging team some included areas of patient screening. The clinical observation sessions helped to build confidence and to learn in addition to the university research tasks prescribed with motivation to learn more. However, the clinical experience was varied and different based on each hospital in the UK and abroad.

5.1.1 Clinical observation sessions attended at various medical imaging departments

The following hospitals in the UK and abroad in the Kingdom of Saudi Arabia (KSA) were attended for this research programme under the agreed supervision of Dr Mansour Youseffi at the University of Bradford to attend clinical observation sessions and to obtain medical images for a number of cancer cases needed for the investigations carried out in this research:

- Ultrasound, Imaging Department, Birmingham City Hospital, Birmingham, UK.
- MRI, Imaging Department, Birmingham City Hospital, Birmingham, UK.
- Mammography, Imaging Department, University Hospitals Birmingham, Queen Elizabeth Hospital Birmingham, Birmingham, UK.

- PET/CT, Imaging Department, University Hospitals Birmingham, Queen Elizabeth Hospital Birmingham, Birmingham, UK.
- Radiology Department, King Faisal Specialist Hospital & Research Centre, Jeddah, KSA.
- Department of Medical Imaging, King Abdulaziz Medical City, Jeddah, KSA.
- Radiology Department, Madina Maternity Children Hospital, Madina, KSA.

5.1.2 Genetic testing carried out for this research work

Appropriate genetic testing was carried out in this work to identify specific gene mutations that cause breast cancer, and to identify the human Y-Chromosome DNA haplogroups for various cancer cases investigated in this work.

Clinical observation session for genetic counselling was attended at:

- Clinical Genetics Department, Birmingham Women's Hospital, Birmingham, UK.

Genetic testing was carried out at:

- West Midlands Regional Genetics Laboratory, Birmingham Women's Hospital, Birmingham, UK,

To be noted is that the West Midlands Regional Genetics Laboratory is the largest genomics facility in the UK.

To identify the human Y-Chromosome DNA haplogroups for the various cancer cases investigated in this research needed to support the new genetic concept of cancer presented in this work (presented in chapter 6 and chapter 7), genetic samples were obtained from a number of participants in this work and the samples were sent for genetic testing to the following approved genetic testing company in the United States:

- Family Tree DNA (FTDNA), genetic testing company, Houston, Texas, USA.

To be noted is that the FTDNA testing company has the world's largest Y-Chromosome DNA chromosome database using advanced Y-Chromosome DNA tests.

5.1.3 Information governance

The names of the patients, the dates of birth and the hospital numbers as well as any direct or indirect identifiers of all the clinical cases that were obtained from the various clinical observation sessions attended at the various hospitals were all deleted. Each case investigated in this work with the analysis of their medical images taken via various medical imaging modalities used in this research and related publications were completely anonymised. Only the minimum amount of data required for the research purposes was recorded such as the age of the patient, gender, and ethnicity, etc., all managed with the guidance outlined in the information governance requirements [184] with the explicit consent given in writing and verbally stated clearly and unmistakably from the all the participants for genetic testing, living cancer patients themselves, family members in the cases of the deceased cancer patients, and consent on behalf of children at least from one parent in the cases of children, to confirm that the law and best practice was complied with in regard to handling information during this research programme under the supervision of Dr Mansour Youseffi at the University of Bradford.

5.2 Introduction to genetic counselling at Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham, UK

Genetic testing or genomic testing is mainly carried out to diagnose patients with rare and genetic (hereditary) health conditions and some cancers such as breast cancer. In case of breast cancer, the test is carried out to find out the chances of a female developing the disease, and also to find out whether she carries a specific gene mutation that could be inherited by her children [185]. Genetic

counselling sessions are run by genetic counsellors, and at the appointment the patient's family history of breast cancer and other types of cancer is discussed in detail. The appointment begins by drawing out the patient's family history as a pedigree. The information provided by the patient is used to draw a pedigree to assess patient's family history so that the patient could understand better the diagnoses of different types of cancer that have been reported in the patient's both maternal and paternal sides. The role of genetic counselling is explained to the patient by the counsellor and that they assess the probability that cancers may have been caused in the patient's family by inheriting a gene change linked to increasing the risk of certain cancers. It is explained to the patient that there is a possibility that the family history of cancer is caused by some specific gene changes or mutations in case if the patient has a known family history and all the types of cancer seen in the family are known, or if the patient belongs to a specific community that is known of having cancer occurring more frequently among them than in the general population. In case if the patient has uncertain family history that does have several members diagnosed with cancers, a full genetic testing is offered. In general, if there are two close relatives of a patient's same family side who have had the same type of cancer or related types of cancer, and they were diagnosed before the age of 50, then this is considered as a strong family history [186]. It is explained to the patient that inherited breast cancer and other related types of cancer are mainly linked to mutations in the genes, BRCA1 and BRCA2. It is also explained that a genetic test is usually available to determine if the patient has BRCA1 and BRCA2 mutations and to find out if the patient is at a higher risk of getting the disease. A leaflet called Hereditary Breast and Ovarian Cancer (HBOC) produced by the Clinical Genetics Unit, Birmingham Women's and Children's, NHS Foundation Trust, is given to the patient which summarises the discussion about BRCA genes and their inheritance pattern. The following image **Fig. 13** is obtained from the Hereditary Breast and Ovarian Cancer (HBOC) leaflet, and it demonstrates how HBOC runs in families [187].

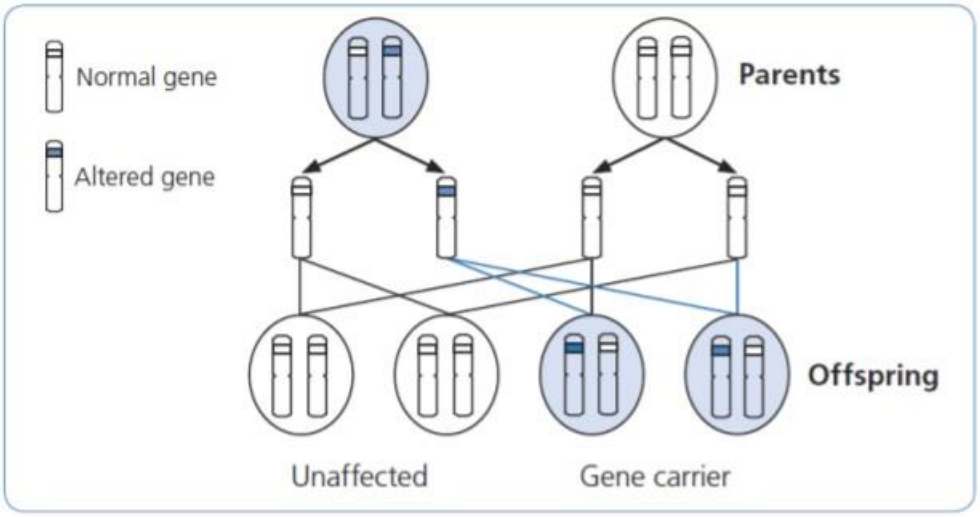

Figure 13 One single gene mutation is needed to cause HBOC [187].

At the appointment, the counsellor also talks to the patient about the results of genetic testing. It is explained to the patient that women who receive a positive BRCA result have an increased risk of developing breast cancer. It is also explained that there is an increased risk of developing ovarian cancer during one's lifetime. The management options available are also discussed with the patient in case if the patient had a positive result which can be either extra breast surveillance or risk reducing surgery. If they discover that the patient carries a BRCA gene change they would recommend yearly Magnetic Resonance Imaging (MRI) scans from age 30 until 49, and mammograms from age 40. The other management option would be a double mastectomy to remove any remaining breast tissue, which is a major surgery and often a difficult decision for women to make. In general, these options would be discussed with the patient later and the patient is referred to the appropriate teams to discuss further. A positive result would mean that the patient's children would be at 50% risk and from the age of 18 they can request genetic testing. It would also mean that the patient's siblings could also get a test. It is also explained to the patient that when this genetic test is carried out, there is a possibility of receiving a genetic test result called a variant of uncertain significance, a VUS. This would mean that the laboratory found a change in a BRCA gene, but it is uncertain if this alteration is the cause for the patient's diagnosis of cancer. With this finding, they would reassess the patient's

cancer risk based on this result and recommend the appropriate screening based on the patient's family history. It is explained to the patient that sometimes these variants are re-classified in time as more is known about them. It is usually suggested that if the patient does receive a VUS result then it is worth ringing the genetics department in a few years' time to see if it has been reclassified. At the end of the appointment if the patient is happy to go ahead with all kinds of above-mentioned testing, then the patient has to sign the consent form so as the hospital could go ahead with the required procedures. A green blood form is given to the patient to take to phlebotomy at the hospital for a blood sample to be taken. This test can take up to 12 weeks to be completed and concluded.

5.3 Dense breast tissue case (Mammography, ultrasound, and genetic testing)

A 30-year-old female patient that has dense breast tissue with previous breast mass and a strong family history of breast cancer and other types of cancer was referred to see a genetic counsellor at Clinical Genetics Unit, Birmingham Women's Hospital for possible genetic testing. A blood sample was taken from the patient to find out if there is any hereditary gene mutations that might have caused cancer to run in her family. A full BRCA gene test was therefore carried out to see if she has any of the known breast cancer risk genes. The results revealed that the patient is not affected and that she does not have any significant changes in the BRCA1 and BRCA2 genes. Receiving a negative BRCA1 and BRCA2 result is reassuring, since these are the two high risk breast and ovarian cancer genes that are known. This has decreased this family member's risk of developing breast cancer and the revised assessment now places her breast cancer risk to that of other normal women. This result also means that her daughters and any future children will not be at risk of inheriting a BRCA gene change from her. Although there was no detection of any known pathogenic changes in the BRCA1 or BRCA2 genes of this patient, however it does not exclude the possibility of the cancer cases found in her family being BRCA1 and BRCA2 related.

5.3.1 Medical history of the patient

The past medical history of the patient included details of treatment of a benign tumour (fibroadenoma) which was surgically removed from the patient's left breast when she was 15 years old. The reason behind receiving surgical removal of the breast lesion was the patient's strong family history of breast cancer and other types of cancer. Malignant transformation of fibroadenomas is usually rare, however women with fibroadenomas and a strong family history of breast cancer are investigated with a high suspicion for malignancy, especially in middle aged women [188]. In general, fibroadenomas are formed with the overgrowth of the breast's glandular tissue and fibrous tissue, and usually found in women aged 15 to 35. Fibroadenomas are very common with an incidence rate of about 18% to 20% [189]. The hormone levels of women can affect fibroadenomas and can become larger in size during gestation or smaller after the menopause. Some women have one fibroadenoma while others have multiple fibroadenomas in the same breast or in both breasts. Fibroadenomas are usually painless and often found on physical exams. Ultrasound imaging is the best medical imaging modality for looking for fibroadenomas as they may not show up on mammography. Ultrasound imaging is also effective in mammographically dense breast tissue [190]. Following the genetic test results, the patient was referred to have mammography and ultrasound imaging.

5.3.2 Breast imaging reporting and data system (BI-RADS)

Breast imaging reporting includes information about breast density, the presence or absence of breast masses, in addition to lesion size and location. Breast Imaging-Reporting and Data System (BI-RADS) is the quality assurance and risk assessment tool established by the American College of Radiology (ACR) [191]. The tool provides a breast imaging lexicon for mammography, ultrasound imaging, and MRI. According to the BI-RADS atlas, the mammography breast composition categories are four categories; A) mostly fatty breast tissue, B) scattered fibroglandular breast tissue, C) heterogeneously dense breast tissue, and D) extremely dense breast tissue, as shown in **Fig. 14** [192].

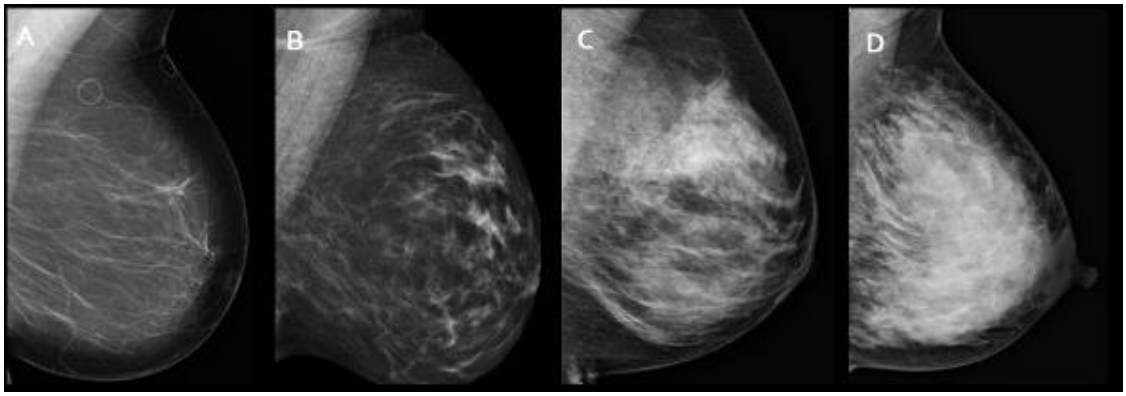

Figure 14 Mammography breast composition categories [192].

On the other hand, BI-RADS assessment categories are seven (0 through 6); BI-RADS 0 means incomplete and additional imaging testing is needed. BI-RADS 1 means negative, i.e., no masses, BI-RADS 2 means noncancerous (benign) finding, BI-RADS 3 means benign with low probability of malignancy, BI-RADS 4 means suspicious for malignancy, BI-RADS 5 means highly suggestive of malignancy and BI-RADS 6 means malignancy [41].

5.3.3 Mammography of the patient

The patient was referred for a mammogram to monitor and detect any breast lesions that the patient might have and in case if it does develop at an early stage due to the fact that the patient has a strong family history of breast cancer and other types of cancer. Women from families that have breast cancer, ovarian cancer in addition to some other types of cancer found among them in one or more than one generation are typically considered to be at a higher risk of getting breast cancer. The following images **Fig. 15** and **Fig. 16** are the mammograms of the patient. The mammography standard views are bilateral craniocaudal (CC) and mediolateral oblique (MLO) views. The following image **Fig. 15** is the mammography of the patient in the right craniocaudal (RCC) view and the left craniocaudal (LCC) view showing extremely dense breast tissue.

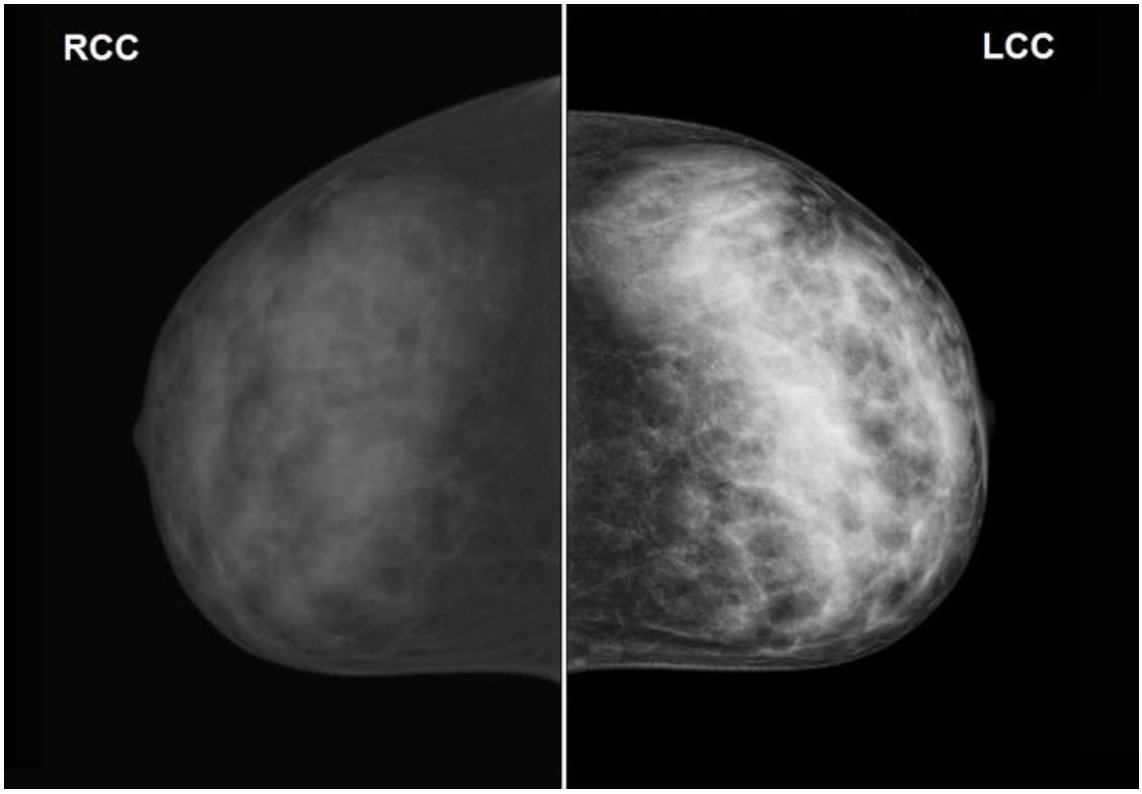

Figure 15 Breast screening mammography in craniocaudal **(CC)** views of the patient demonstrating extremely dense breast tissue.

In the craniocaudal (CC) view the image shows the entire part of the breast. The nipple is clearly depicted in this view. The fat tissue appears as a dark strip because fat is radiolucent, i.e., it permits the passage of X-rays. The mammography of the patient demonstrated extremely dense breast tissue (BI-RADS category D) which reduced the sensitivity of the mammogram. No obvious speculated masses, suspicious grouped microcalcifications, architectural distortion or nipple retraction could be seen bilaterally. The following image **Fig. 16** is the mammography of the patient in the right mediolateral oblique (RMLO) view and left mediolateral oblique (LMLO) view. The image in the mediolateral oblique (LMLO) view shows most of the breast tissue in the upper outer quadrant and the axilla.

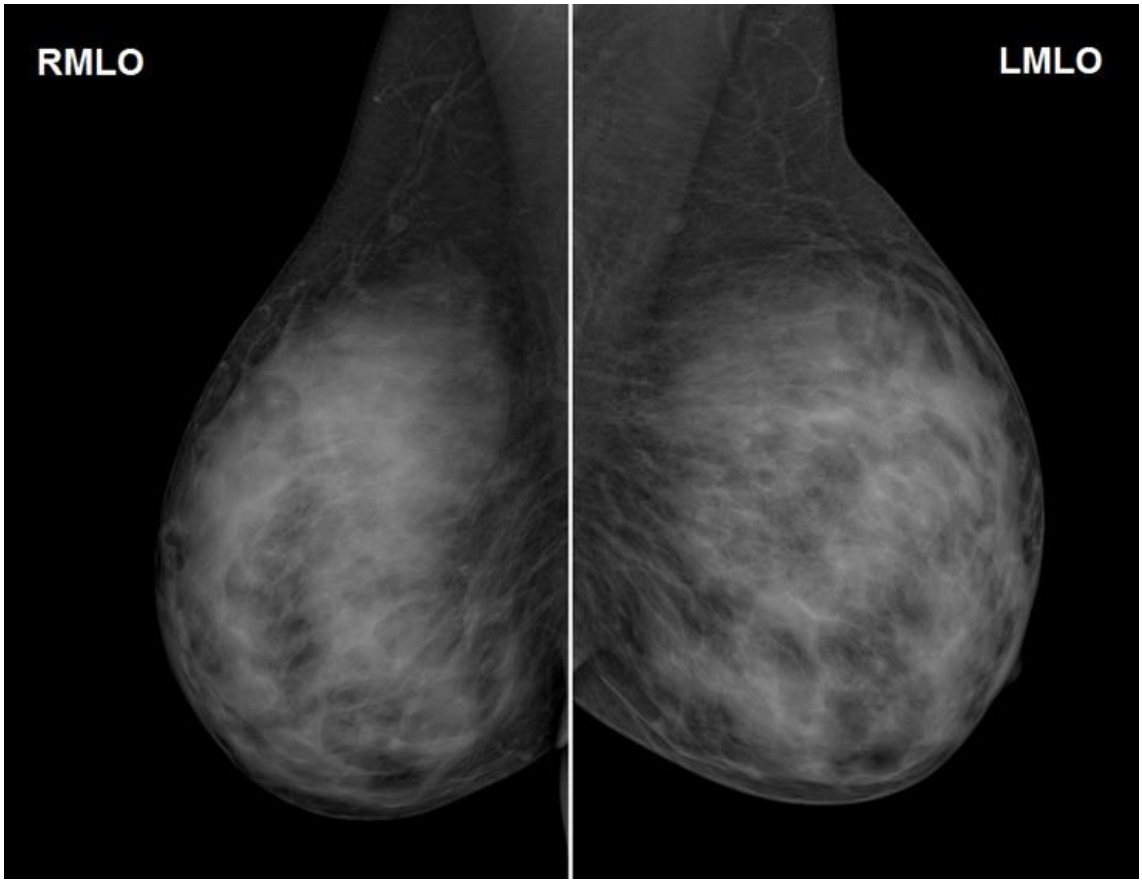

Figure 16 Mammograms of the patient in mediolateral oblique views showing extremely dense breasts.

The axilla demonstrated no enlarged lymph nodes. The mammography showed no evidence of any microcalcification or breast masses or any obvious abnormality. The patient's breast imaging-reporting and data system (BI-RADS) assessment was therefore category 0 (BI-RADS 0) which means imaging is incomplete, not clear and more tests are needed. Ultrasound imaging was therefore recommended due to dense breast tissue.

5.3.4 Ultrasound imaging of the patient

The patient was scanned at the same site and multiple selected ultrasound images of her breasts were compared to her mammography results dated one day earlier. The ultrasound imaging results showed heterogeneous background echotexture of both breasts. The results also demonstrated a bi-lobed

hypoechoic (solid) with inhomogeneous echotexture but with well-defined margin and no associated calcification of right breast lesion as shown in **Fig. 17** and measures 1.8 x 0.8 cm seen at 2 o'clock. This was not seen on the breast mammography due to dense breast tissue.

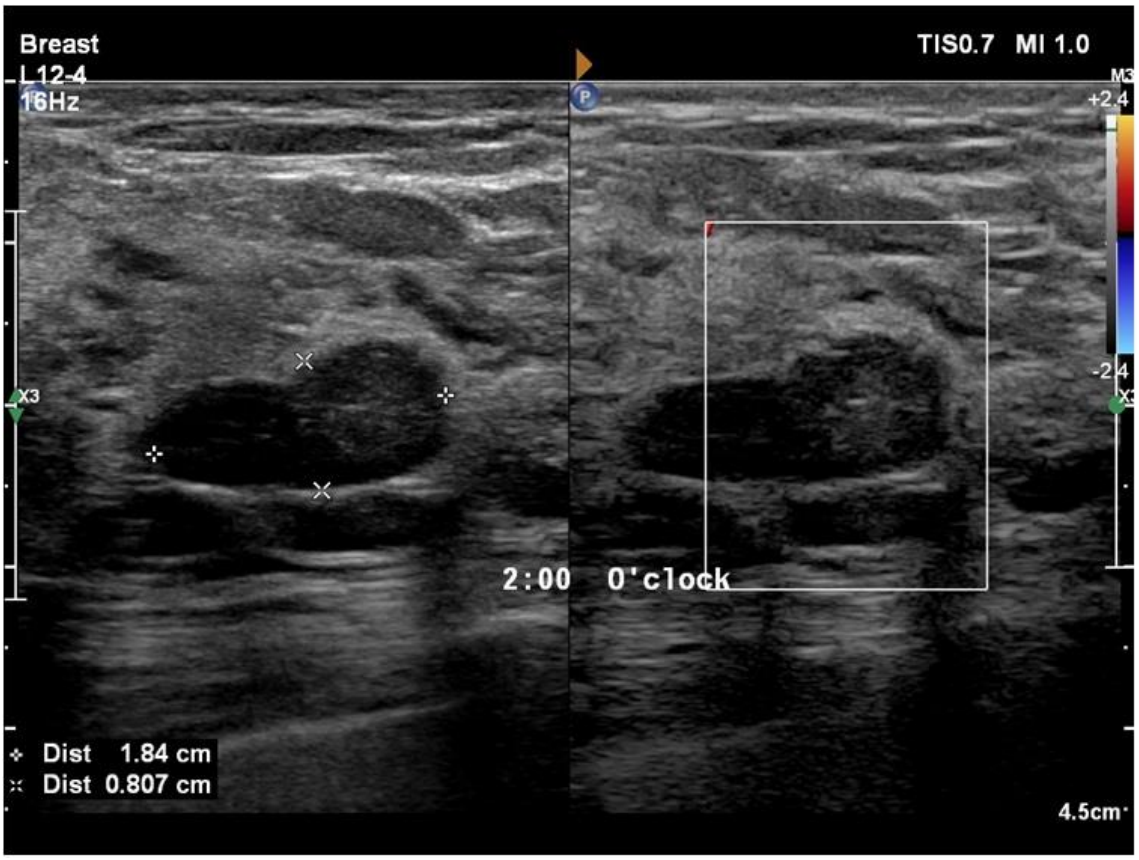

Figure 17 Ultrasound imaging of the patient demonstrating right breast lesion with no architectural distortion surrounding the lesion.

The right breast lesion was not seen on the breast mammography due to dense breast tissue. However, the breast mass represents a fibroadenoma (a benign breast tumour), given its inhomogeneity with presence of hypoechoic component to it. Normal right nipple as shown in **Fig. 18** and the axilla demonstrated no enlarged lymph nodes. On the other hand, ultrasound imaging of the left breast demonstrated normal left nipple, normal subcutaneous tissue, and no left breast masses. Therefore, the patient's breast imaging-reporting and data system assessment was BI-RADS 1 for the left breast. BI-RADS 1 means the test result is normal.

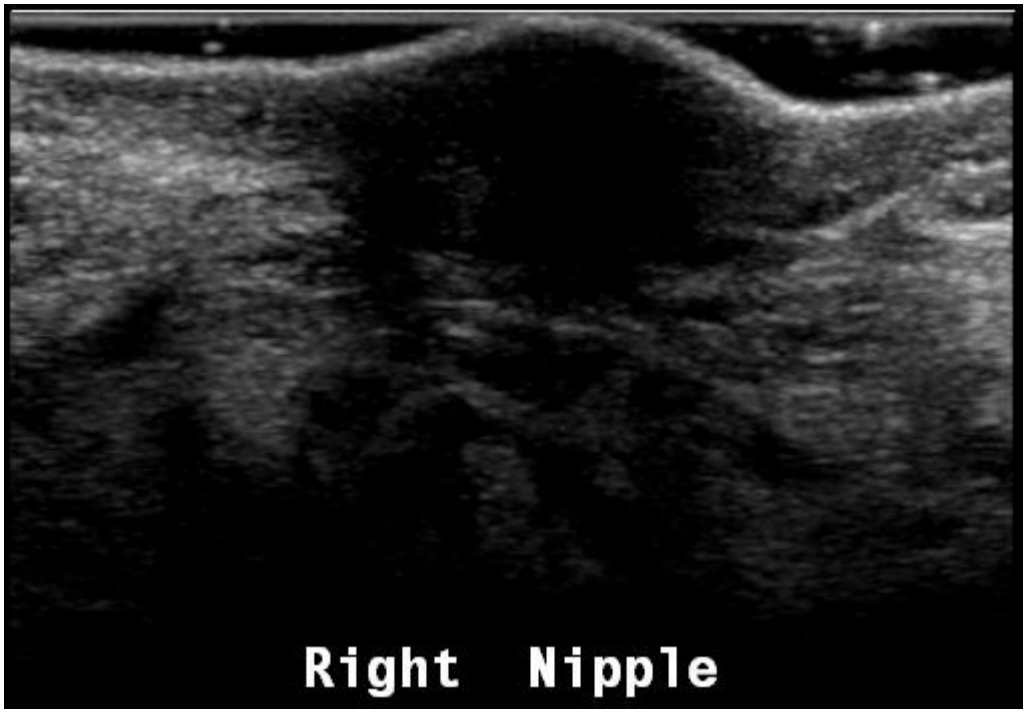

Figure 18 Normal right nipple ultrasound of the patient.

5.3.5 Treatment of the patient

The patient was recommended to have the breast mass removed by surgery based on imaging tests and due to the patient's strong family history of breast cancer and other types of cancer, in addition to the patient's medical history of previous fibroadenoma in the opposite breast at around age 15 which was then removed through surgery. In general, patients with simple fibroadenomas along with no family history of breast cancer are at lower risk of developing breast cancer. If a fibroadenoma is not removed, it is usually followed-up with ultrasound imaging every 6 months for 2 years to monitor any increase in size.

5.3.6 Discussion and concluding remarks

According to the American College of Radiology (ACR), breast density has an impact on mammographic screening and ACR's instructions are to include their breast density categories information in patient's medical reports [191]. Dense breasts are not related to the size of the breasts, and it cannot be self-examined,

however on a mammogram a way to measure the breast density is by measuring the thickness of the breast tissue. ACR's Breast Imaging Reporting and Database System (BI-RADS) includes information on breast density, and it categorises breasts as: A) mostly fatty, B) scattered fibroglandular density, C) heterogeneously dense, and D) extremely dense. The density of breast can be inherited, i.e., if mothers have dense breast tissue, then daughters are more likely to have dense breasts [40]. In this case study full genetic testing of BRCA1 and BRCA2 was carried out for a female patient with a strong family history of breast cancer and other types of cancer. However, the genetic testing results confirmed that the patient did not have any significant changes in the BRCA1 and BRCA2 genes. Mammography was recommended for the patient, which demonstrated dense breast tissue, BI-RADS category D, i.e., extremely dense, and therefore no pathology could be found. Breast ultrasound was, therefore, recommended following mammography, and the diagnosis obtained using ultrasound imaging indicated a breast mass (fibroadenoma) in the right breast. Due to the patient's strong family history of cancer, and also the patient's previous case of breast fibroadenoma in the left breast at age 15, surgical removal of the breast lesion was recommended based on the imaging tests only i.e., no biopsy or other imaging tests were carried out. The common sizes of fibroadenomas are 1 to 3 cm, but they may increase up to 10 cm, and giant fibroadenoma (GFA) are larger than 5 cm [193]. In this case study ultrasound imaging technique was identified as an effective medical imaging technique used in the assessment of a patient with dense breast tissue in addition to meeting all the physical and health and safety considerations related to imaging process and procedure.

5.4 Breast cancer case (Mammography and PET/CT scan)

The breast cancer case discussed in this section along with the medical images taken via breast screening mammography in addition to positron emission tomography combined with computed tomography (PET/CT) scan, are for a middle-aged woman with metastatic breast cancer. Metastatic breast cancer is invasive breast cancer that has spread from where it started in the breast to other parts of the body. Advanced breast cancers typically spread to the bones (bone

metastasis) which was the case with this patient, and to other body parts and organs such as the liver, the lungs and the brain. The patient had breast screening mammography which showed abnormality in her breasts. The patient was subsequently referred for FDG PET/CT evaluation to confirm primary breast cancer and to find out if cancer has spread to other parts of the body. The PET/CT images confirmed primary breast cancer in the right breast and also revealed the occurrence of bone metastasis.

5.4.1 Breast screening mammography

The following image **Fig. 19** is the breast screening mammography of the patient in the standard bilateral craniocaudal (CC) views showing abnormality in the breasts.

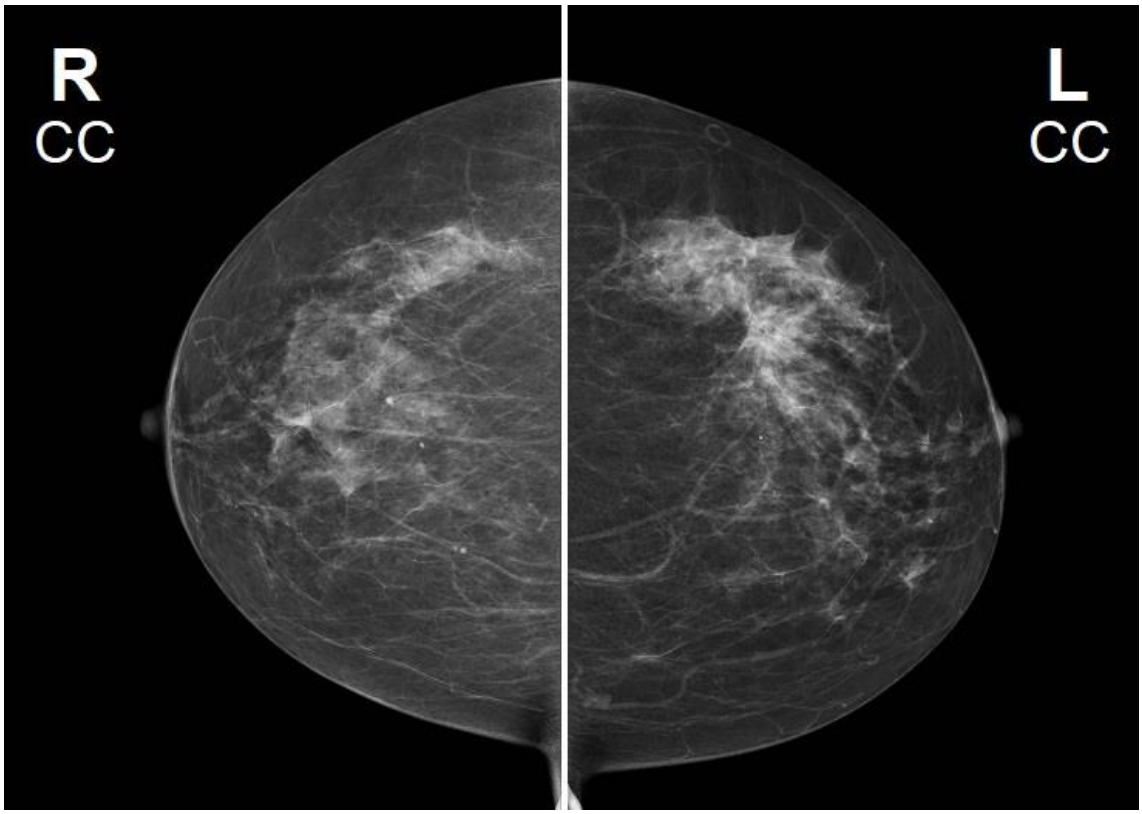

Figure 19 Breast screening mammography of the patient in the right craniocaudal (RCC) view and the left craniocaudal (LCC) view with abnormality detected in the breasts.

The following image **Fig. 20** is the breast screening mammography of the patient in the standard right mediolateral oblique (RMLO) view and the left mediolateral oblique (LMLO) view of the patient showing the abnormality in the breasts.

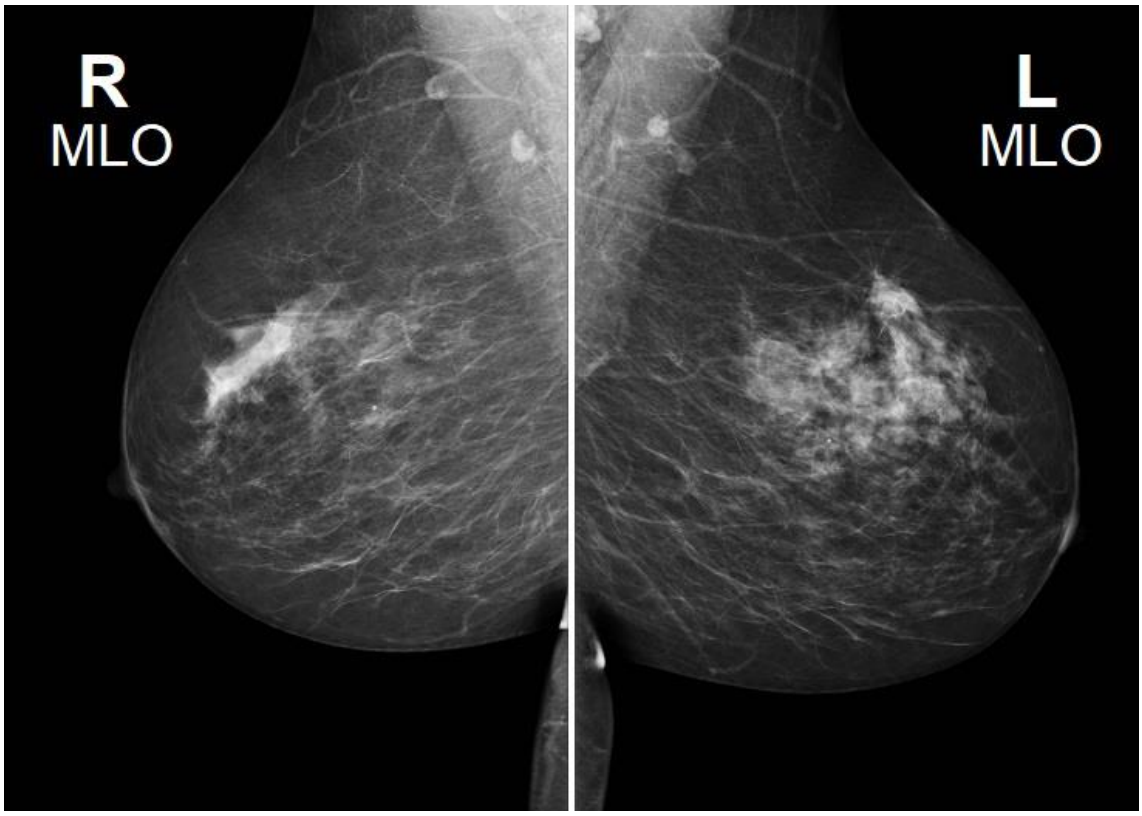

Figure 20 Mammograms of the patient in the right mediolateral oblique (RMLO) and the left mediolateral oblique (LMLO) views, demonstrating abnormality in the breasts.

5.4.2 Breast cancer and bone metastasis on PET/CT scan of the patient

The patient subsequently had a PET/CT scan. PET scans use the radioactive tracer Fluorine-18 (^{18}F) FDG which settles in the cancer cells and releases positrons that can be detected by the PET scan. When PET is combined with CT, it can provide information about both the function and the structure of the body tissues and organs. PET/CT is effective for confirming primary breast cancer and staging locally advanced and inflammatory breast cancers. The following image **Fig. 21** is the axial PET/CT scan of the patient. The image shows the

physiological Fluorine-18 (^{18}F) FDG uptake in the right breast and it demonstrates primary breast cancer in the right breast (the arow).

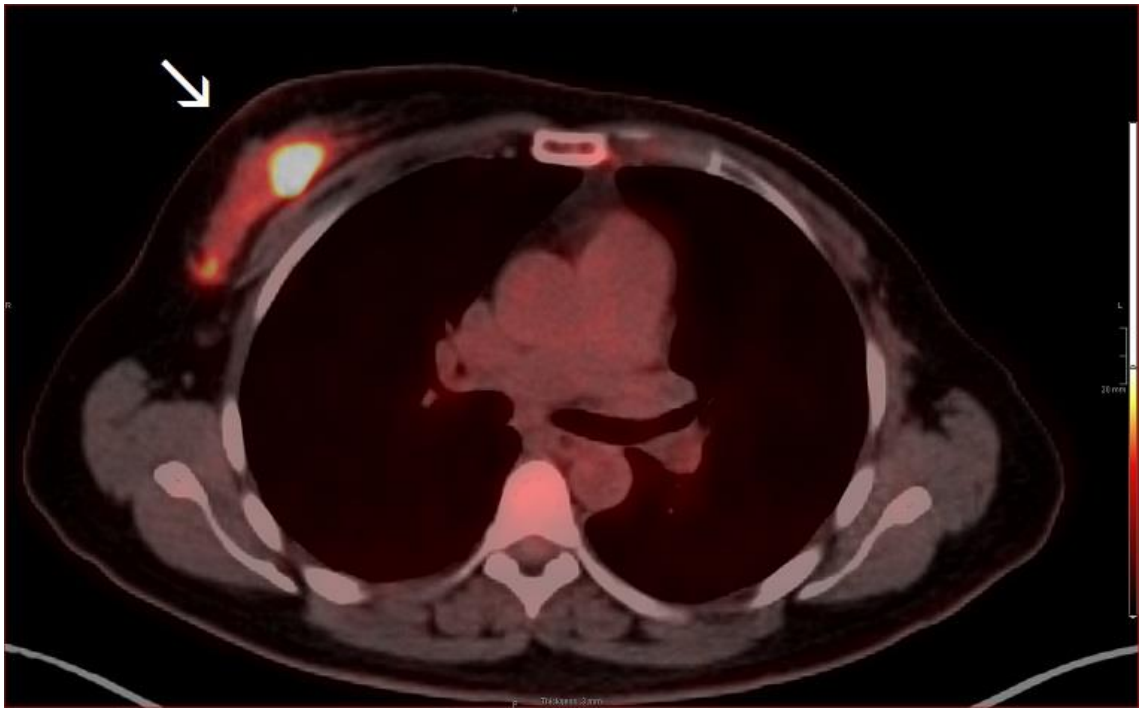

Figure 21 Axial PET/CT image demonstrating primary breast cancer in the right breast (the arrow).

Cancer cells have a higher metabolic rate than normal cells, and they show up as bright spots on PET/CT scan, therefore PET/CT scan can help in differentiating between cancerous and noncancerous masses. Advantages of PET/CT scan is that it examines extra-axillary nodes as well as the chest, the abdomen, and the bones in one scanning session. PET/CT scan measures both the anatomy and the metabolic function of the body of the patient and can confirm the primary breast cancer detected on screening mammography. PET/CT is effective to find out if cancer has spread to other parts of the body, and to see if treatment is working. The following image **Fig. 22** is the axial Fluorine-18 (^{18}F) FDG PET/CT image, showing bone metastasis in the same patient (the arrow).

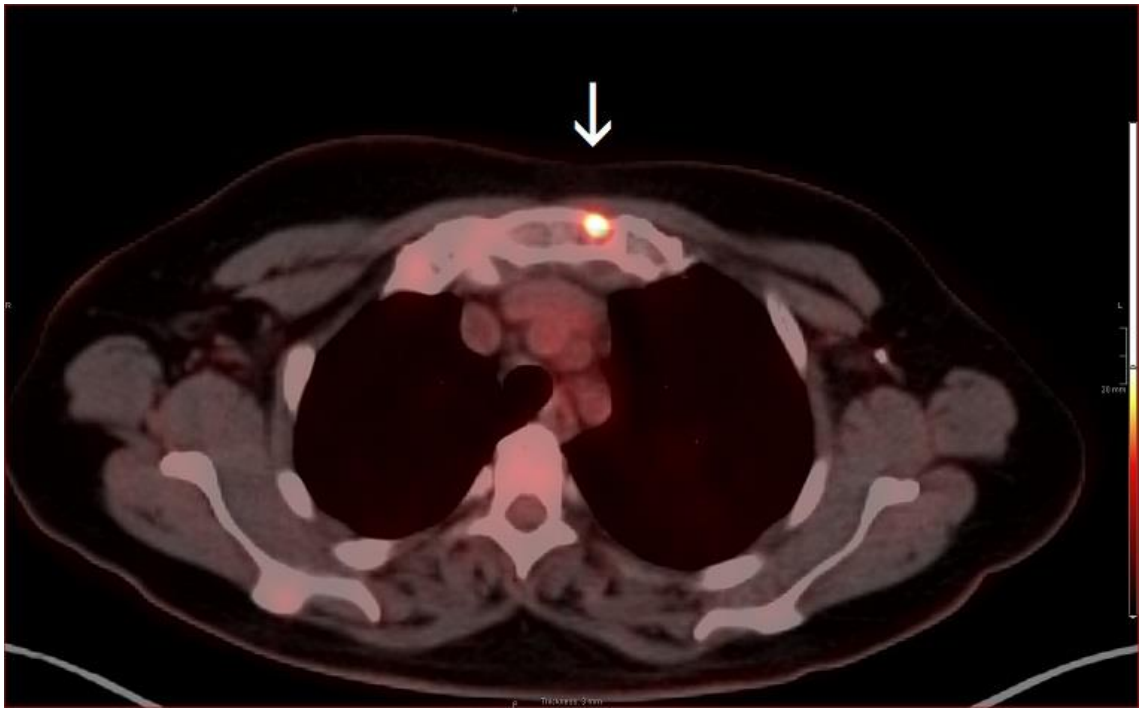

Figure 22 Axial PET/CT image demonstrating bone metastasis in the same patient (the arrow).

5.4.3 Discussion

PET and PET/CT imaging can examine both the cellular metabolism as well as the anatomy of patients with breast cancer fully in one scan and they have shown to be effective in the management of breast cancer in all stages in patients with primary breast cancer and in patients with suspected tumour recurrence. These imaging techniques have shown the capability of detecting the early treatment response and help to choose the most effective treatments. With PET/CT imaging technique, it is not the architecture of the lesion that is looked at, which is the case with mammography, but rather the metabolic activity of the lesion. PET scan uses radioactive tracers to show the activity of the tissues and organs in the body and has the ability to detect cancer before they appear on other imaging techniques. PET/CT imaging modality has become a popular imaging technique for the overall assessment of breast cancer. However, PET/CT system is mostly used in research, and it is not part of the routine breast management.

5.5 Normal brain MRI

The MRI images discussed in this case study are for a 40-year-old male patient known to have migraine, otherwise well. The patient was referred to have MRI of head and brain due to worsening of headache and change in nature of migraine. Headache changed in nature to more severe and continuous a few weeks prior to the referral. The following image **Fig. 23** demonstrates the T1-weighted sagittal brain MRI image of the patient, showing an essentially normal brain MRI with unremarkable midline structures.

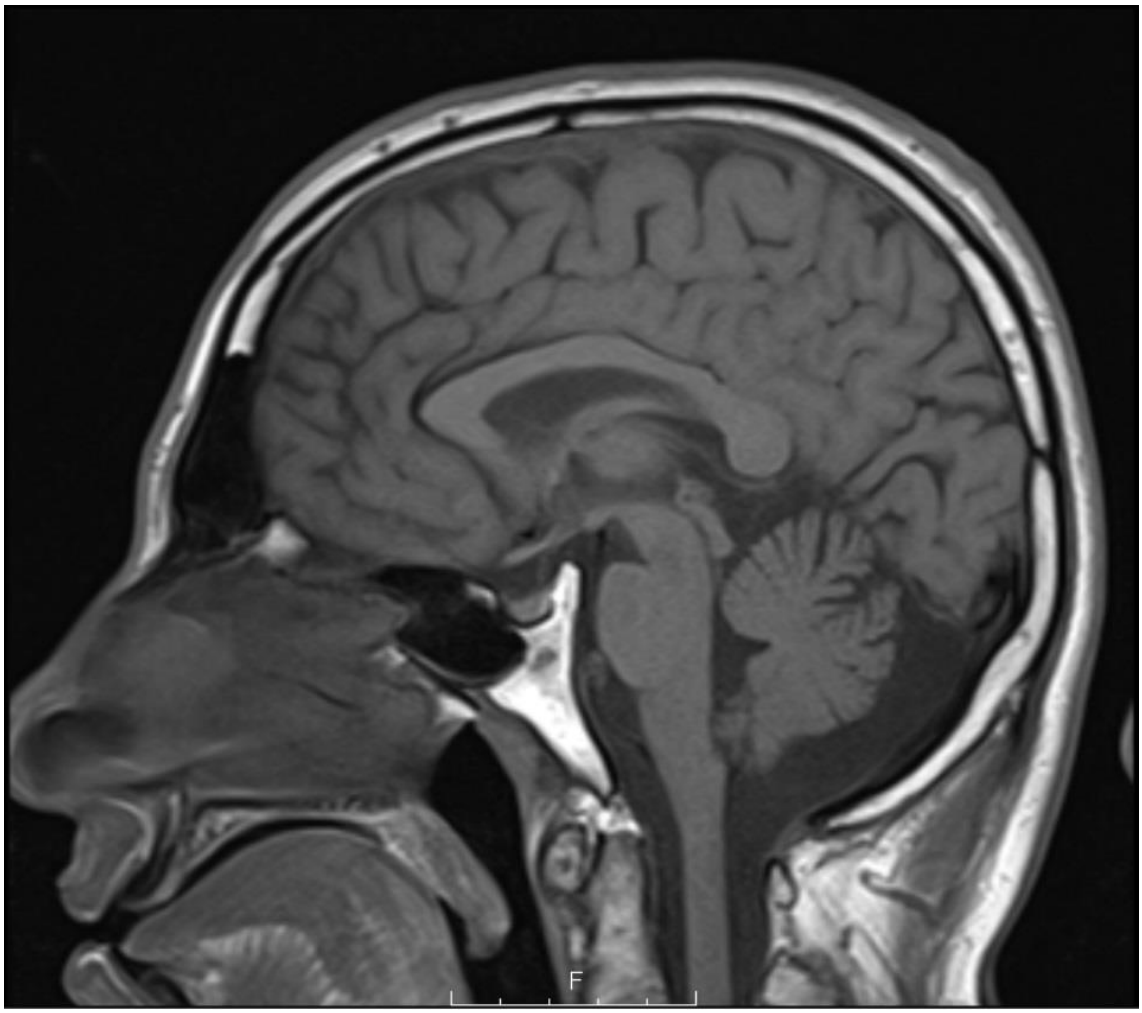

Figure 23 T1-weighted sagittal turbo spin echo (TSE) MRI of the patient showing normal appearance of the brain.

Turbo spin echo MRI sequence is an acquisition technique which uses several 180 refocusing radiofrequency pulses and results in fast imaging times [194]. The

following image **Fig. 24** are the coronal T2-weighted MRI images (**A**), (**B**), (**C**) and (**D**) of the patient. The images demonstrate no suspicious intracranial lesions. The ventricular system is normal as in the previous image **Fig. 23** of the patient. Both orbits are unremarkable on the images.

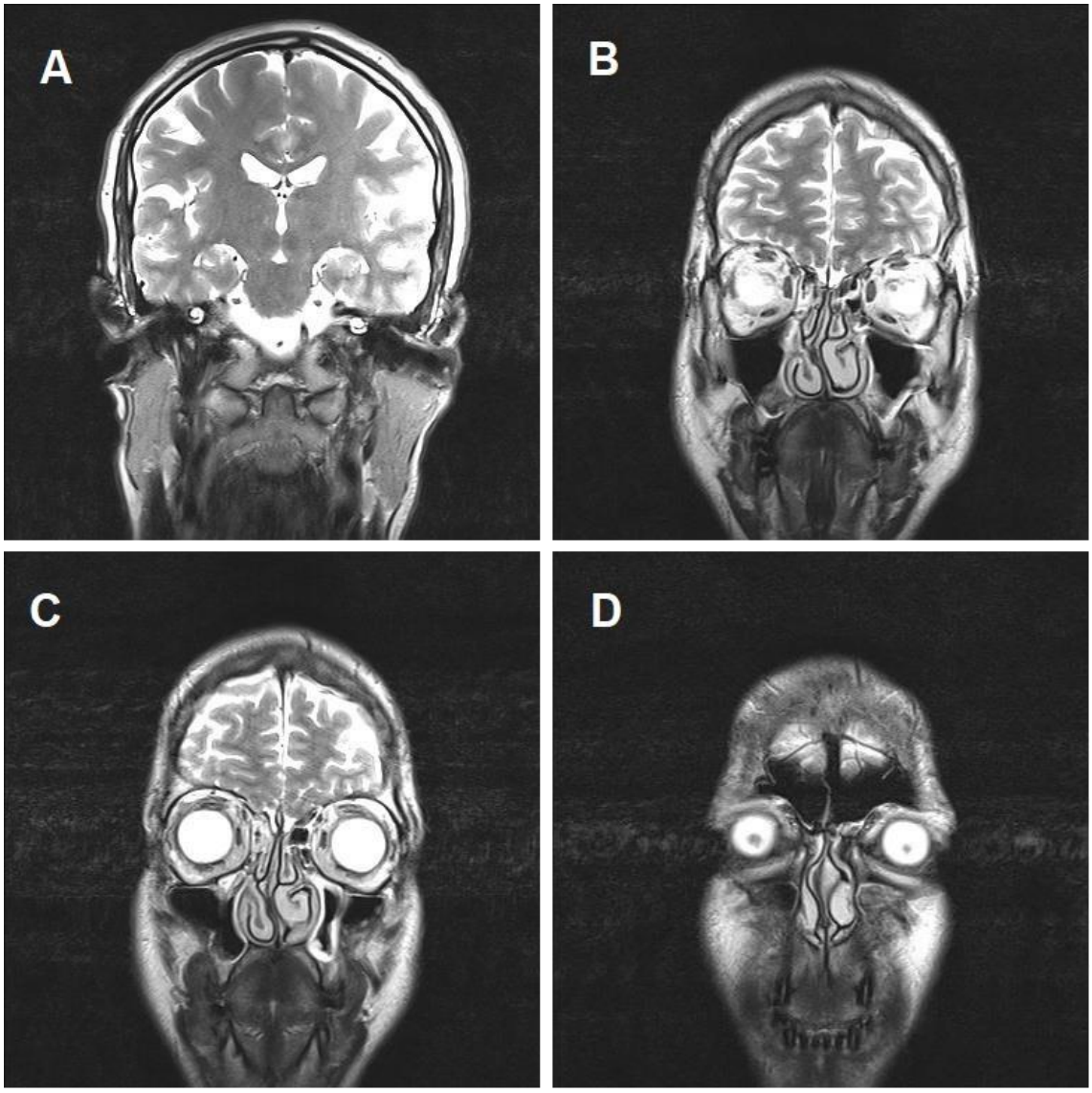

Figure 24 T2-weighted coronal turbo spin echo (TSE) MRI images of the patient demonstrating Normal brain appearance on normal orbits.

The images also show minimal chronic inflammatory mucosal changes of maxillary sinuses and ethmoid air cells bilaterally. The following image **Fig. 25** is the axial T2-weighted dark fluid MRI image of the patient demonstrating unremarkable ventricular system. The dark fluid sequence (or fluid attenuated

inversion recovery (FLAIR)) is an MRI technique that shows cerebrospinal fluid (CSF) dark instead of bright and the tissue bright to reveal lesions.

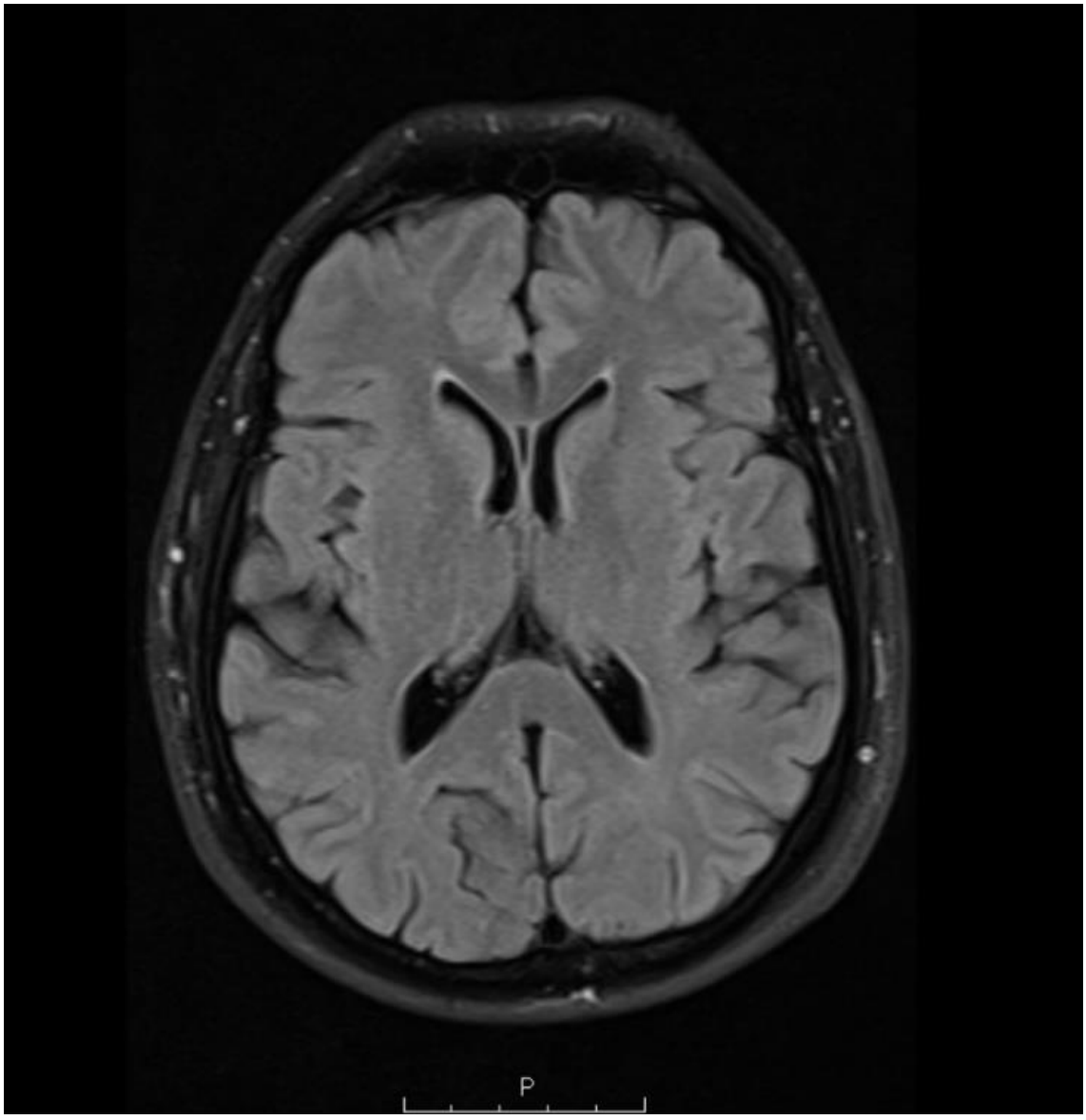

Figure 25 Normal axial T2-weighted dark fluid MRI image of the brain of the patient.

The following image **Fig. 26** shows the axial proton density (PD)+T2-weighted turbo spin echo (TSE) MRI images (**A**) and (**B**) of the patient demonstrating unremarkable ventricular system. Proton density (PD) images show higher or density and concentration of protons for stronger signals and brighter tissue.

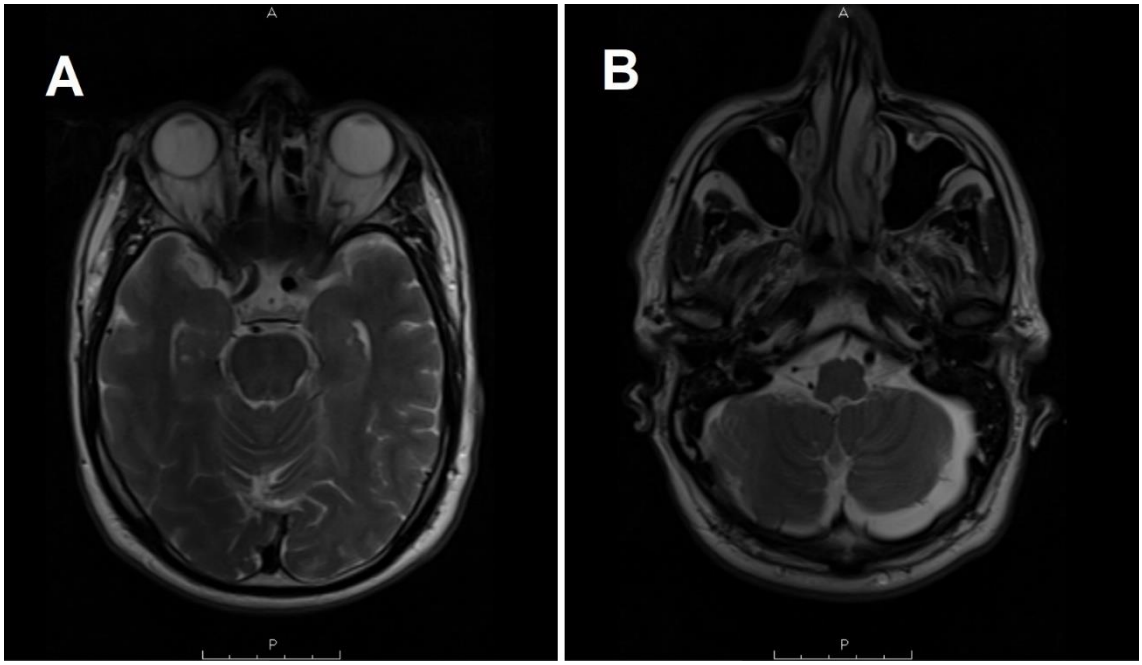

Figure 26 Normal axial proton density (PD)+T2-weighted turbo spin echo (TSE) MRI images of the patient.

5.5.1 Discussion

The patient discussed in this case did not have previous cross-sectional head imaging for comparison. The MRI images demonstrated essentially normal brain MRI with no suspicious intracranial lesions, as well as no acute intracranial findings. To be notes is that it was essential to present medical imaging of a normal head and brain case for reference when discussing the head and brain tumour cases in the clinical cases chapter 7 of this thesis.

CHAPTER 6

CANCER GENETICS

6.1 A new genetic concept of cancer and prevention strategies

In this chapter a new genetic concept of cancer investigated in this research work is presented. The new genetic concept of cancer is based on understanding the links between the human population origins and migrations, environmental factors and gene mutations, and the development of cancer. The new genetic concept of cancer requires understanding the topics of the human Y-Chromosome DNA and the human Y-Chromosome DNA haplogroups which provide information on the geographic and historic origin of the human populations and their migration routes. Testing the human Y-Chromosome DNA is therefore needed to identify the human Y-Chromosome DNA haplogroups of the participants in this study to support the new concept of cancer. The chapter also discusses the topics of natural physical boundaries and political boundaries to present a new definition of race and ethnicity based on the various human Y-Chromosome DNA haplogroups that gives the actual race and ethnicity of the people. The new definition of race and ethnicity proposes a new classification and list of ethnic groups in the UK and the rest of the world by classifying the world's human populations according to the major human Y-Chromosome DNA haplogroups. Likewise, the genetic test results are discussed, and the new proposed genetic concept of cancer is presented in addition to proposed cancer prevention strategies.

6.1.1 Methodology

The new genetic concept of cancer investigated, detected, and discussed in this work links between the human population origins and migrations and the environmental factors causing gene mutations leading to the development of cancer, and it works as a prevention strategy to avoid people from getting cancer. This investigation and its novelty have been carried out in a number of hospitals in the UK and abroad which involved participants/volunteers from families with histories of breast cancer and other types of cancer in close families and relatives. In order to achieve the objectives of this research programme, one of the main methodologies (strengths) is based on (clinical) case studies which are essential

to provide in-depth analyses of the new genetic concept presented in this work which include various cancer cases, medical imaging, and genetic testing followed by discussion and analyses of all the results. Therefore, the research work carried out over the past years, included obtaining various cancer cases with detailed analyses to reinforce the proof of the newly proposed concept in gene mutations leading to the development of breast cancer and other kinds of cancer. Genetic testing was carried out with detailed analysis of the results for recruited participants including their family history of cancer and full medical history and medical imaging taken by different imaging techniques. The recruited participants for genetic testing are members of families that have the history of either one single cancer case or multiple cancer cases among them. For studying each family up to 5 generations were investigated. The genetic testing used to identify the human Y-Chromosome DNA haplogroups for the families with cancer that are investigated in this work, one genetic sample from a male member of each family investigated is needed for studying the cancer cases among them. Each sample obtained from each individual represents a branch that is investigated for up to 5 generations which means each single sample tested is true for all the families that are formed under that branch in 5 generations. Therefore, the methodology for doing this research is not by taking genetic samples of 1000/many individuals, because that means finding 1000/many families with the history of cancer cases which is not possible and also the cost of each genetic testing including the postage is around £100 which means for 1000 families it would be at £100,000, and this is not required at all. The genetic testing for this research is not about the number of samples but the branches of each family which represent bigger families or tribal haplogroups. This work allows having a number of participants in order to present evidence to back up the new genetic concept of cancer.

6.1.2 Literature review on the human Y-Chromosome DNA haplogroups

The topic of human Y-Chromosome DNA haplogroups is not well known nor widely researched therefore literature is carried out on the human Y-Chromosome DNA haplogroups in relation to this work in order to have wider

proof/evidence of the newly proposed concept of cancer. Literature review is carried out regarding the distribution of native human populations on the earth's surface and how each native population belongs to a human Y-Chromosome DNA haplogroup that has a site of origin. Therefore, explanation is provided on how each native population has developed a distinct mutation that allows them to adapt to the environment of their geographic zone. Therefore, systematic review is conducted to identify, evaluate, and summarise the findings of all relevant studies available with supporting evidence to show that each native population is unique from any other population and that each population has a site of origin that has natural physical boundaries. For example, Black Africans are the native people of Africa, and the Chinese people are the native people of China, and if a Chinese individual migrates to Africa and settles there, there is no way that this Chinese individual and his descendants will become Black Africans and native people of Africa. Therefore, the human Y-Chromosome DNA haplogroups are explained with maps of the geographic distribution of the native population obtained from various sources and studies.

6.1.3 Various other methodologies to investigate the available rates of breast cancer and other types of cancer

Various other standard methodologies are used to investigate the data available on cancer incidence among the various races and ethnicities around the globe. Work is carried out on the incidence of breast cancer and other types of cancer among individuals from different races and ethnicities in a number of countries especially in the UK and the US. For instance, the data and analysis from the National Cancer Intelligence Network (NCIN) of the Public Health England shows the highest myeloma incidence rate (number of cases per 100,000 population) amongst the Black ethnic group (Black ethnic, i.e., the people who migrated to the UK), and lowest in the White ethnic category (White ethnic i.e., the native inhabitants of the UK). Likewise, according to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) int the U.S. the incidence rate of breast cancer amongst the US women by race and ethnicity shows that White and Black women (White and Black, i.e., the

individuals who migrated to the U.S.) have the highest incidence rate compared to the American Indian and Alaska Native women (i.e., the native inhabitants of the US) who have the lowest incidence rate. Therefore, this work includes the relevant data regarding the available cancer incidence rates by race and ethnicity in the UK and the US published by various sources.

6.1.4 The Million Women Study (MWS)

The Million Women Study is a population-based prospective study of 1.3 million women in the UK conducted by a team of researchers at the Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford. MWS is publicly funded and information on its data access is available at www.millionwomenstudy.org/data_access. This work includes aggregate data for all incident cancers to end 2017 supplied through direct contact by the MWS Principal Investigators to be included in this thesis. The aggregate data was supplied with the approval of Professor Jane Green from the University of Oxford under the supervision of Dr Mansour Youseffi to support the new genetic concept of cancer presented in this research.

6.1.5 Cancer prevention strategies

The new genetic concept of cancer presented in this work includes investigation and discussion on cancer prevention strategies such as naturally available methods to prevent people from getting the disease whether they stay within the geographical regions that they belong to or in case if they left their sites of origin and migrated to other parts of the world. Cancer is caused by gene mutations that occur due to risk factors, however cancer could be controlled and prevented through avoiding and controlling the risk factors responsible for causing cancer. Therefore, the topic of cancer prevention strategies is very important and critical due to the fact that it is essential to educate people how to avoid and modify the risk factors linked to various types of cancer. The world health organisation (WHO) has advised people to avoid a number of key risk factors that are known to be linked to cancer to help prevent people from getting the disease, such as

avoiding tobacco, maintaining a healthy weight, avoiding exposure to ionisation, etc. [195], however one major key risk factor has been suggested in this work based on the conducted research which links the development of cancer to gene mutations and human population origins and migrations. Evidence-based protection and prevention strategies have therefore been suggested in this thesis. One of the main prevention strategies suggested is that it is essential for people who live in environments other than their site of origin, to keep the environment around them similar to the environment of where they belong to. Therefore, the work carried out in this research on the link between development of cancer and the human Y-Chromosome DNA haplogroups is to present the prevention strategies critical to help avoid people from getting the disease.

6.2 Introduction to the new concept (Chromosomes, DNA and Genes)

Every human being starts as a single cell, a human zygote, which is formed when a sperm cell (the male gamete) fertilizes an ovum (the female gamete). The 23 chromosomes from the haploid sperm come together with the 23 chromosomes of the haploid ovum to produce a diploid zygote that has 23 pairs of chromosomes, as shown in **Fig. 27** [196]. The zygote divides and differentiates and eventually becomes an embryo and later a foetus until birth.

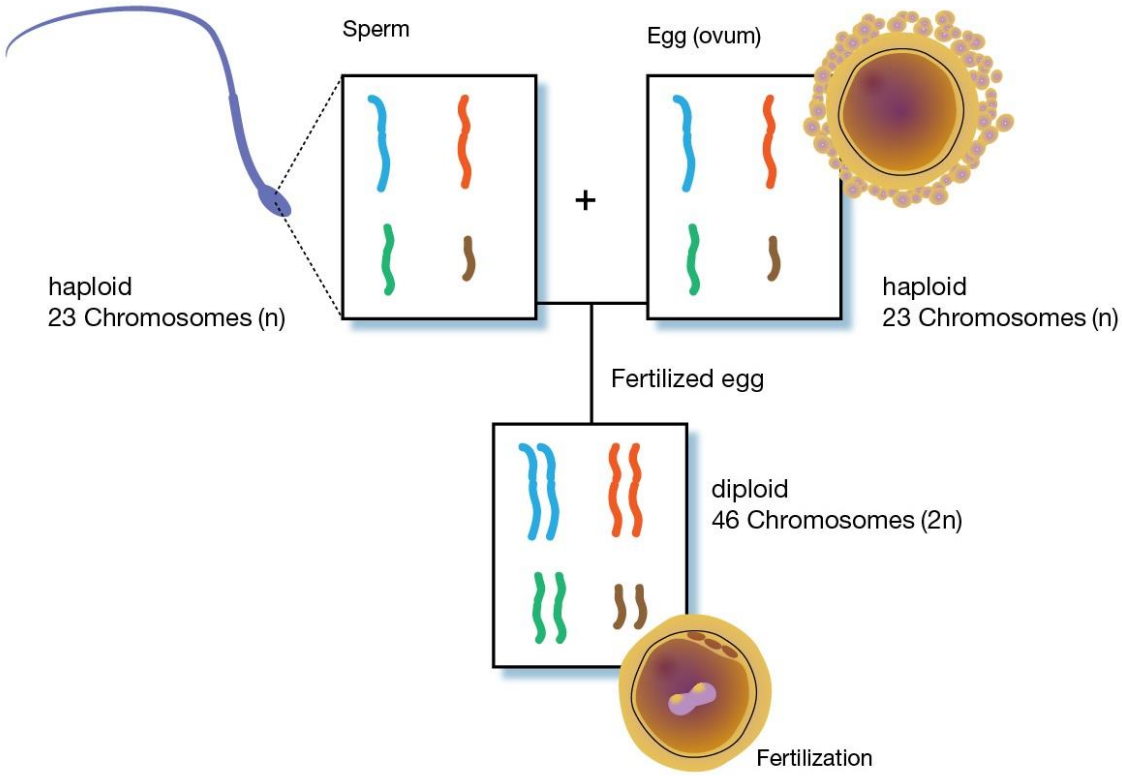

Figure 27 Sexual reproduction in humans [196].

Normally, each human cell contains 23 pairs of chromosomes and are located inside the nucleus of the cell. 22 pairs of the chromosomes are known as autosomes, which look the same in both males and females and are numbered by size and centromere position. The 23rd pair of chromosomes are the sex chromosomes that differ between females and males. Females have two copies of the X-Chromosome, while males have one X-Chromosome and one Y-Chromosome. The following image **Fig. 28** shows the human chromosomes grouped and numbered in pairs [197]. Note the X and Y sex chromosomes.

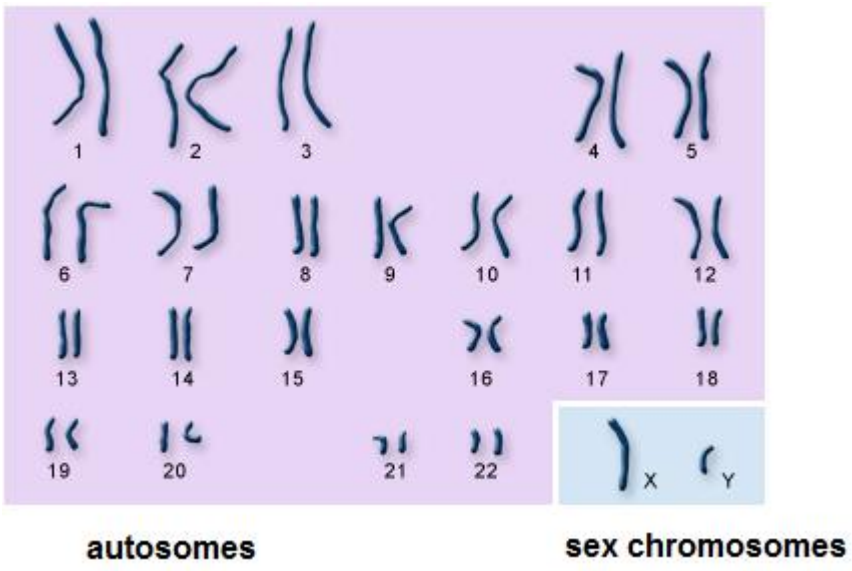

Figure 28 Human chromosomes in groups [197]**.**

Chromosome are made up of DNA and have constriction points known as centromeres. Centromeres divide chromosomes into two short and two long arms, the short arm is called p arm and the long arm is called q arm. DNA is a long coiled double helix, which is firmly coiled around a type of protein known as histones. A section of the DNA is called a gene. A normal individual has two copies of each gene, one is inherited from father and one from mother. DNA molecules are made up of four bases (nucleotides): adenine (A), guanine (G), thymine (T), and cytosine (C). Determining the order of these nucleotides within a gene via any technology or method is called DNA sequencing. Each gene carries the information and instructions needed to direct the human body cells what to do and how to behave and when to grow, reproduce and die [198]. Therefore, all cells in the human body start with nuclear DNA, apart from mature red blood cells (RBCs) and cornified (dead) cells that lack nuclei. Mature RBCs don't have nucleus, mitochondria, Golgi apparatus, and endoplasmic reticulum, to accommodate maximum space for haemoglobin used for carrying oxygen molecules, in addition to maintain its characteristic biconcave shape allowing easy diffusion in blood vessels. The following image **Fig. 29** shows a chromosome structure in detail [197].

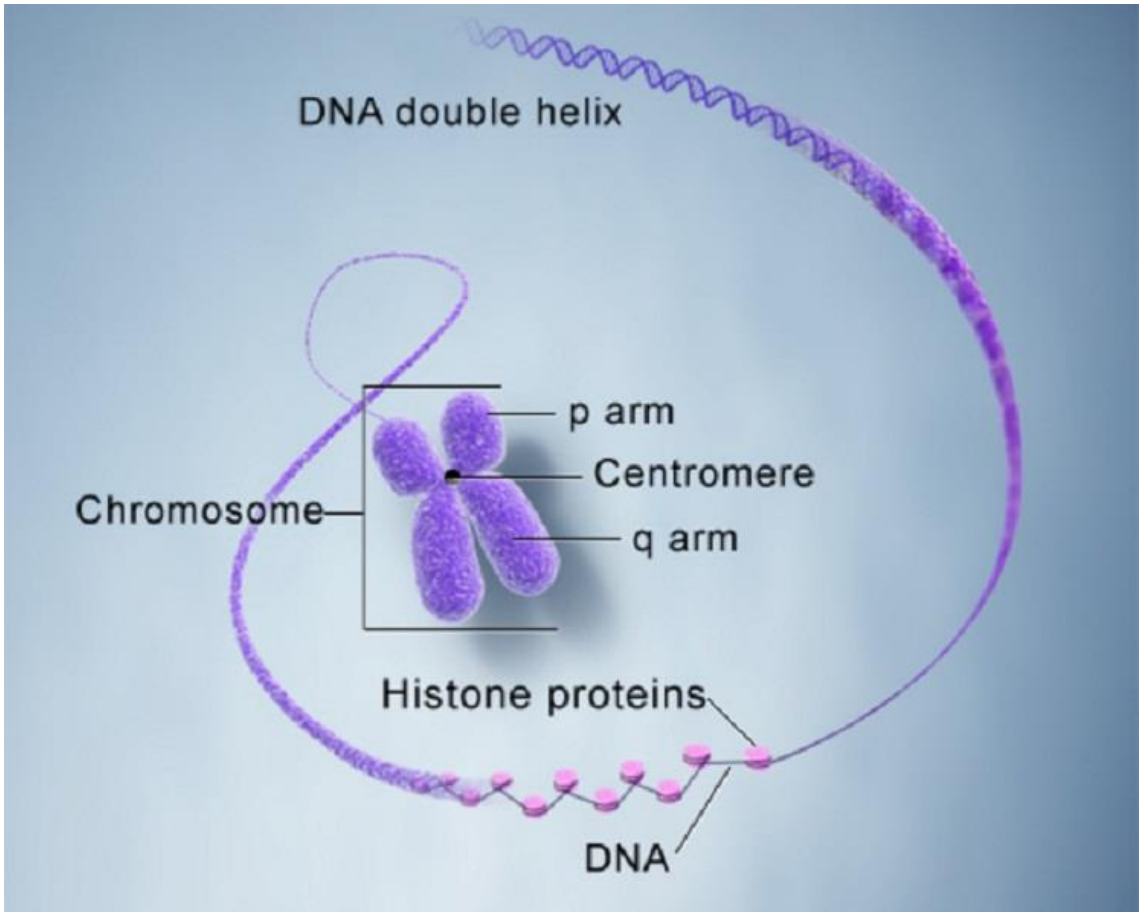

Figure 29 Chromosome structure [197]**.**

6.2.1 The human Y-Chromosome DNA

The Y-Chromosome is the sex-determining chromosome, and it is only found in males. A male inherits the Y-Chromosome from his father, who inherited it from his father, and so forth, and it remains almost unchanged across generations as it undergoes very little recombination with the X-Chromosome [199]. It follows, therefore, that a direct paternal line can be traced by testing special sections on the Y-Chromosome DNA.

6.2.2 The human Y-Chromosome DNA haplogroups

According to genetics, our human ancestors migrated from one place to another thousands of years ago and developed distinct mutations after reaching different geographic regions, allowing them to adapt to new environments leading to the

formation of new populations. Each genetic population has a group of mutations known as haplogroups. The haplogroups that are passed down along the patrilineal line are the human Y-Chromosome DNA haplogroups. The human Y-Chromosome DNA haplogroups describe single branches and their related branches by tracing them back to a single mutation. A mutation that is shared by many people is called Single Nucleotide Polymorphism (SNP) and so every single Y-Chromosome DNA SNP represents a new branch on the Y-Chromosome tree. Likewise, each human Y-Chromosome DNA haplogroup is defined by a specific SNP. For example, the major human Y-Chromosome DNA haplogroup J is defined by the SNP mutation M304. Moreover, each major human Y-Chromosome DNA haplogroup has a site of origin that has natural physical boundaries. For example, Western Asia is recognised to be the geographic origin of the major human Y-Chromosome DNA haplogroup J- M304 [200].

6.2.3 The Y-Chromosome DNA testing types

There are two types of testing the Y-Chromosome, Short Tandem Repeat (STR) test which is used for investigating recent ancestry, and Single Nucleotide Polymorphism (SNP) test which is used for studying ancient ancestry. Y-Chromosome DNA SNP tests determine the human Y-Chromosome DNA haplogroups which can be used to determine geographic origins. Each SNP is a genetic variation that represents a new branch on the Y-Chromosome DNA tree. Testing the Y-Chromosome can only be done on males as only males have the Y-Chromosome, females do not. However, for a female to know her family roots a genetic sample can be taken from her father, her brother, or a male relative so as to have the test done appropriately. The Y-Chromosome DNA STRs are also known as markers. Each marker represents a series of repeating nucleotides (adenine (A), cytosine (C), guanine (G), and thymine (T)). The STR in the following: (TGT**GTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTT**GAC), is the repeated **GTT** segments [201]. Y-Chromosome DNA STR tests look for matching STRs and are used to verify close relationships between two males and to find genetic matches that are on the same paternal line. DNA sequencing is the method or technology used to determine the order of the nucleotides within a

gene. At the Family Tree DNA (FTDNA) genetic testing company, the next generation sequencing (NGS) is used for the Big Y test as the most advanced technology for SNP testing and SNP discovery at high speed [202]. The Big Y-700 test from FTDNA examines more than 200K SNPs on the Y-Chromosome [200]. FTDNA also recommends and links the search available at the National Center for Biotechnology Information (NCBI) via the following website (https://blast.ncbi.nlm.nih.gov/Blast.cgi) to use the Basic Local Alignment Search Tool (BLAST) to instantly search for matches.

6.2.4 The geographic origins of the human Y-Chromosome DNA haplogroups

There are 20 major human Y-Chromosome DNA haplogroups, namely, A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S and T. Each major haplogroup has a site of origin that has natural physical boundaries such as mountain ranges and oceans. For instance, the human Y-Chromosome DNA haplogroup R is common among the native people of Europe, while the human Y-Chromosome DNA haplogroup E is the haplogroup of the native people of Africa. Furthermore, the human Y-Chromosome DNA haplogroup J is common among the native people of Western Asia, and the human Y-Chromosome DNA haplogroup O is common in China, etc. Descendants of each human Y-Chromosome DNA haplogroup are descendants of one most recent male from which all the individuals in that haplogroup are directly descended. In genetic genealogy the most recent male is known as the most recent common ancestor (MRCA) [203]. The geographic regions and the environmental boundaries are the main reasons behind the distinct mutation of each haplogroup. Individuals of each haplogroup share a distinct mutation that has made them able to live in a particular habitable zone and be successful in their unique environment.

6.2.5 Gene mutations and the human Y-Chromosome DNA haplogroups

The genetics of human migrations explains that our human ancestors migrated across the continents thousands of years ago, and each population developed specific gene mutations after reaching new destinations to get used to the new environments. These gene mutations have made each descendant population unique from any other population. These groups of mutations are known as haplogroups [200]. According to the human Y-Chromosome DNA haplogroups, native human populations are distributed on earth's surface in a way that individuals of each human Y-Chromosome DNA haplogroup share a distinct mutation that shapes their physical features, their skin, their metabolism of food, and their immune system to deal with different environmental pathogens, specifically for the geographic region where their human Y-Chromosome DNA haplogroup is originated from. Therefore, descendants of each human Y-Chromosome DNA haplogroup are genetically designed to live safely within the geographic regions of their haplogroups and without developing unrelated health conditions i.e., their body is genetically designed specifically for the environments of where they belong to. These successful adaptations to constant environmental stress, occurred thousands of years ago and it can no longer be changed. For example, native populations of coldest places on earth, where there is low ultraviolet (UV) radiation, are genetically designed to have light skin colour due to less melanin pigmentation in their skin. The light skin provides the native inhabitants with better UV radiation absorption which helps their body to produce more vitamin D needed by the body for important body functions including better immunity. On the other hand, native populations of the hot/sunny parts of the world where there is high UV radiation, have dark skin colour being rich in melanin pigments. This dark skin protects their body from the damaging effects of UV radiation of the hot/sunny climate conditions. Vitamin D’s classic effects are on calcium and bone homeostasis, however deficiency in vitamin D is also associated with increased susceptibility to infection and an autoimmunity disease [204]. Therefore, if a dark-skinned individual migrated to a low UV radiation geographic zone, then they are at higher risk of developing immunity related health conditions due to the high melanin pigmentation in their skin which makes

it difficult for their body to get the vitamin D needed for the important body functions. Therefore, light-skinned individuals moving to high sunlight places, will be at an increased risk of getting gene mutations that will cause cancer, especially skin cancer. On the other hand, dark-skinned individuals who live in places with mild sunlight, will also be at an increased risk of getting gene mutations that will cause numerous types of cancers [205].

6.2.6 Natural physical boundaries and political boundaries

When our human ancestors migrated from one geographic region to another thousands of years ago, they developed distinct gene mutations following reaching different geographic regions to allow them to adapt to the new climate conditions, leading to the formation of regional human populations. The individuals of each established regional population share a distinct gene mutation as descendants of one Y-Chromosome DNA haplogroup living in a specific geographic region that has natural physical boundaries. The past migrations of our human ancestors have established our present regional human populations and it has become very much similar to a system that has been established for good and it cannot be changed. The following example is based on the work carried out in this research and it explains what is meant by a system that has been established for ever and it cannot be modified: The descendants of the human Y-Chromosome DNA haplogroup J-M267 are descendants of a most recent male who lived in the geographical region of the Arabian Peninsula, and the descendants of the human Y-Chromosome DNA haplogroup R-M198 are descendants of a most recent male who lived in the geographical region of the Central and Eastern Europe. It follows that if individuals of the human Y-Chromosome DNA haplogroup R-M198 migrated to the geographical region of the Arabian Peninsula and settled there, they remained descendants of the human Y-Chromosome DNA haplogroup R-M198 never became descendants of the human Y-Chromosome DNA haplogroup J-M267 or native clans of Arabia. Another simple example is that if a child from a geographical region was adopted by a family from another geographical region and settled with them in that geographical region, there is no way that the child will become their biological

child and that his Y-Chromosome DNA will change to the same Y-Chromosome DNA of the father. In genetic genealogy, the most recent common ancestor (MRCA) of a human Y-Chromosome DNA haplogroup is the most recent man from whom all the people of the haplogroup are descended and they all belong to a geographical region in which that common ancestor lived [203]. Each human Y-Chromosome DNA haplogroup has a site of origin that has natural physical boundaries. Natural physical boundaries are not political boundaries between countries, for instance Western Asia as a geographic region has natural physical boundaries, however it includes many independent countries that have political boundaries. Since Western Asia is the home of the human Y-Chromosome DNA haplogroup J, and thus the indigenous people of all the independent countries of Western Asia are descendants of the human Y-Chromosome DNA haplogroup J i.e., they are all descendants of one most recent male or one most recent common ancestor, and therefore native inhabitants of a geographic region who belong to the same human Y-Chromosome DNA haplogroup have the same bloodline as they all descend from one recent male. However, geographic regions may include more than one country with political borders and therefore descendants of a human Y-Chromosome DNA haplogroup may not have shared traditions and may not speak a common language or they may have shared traditions and may speak the same language. For example, the native Arab tribes in Yemen, Yemen as an independent country on the southern tip of the Arabian Peninsula that has political borders, are descendants of the same most recent ancestor as the Arab tribes in the south of Saudi Arabia (Saudi Arabia as an independent country that has political borders) i.e., even though Yemen and Saudi Arabia are two different independent countries that have political boundaries, their native Arab tribes belong to the same human Y-Chromosome DNA haplogroup. Similarly, the indigenous people of the Fertile Crescent (which comprises a number of independent countries that have political boundaries), however they all belong to the same human Y-Chromosome DNA haplogroup, which means they all have the same bloodline due to the fact that they all are descendants of one recent common ancestor. However, the descendants may have different traditions and speak different languages or some of them may have very close traditions and speak the same language with different dialects.

6.3 A proposed definition of race and ethnicity described in this work

According to the research work carried out in this study, a new definition of race and ethnicity is proposed which suggests a new classification and list of ethnic groups in the UK and the world through classifying the human populations of the world according to the major human Y-Chromosome DNA haplogroups. Therefore, according to this work race is defined as a term which refers to the descendants of each major human Y-Chromosome DNA haplogroup that all share one distinct mutation and all have one bloodline as descendants of one most recent male, regardless of having shared traditions or a common language. The mother side is not counted in this proposed new definition of race because the Y-Chromosome is the sex-determining chromosome and is only found in males through which a direct paternal line is traced since the Y-Chromosome undergoes almost no recombination. A male inherits the Y-Chromosome from his father, who inherited it from his father, who inherited it from his father and so forth, however the race of a female is the same race as her father exactly like how surnames follow paternal lines in almost every culture around the world. Descendants of each major human Y-Chromosome DNA haplogroup, according to the new definition of race and ethnicity proposed in this research, are suggested to be named after the names of their human Y-Chromosome DNA haplogroups i.e., the racial classification is not referred to as African, Asian or European or White or Black, etc., hence the proposed racial classification is referred to as being from which major human Y-Chromosome DNA haplogroup such as the human Y-Chromosome DNA haplogroup E, the human Y-Chromosome DNA haplogroup J, or the human Y-Chromosome DNA haplogroup R, etc. The importance of the new proposed definition of race and ethnicity in this work is that it gives the actual race and ethnicity classification. The proposed classification is therefore to classify the human populations of the world after the names of the 20 major human Y-Chromosome DNA haplogroups which are A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S and T. Since each major haplogroup has a site of origin that has natural physical boundaries, the proposed ethnic grouping gives the real site of origin which is not always the country or place of birth, in addition to other data that are of high importance especially in the medical

field including disease control and prevention to deal with diseases such cancer and the risk factors that affect the communities as well as pandemic outbreaks, for example coronavirus disease 2019 (COVID-19). Furthermore, the classification and the modified list of ethnic groups proposed in this work avoids all forms of racial discrimination by avoiding identifying and listing people after their skin colour or as Blacks or Whites or Europeans or Asians or BAME i.e., Black, Asian and Minority Ethnic. Surveys have reported that many people feel nervous or uncomfortable using these terms and described as inappropriate terms [206]. Therefore, the proposed pattern is to ask about the ethnic group is equal to all people and the questions is simply what is their haplogroup instead of asking what their ethnic group is and the answer is a letter of the haplogroups.

6.4 The new genetic concept of cancer

A new genetic concept of cancer has been investigated and presented in this research work as an original work. The new genetic concept of cancer links the development of cancer to the human population origins and migrations, and the environmental factors and gene mutations. The new genetic concept of cancer presented in this work is based on understanding the human Y-Chromosome DNA haplogroups and their sites of origin, and it works as an important prevention and protective strategy for individuals, families and populations to keep them away from getting the disease. The new genetic concept of cancer explains that if individuals of one of the human Y-Chromosome DNA haplogroups leave their geographic zone and move to other geographic regions that belong to other human Y-Chromosome DNA haplogroups, will be at an increased risk of getting gene mutations that will cause cancer. The reason behind that is that when our human ancestors migrated from one place to another, changes in their environments forced them to adapt to fit the new environments, eventually causing each population to evolve into a new population. Distinct mutations made each population to have new physical features specifically for their new environment. These successful adaptations to constant environmental stress and the formation of new populations with distinct mutations, each time, took thousands of years and over many generations within each population. However,

the past human migrations have formed the present human populations and therefore if humans now migrate from one place to another, again changes in their climate conditions, will force them to get used to the new conditions, which may cause mutations. However, these new gene mutations now will not form new human haplogroups like how it occurred in the past over thousands of years with our human ancestors. Instead, these mutations cause an abnormal growth of the body cells which tend to multiply without control, starting in one place and later may spread to the rest of the body. And this is the new concept of cancer, investigated with evidence using family history and genetic testing supported by data from affected individuals obtained from the hospitals where they received treatments.

6.5 Acquired gene mutations caused by environmental factors

Past studies have highlighted that up to 90% of gene mutations that cause cancer are caused by environmental factors and they tend to occur later in life when compared to similar types of inherited cancers [207] [2]. Inherited gene mutations that cause cancer run in families, and similarly, non-inherited genetic cancers may also look to run in families when a common environment and lifestyle is shared by them. The research carried out in this work confirms that cancers caused by acquired gene mutations do look to run in families when they share a common environment and lifestyle, and evidence is presented in this study based on numerous case studies which show that when families with multiple cancers running amongst them generation after generation are investigated, results confirm that the cancers are caused by acquired gene mutations due to living in an environment of a geographic region that they don't belong to, supported by genetic testing. Mutations may occur either naturally or because of many other factors, such as radiation, chemicals, smoking, poor diet etc, however according to the new concept of cancer presented in this study, these gene mutations take place because the human body tries to change itself to get used to the aforementioned factors. For example, smokers are at high risk of getting lung cancer, because their lungs are designed in the first place to take fresh air, however when an individual smokes, they take toxic polluted smoke that their

lungs are not genetically designed for, and eventually gene mutations occur to start and eventually produce a different form of lungs that can adapt to the toxic conditions that smokers create. Another example is when an individual is exposed to radiation, their skin in the first place is not genetically designed for such type of radiation and therefore gene mutations start to occur in the body to give new instructions to produce new cells for a new type of skin cells that can adapt to the radiation. This new concept of cancer further explains that these genetic instructions are eventually spread to the other parts of the body as well in a way a new body of cells and tissue to be produced with the capability of living with the smoke or radiation they had exposed to. However, this process is not possible to be completed and therefore individuals with such gene mutations eventually die. This explanation is based on the fact that when the past human migrations formed the present human populations it has become similar to a system that cannot be modified. Therefore, when present environmental factors cause gene mutations amongst the present-day humans to adapt to such factors, they will not form new humans but abnormal body cells (cancer cells). The following phylogenetic tree **Fig. 30** presented in this work is the human Y-Chromosome DNA haplogroups tree and it demonstrates the major human Y-Chromosome DNA haplogroups starting with the major human Y-Chromosome DNA haplogroup A [208]. The human Y-Chromosome DNA haplogroup A is the most recent male and it is known as the most recent common ancestor (MRCA) and it demonstrates the root of the tree [203]. The shown phylogenetic tree is based on the gene mutations that occurred thousands of years ago due to the past migrations of our human ancestors which led to the establishment of the major human Y-Chromosome DNA haplogroups. Likewise, each major human Y-Chromosome DNA haplogroup represents a distinct population belonging to a specific geographical region that has natural physical boundaries allowing the descendants of each human Y-Chromosome DNA haplogroup to live safely and without developing gene mutations responsible for causing unrelated health conditions and illnesses.

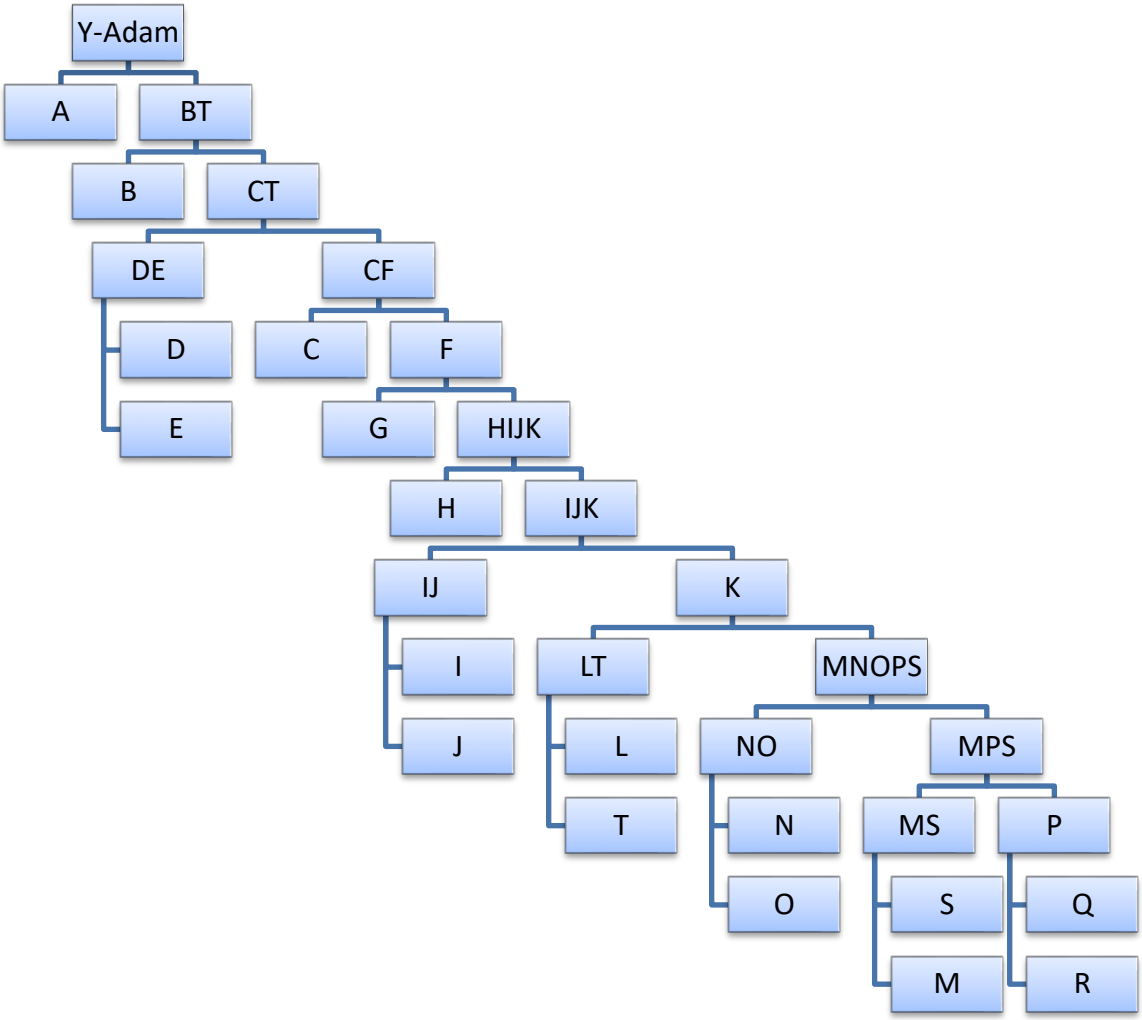

Figure 30 Phylogenetic tree of the human Y-Chromosome DNA haplogroups**.**

6.6 Genetic testing carried out in this work in support of the new genetic concept of cancer

Genetic testing was carried out in this work to investigate a number of families and to identify the human Y-Chromosome DNA haplogroups for each family. The families were investigated based on studying the history of cancer among the members of each family investigated for up to five generations representing roughly from 100 to 1000 family members for each family due to the fact that some families had smaller, and others had larger household sizes. One human genomic DNA sample was collected through non-invasive DNA method (cheek swab) using the Family Tree DNA snap-off swab test kit from one male member

of each family participated in this study. The number of participants tested was a total number of 15 male members representing 15 families with each family being investigated up to five generations i.e., the total number of family members investigated being approximately ranging from 1500 to 15000 family members for this research programme. 15 novel human Y-Chromosome DNA haplogroup results were obtained for the 15 families that have never been tested before. The human Y-Chromosome DNA test results of the participants were positive to the major human Y-Chromosome DNA haplogroup J, and the major human Y-Chromosome DNA haplogroup R. The methodology followed was to study each family on its own to investigate their cancer history for up to five generations to see if there any cancer cases ever found amongst them, and then to test a male member from each family for genetic testing to find out if they have lived in a geographic region of their major human Y-Chromosome DNA haplogroup. It was found that the families that have no patterns of cancer running among them have always lived in the geographic regions of their human Y-Chromosome DNA haplogroup. However, it was found that one family had various cancers running among them in multiple generations and following the genetic testing of a male member of the family, it was found that the family has lived in a geographic region that they don't belong to. Importantly, a blood sample was obtained from a female member of the family to find out if there are any hereditary gene mutations running in the family that are known for causing breast cancer and other related cancers, but the results were negative and that there were no changes detected in their genes. The genetic samples of the participants in this study and their test results are presented as kit numbers starting from 1 to 15, for example kit number 1, kit number 2, kit number 3, and so on to kit number 15. All the DNA samples were tested at the labs of the approved genetic testing company Family Tree DNA (FTDNA) in the United States. Y-Chromosome DNA Short Tandem Repeat (STR) test was ordered Y-12 which examines 12 STRs (markers) on the Y-Chromosome for each participant, and then Y-Chromosome DNA Single Nucleotide Polymorphism (SNP) test was ordered for each DNA sample to determine their human Y-Chromosome DNA haplogroups with 100% confidence using the Backbone SNP test. However, two DNA samples were also tested for the big Y-700 test which examines 700 STRs and more than 200K SNPs on the

Y-Chromosome. The Y-Chromosome DNA STR markers that were tested at the labs of FTDNA are their standard Y-12 markers shown in their panel 1 (1-12): DYS393, DYS390, DYS19 (also known as DYS394), DYS391, DYS385, DYS426, DYS388, DYS439, DYS389I, DYS392, DYS389II. The DYS prefix is part of the STR scientific name on the Y-Chromosome in which D stands for DNA, Y stands for Y-Chromosome, and S stands for a unique segment. Each STR markers has a unique identification number such as 393 or 390 etc., all named according to the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC) guidelines [209]. The investigation carried out in this research followed a population genetics research methodology to provide a clear understanding of the gene mutations that occurred overtime and caused various cancer cases to affect families specifically lived in the known geographic region of Western Asia to present evidence that cancer caused by acquired gene mutations does appear to run in families when a common environment is shared by them. Therefore, the investigation started by genetically testing a family that has had multiple cancers running among them. The results showed that the family is from the geographic region of the Central and Eastern Europe and has lived in the geographic region of the Arabian Desert in the Arabian Peninsula. Comparably, a number of families were investigated and genetically tested from native tribes of the geographic region of Western Asia. The DNA samples that were obtained for this investigation were obtained from members of families from the main well known native Arab tribes that are known to be indigenous clans of the Arabian Peninsula. The DNA samples represent covering almost the entire geographical region of the Arabian Peninsula in addition to a number of samples from the northern part of the geographical region of Western Asia. The results of the tested DNA samples of the native families who have always lived in the geographical regions that they belong to, revealed no patterns of any types of cancers running among them. However, the cancer cases that were found in some of the families were of known risk factors not being related to being living in geographical regions that they don’t belong to.

6.6.1 Genetic testing for kit number 1

A DNA sample (kit number 1) was obtained from a male participant who is a member of a family that has had multiple cancers running among them. The historical evidence provided by the family regarding their origins and migrations revealed that their ancestors arrived in the northern Arabian Peninsula roughly around 450 years ago. The family later settled among the Arab tribes through purchasing properties as well as marriages. The following table (**Table 2**) is the Y-Chromosome DNA standard STR markers Y-12 test results of the standard FTDNA panel 1 (1-12) for the DNA sample (kit number 1).

Table 2. Y-Chromosome DNA standard Y-STR values for the DNA sample kit number 1.

PANEL 1 (1-12)											
Marker	DYS393	DYS390	DYS19	DYS391	DYS385	DYS426	DYS388	DYS439	DYS389I	DYS392	DYS389II
Value	13	25	16	10	11-14	12	12	10	13	11	30

The analysis of the DNA test results as given in (**Table 3**) showed that the family is positive to the human Y-Chromosome DNA haplogroup R-M198. The human Y-Chromosome DNA haplogroup R-M198 has the highest frequency in the geographic region of the Central and Eastern Europe [210], not the Arabian Peninsula.

Table 3. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 1.

SNP Name	Test Results	Test Type
M198	Positive (+)	Y-HAP-Backbone

The major human Y-Chromosome DNA haplogroup R (also known as R-M207) has two major lineages, the human Y-Chromosome DNA haplogroup R1 (also known as R-M173) and the human Y-Chromosome DNA haplogroup R2 (also

known as R-M479). Likewise, the human Y-Chromosome DNA haplogroup R1 has two descendant subclades, the human Y-Chromosome DNA haplogroup R1a (also known as R-M420) and the human Y-Chromosome DNA haplogroup R1b (also known as R-M343). Furthermore, the human Y-Chromosome DNA haplogroup R1a has two descendant subclades, the human Y-Chromosome DNA haplogroup R1a1 (also known as R-M459) and the human Y-Chromosome DNA haplogroup R1b1 (also known as R-YP4141). Moreover, the human Y-Chromosome DNA haplogroup R1a1 has two descendant subclades, the human Y-Chromosome DNA haplogroup R1a1a (also known as R-M198) and the human Y-Chromosome DNA haplogroup R1b1b (also known as R-YP1301), as shown in the following image **Fig. 31** [211].

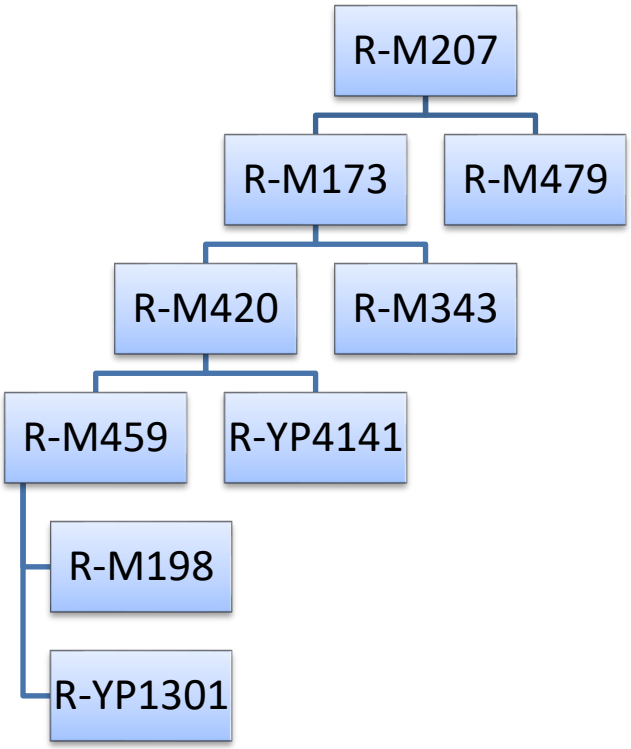

Figure 31 The major human Y-Chromosome DNA haplogroup R or R-M207 branch of the Y-Chromosome DNA Haplotree by FamilyTreeDNA (FTDNA). Highlighted is the confirmed human Y-Chromosome DNA haplogroup of kit number 1 which is R-M198 **[211]**.

Typically, the climate of majority of the Central and Eastern Europe region is classified as moderately continental with cool humid continental summers but

warmer summers in the lowlands, and extremely cold long-lasting winters with mist, fog, and rain during the winter months and plenty of mountain snowfalls [212]. The following image **Fig. 32** represents the distribution map (with high frequency in the Central and Eastern Europe) of the human Y-Chromosome DNA haplogroup R1a1a or R-M198 [210].

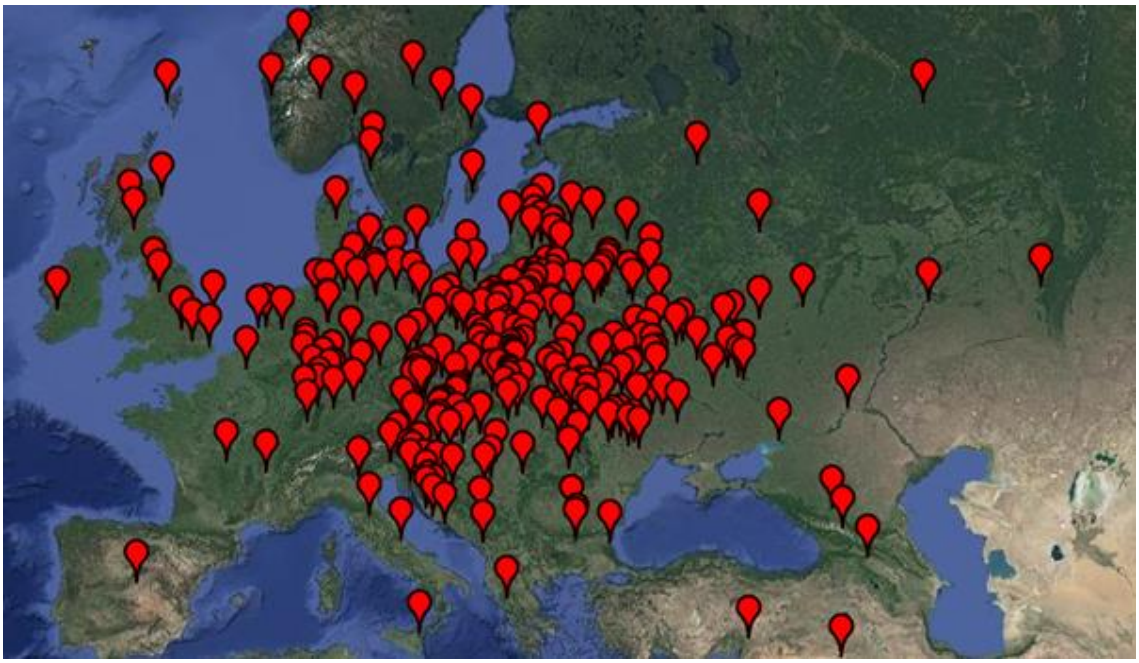

Figure 32 Haplogroup R-M198 matching map of [210]**.**

As explained the members of the family discussed in this section are native inhabitants of the Central and Eastern Europe region and they are genetically designed to live safely in the climate conditions of their geographic zone and without developing unrelated health issues and gene mutations. However, due to the fact that they have left their site of origin and moved to a geographic region that they don't belong to i.e., the hot desert climate of the Arabian Peninsula. Changes in their climate conditions have therefore forced them to adapt to the new environments and they have become at a higher risk of getting gene mutations that cause difficult health conditions such as cancer running among them as demonstrated unlike the native inhabitants of the Arabian Peninsula who are genetically designed to live safely in the hot desert climate. The indigenous people of the Arabian Peninsula are the original Arab clans that have specific

physical features and behavioural adaptations that allow them to live and survive the hot desert climate conditions. The indigenous tribes of the Arabian Peninsula are descendants of the major human Y-Chromosome DNA haplogroup J (also known as J-M304). The human Y-Chromosome DNA haplogroup J is believed to have evolved in the geographic region of Western Asia. The following image **Fig. 33** represents the map of Western Asia as described above [213].

Figure 33 Map of Western Asia [213]**.**

As a geographic concept, Western Asia includes the Arabian Peninsula, the Sinai Peninsula, the Levant, Mesopotamia (the land between the two rivers), Anatolia, Iran, the Armenian Highlands, as well as the South Caucasus. Western Asia is surrounded by seven major seas, the Arabian Sea, the Red Sea, the Mediterranean Sea, the Aegean Sea, the Black Sea, the Caspian Sea, and the Persian Gulf. To the north, the Caucasus Mountains delimit Western Asia from Europe. While to the southwest, the Isthmus of Suez delimits Western Asia from Africa. To the east, the Low Plains and Emptiness Plain deserts in eastern Iran

naturally delimit Western Asia from Asia itself. Western Asia can be described as two main regions, the northern part which comprises the Fertile Crescent, and the southern part which comprises the Arabian Desert. The Euphrates River acts as a natural border dividing Western Asia into the northern part and the southern part. The Arabian Desert region is adjacent to the tropics, and it has a subtropical, hot desert weather, mainly hot and arid with sunshine. The northern part of Western Asia and with the presence of the two rivers, Tigris and Euphrates, has a humid fertile climate with rainfall in the winter months but colder and usually rainier in the mountains, and a sunny and hot weather in the summertime. The major human Y-Chromosome DNA haplogroup J (also known as J-M304) has two main descendant subclades, the human Y-Chromosome DNA haplogroup J1 (also known as J-M267) and the human Y-Chromosome DNA haplogroup J2 (also known as J-M172) as shown in the following image **Fig. 34** [214].

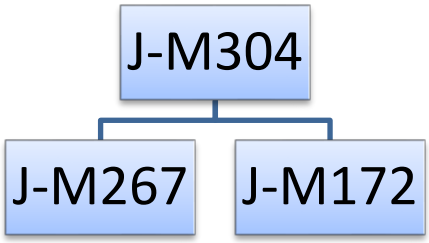

Figure 34 The major human Y-Chromosome DNA haplogroup J and its two descendant subclades, the human Y-Chromosome DNA haplogroup J1 (or J-M267) and the human Y-Chromosome DNA haplogroup J2 (or J-M172) [214].

The human Y-Chromosome DNA haplogroup J1 or J-M267 is most frequent in the southern part of the geographical region of Western Asia i.e., the Arabian Peninsula. The human Y-Chromosome DNA haplogroup J1 is the main haplogroup found among the tribes of Arabia i.e., the indigenous people of the geographical region of the Arabian Desert. On the other hand, the human Y-Chromosome DNA haplogroup J2 is believed to have been originated in the northern part of Western Asia. The human Y-Chromosome DNA haplogroup J2 is the main haplogroup of the people of the Fertile Crescent where people started and developed farming and agriculture due to the fertility of its land [200]. The

following genetic pedigree **Fig. 35** has been created in this work which shows the investigated (kit number 1) family's health details of multiple generations.

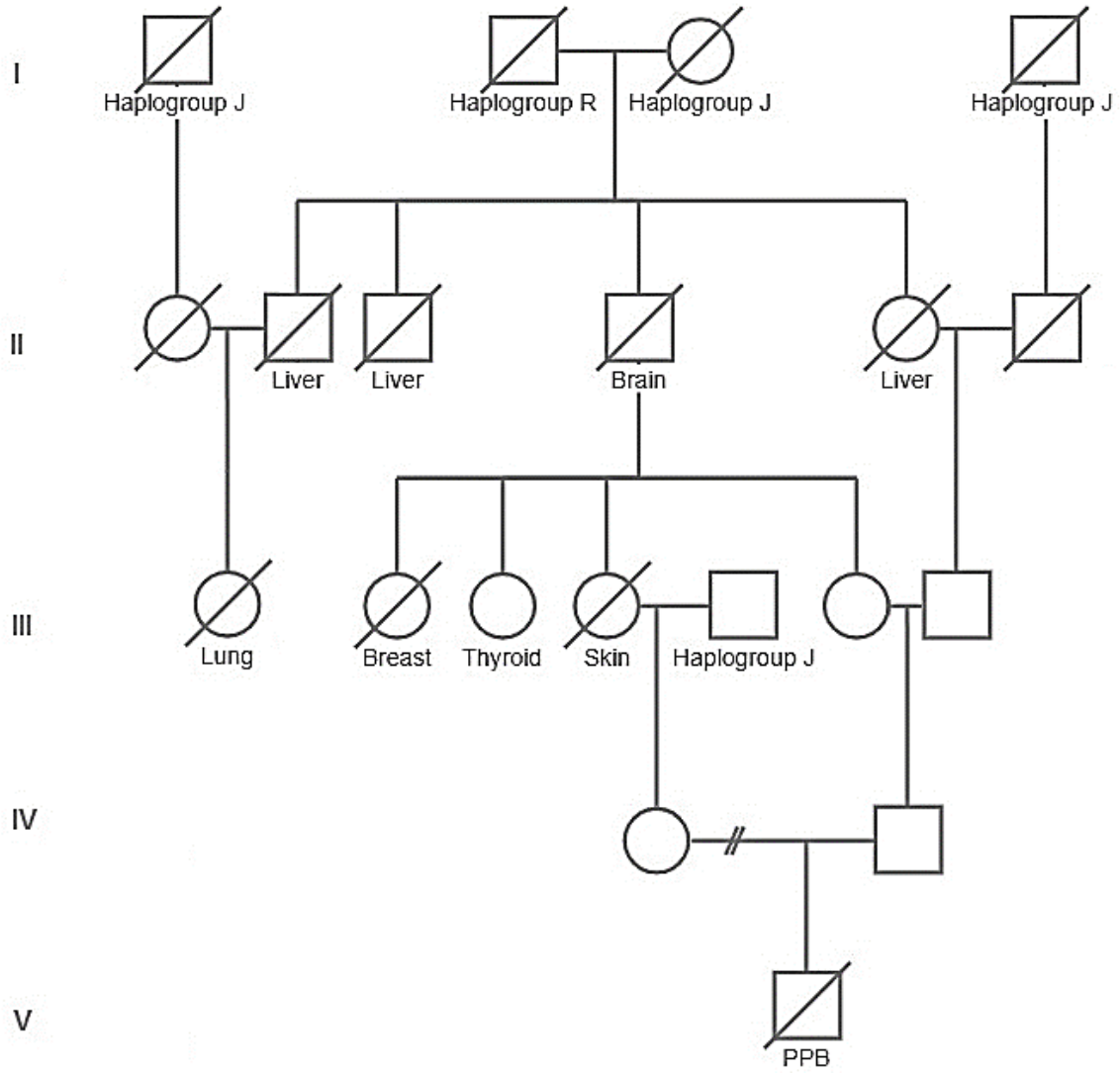

Figure 35 A five generation pedigree created in this work showing the health history of the family with the Roman numerals I, II, III, IV and V, represent the generations of the family.

The squares in the pedigree stand for the male individuals of the family and the circles represent the female members. In generation I the subtext shows the major human Y-Chromosome DNA haplogroup that each individual of the family belongs to. The subtext in the rest of the generations of the pedigree shows the

type of cancer of each affected individual in the family. The deceased members of the family are demonstrated in the pedigree as crossed out squares and circles. The five-generation pedigree presented in this study represents the health history of the human Y-Chromosome DNA haplogroup R-M198 family investigated in this work approximately for the past 150 years. The pedigree starts with the great grandfather of the family and his wife. To be noted is that it wasn't possible to find any health records in regard to any of them. However, historical evidence regarding the ancestry of the wife was available including information about her relatives and more importantly her male relatives from her father side who are still alive, and this was very essential in order to obtain a DNA sample from one of them. The genetic testing for confirming the human Y-Chromosome DNA haplogroup can only be conducted on male members of the family from the father side. Therefore, a male relative from the father side of the wife was very crucial for obtaining a DNA sample from him needed for confirming the ancestry of the family of the wife, and to investigate and to confirm the human Y-Chromosome DNA haplogroup of her family to find out what might have caused the incidence of multiple cancers among their descendants to support the new genetic concept of cancer presented in this research.

6.6.2 Genetic testing for kit number 2

A DNA sample was obtained from a male relative of the Arab wife (kit number 2) for genetic testing. However, it was important for the DNA sample to be tested for Big Y-700 test. The Big Y-700 test can find unique Y-Chromosome DNA variants carried by and specific to the paternal line of the tested individual. The Big Y-700 test examines 700 STR markers of the standard FTDNA panels from panel 1 to panel 7. The Big Y-700 test also examines more than 200K SNPs on the Y-Chromosome and can find male relatives who share a direct paternal line up to 20 generations back. Big Y-700 test was essential to collect more information about the origins of the family of the Arab wife to exclude her family side from being responsible for the cancer cases running in the family of her husband investigated in this study. The following table (**Table 4**) is the Y-Chromosome DNA standard STR markers Big Y-700 test results (only 3 panels are displayed)

of the standard FTDNA panel 1 (1-12), panel 2 (13-25) and panel 3 (26-37) for the DNA sample (kit number 2).

Table 4. Y-Chromosome DNA standard Y-STR values for the DNA sample kit number 2.

PANEL 1 (1-12)											
Marker	DYS393	DYS390	DYS19	DYS391	DYS385	DYS426	DYS388	DYS439	DYS389I	DYS392	DYS389II
Value	13	22	14	10	12-14	11	16	11	14	11	31

PANEL 2 (13-25)									
Marker	DYS458	DYS459	DYS455	DYS454	DYS447	DYS437	DYS448	DYS449	DYS464
Value	16	8-9-9	11	11	26	15	21	30	13-13-16-16-17-18

PANEL 3 (26-37)										
Marker	DYS460	Y-GATA-H4	YCAII	DYS456	DYS607	DYS576	DYS570	CDY	DYS442	DYS438
Value	10	10	19-22	15	12	19	18	35-37-37	11	9

The following table (**Table 5**) is the SNP test results (only 10 SNP test results are displayed) for the DNA sample (kit number 2). The analysis of the results showed that the family of the Arab wife is positive to the human Y-Chromosome DNA haplogroup J2 or J-M172. The human Y-Chromosome DNA haplogroup J-M172 is believed to have evolved in the geographic region of the northern part of Western Asia. Historic data and sources confirmed that up to date, no cancer cases ever occurred among the members of this family i.e., the family of the Arab wife. The sources also confirmed that the family has always lived in the geographic region of northern Western Asia near northern Arabian Peninsula. The results are very important for supporting the investigation carried out in this study because it is evidence that the cancer cases occurred among the family of her husband due to the human Y-Chromosome DNA haplogroup R-M198 ancestry, not the human Y-Chromosome DNA haplogroup J-M172 family.

Table 5. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 2. To be noted is that only 10 SNP test results are displayed in the table.

SNP Name	Test Results	Test Type
M172	Positive (+)	Y-HAP-Backbone
A2578	Positive (+)	Big Y-700
A2594	Positive (+)	Big Y-700
A2606	Positive (+)	Big Y-700
A2614	Positive (+)	Big Y-700
A2636	Positive (+)	Big Y-700

These results are also evidence that due to the fact that since this human Y-Chromosome DNA haplogroup J-M172 family has been living in the geographic region that they belong to, thus according to the new concept of cancer presented in this work, they never needed their body to redesign itself as they never needed to adapt to the climate conditions, and therefore their body needed no gene mutations and so these gene mutations never occurred to cause even one single cancer case among them. It follows, therefore, that the cancer cases found among their descendants in generation II of the pedigree is because of the human Y-Chromosome DNA haplogroup R-M198 lineage. Important as the starting point to explain what past studies have highlighted how non-inherited cancers caused by non-inherited gene mutations may also appear to run in families when a similar environment is shared by them [5] [6]. In generation II of the pedigree, three liver cancer cases were found in two males and one female, in addition to one brain cancer case found in one male. Each individual in generation II, had married and had descendants that formed generation III. Likewise, in generation III four cancer cases were found among them. One lung cancer case, one breast cancer case, one thyroid cancer case, and one skin cancer case, all of which affected female

individuals. Investigating the cancer cases found in generation III, formed the very vital foundation/key in supporting the new concept of cancer presented in this research, because it is also evidence that the cancer cases again occurred due to the haplogroup R-M198 ancestry.

6.6.3 Genetic testing for kit number 3

The case of the female family member with liver cancer in generation II of the pedigree was investigated in detail in this study. Historical data and sources confirmed that she had married to a man who is a member of an Arab tribe that is known to be native inhabitants of the Arabian Peninsula. A genetic sample was therefore obtained from one of the male relatives of the husband, and the results as given in (**Table 6**) showed that they are positive to the human Y-Chromosome DNA haplogroup J-M267. Historical data and sources also confirmed that none of their children ever had cancer even with their mother as shown in generation II of the pedigree being from the human Y-Chromosome DNA haplogroup R-M198 family.

Table 6. Single Nucleotide Polymorphism (SNP) test results of the DNA sample kit number 3.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

This case study is very important as it shows evidence that because she had married to a man from a geographic region that he belongs to, no cases of cancer were found among their children. For the same reason that their children are descendants of a father who is from the human Y-Chromosome DNA haplogroup J-M267 which means their children are also from the human Y-Chromosome DNA haplogroup J-M267, and according to the new genetic concept of cancer presented in this study, as they had all lived in the geographic region of their human Y-Chromosome DNA haplogroup, the children never needed to redesign

their body as they live in the right environment of their human Y-Chromosome DNA haplogroup.

6.6.4 Genetic testing for kit number 4

To support the new genetic concept of cancer presented in this work with even more evidence, the following case is another cancer case of another member of the family found in the same generation (generation II) of the family. The affected member of the family is a male member with liver cancer. To be noted is that this affected male member of the family had married to a woman from a well-known Arab tribe in the Arabian Peninsula. This liver cancer case is similar to the previous case, and it explains the power and the role of the human Y-Chromosome DNA haplogroups in the formation, design and shaping of the characteristics of each human population and it further provides evidence and explains that it is the human Y-Chromosome i.e., the father side, not the mother side, that shapes the families and their branches, and therefore it is subsequently responsible for causing or preventing cancer to occur in each family. As it can be seen in generation II of the pedigree of the family investigated in this study, a male member of the family with liver cancer had married to an Arab woman. To confirm the ancestry of the Arab wife, a DNA sample (kit number 4) was obtained from a male relative of the Arab wife and her ancestry was confirmed as shown in the following table (**Table 7**) which revealed that her family is positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 7. Single Nucleotide Polymorphism (SNP) test results of the DNA sample kit number 4.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Data and sources confirmed that their daughter had died of lung cancer as seen in generation III of the pedigree while her mother as confirmed was from the

human Y-Chromosome DNA haplogroup J-M267 family. This cancer case is again evidence to support the new genetic concept of cancer presented in this work as it also shows that the lung cancer case occurred in the family due to the father side being from the human Y-Chromosome DNA haplogroup R-M198 ancestry and had lived in a geographic region different from their site of origin. These two cases are further evidence when protective and prevention strategies are suggested one being through marriage as it was learned from the previous two cases that when a female individual from the human Y-Chromosome DNA haplogroup J-M267, and had lived in the site of origin of their human Y-Chromosome DNA haplogroup, had married to a man from the human Y-Chromosome DNA haplogroup R-M198 who had lived in the geographic region of the human Y-Chromosome DNA haplogroup J-M267, their children still had cancer. However, no cancer cases were found among their children when a male individual from the human Y-Chromosome DNA haplogroup J-M267 and had lived in the site of origin of their human Y-Chromosome DNA haplogroup, had married to a female from the human Y-Chromosome DNA haplogroup R-M198 who had lived in the geographic region of the human Y-Chromosome DNA haplogroup J-M267.

Likewise, another male family member with liver cancer found in generation II of the pedigree who also died of the disease, however sufficient medical history was not possible to be obtained regarding his case and family. Similarly, another male family member with brain cancer found in generation II of the pedigree who also died of the disease and again an adequate amount of medical history with medical imaging and medical reports was not possible to be obtained regarding his illness. However, various cancer cases were found among his children, and therefore studying this brain cancer case found in generation II was very important as three different cancer cases were found among his daughters as seen in generation III of the pedigree, and they are one breast cancer case, one thyroid cancer case, and one skin cancer case.

6.6.5 Genetic testing for kit number 5

In order to study the skin cancer case found in generation III of the pedigree, data and sources from the family confirmed that the skin cancer woman had married to a man from a known Arab tribe living in the Arabian Peninsula. However, the ancestry of the Arab husband was confirmed through DNA testing. A DNA sample was obtained from his son, and it was genetically tested. To confirm, as seen in the following table (**Table 8**) that his family is positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 8. Single Nucleotide Polymorphism (SNP) test results of the DNA sample kit number 5.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Information from the family also confirmed that although their mother, who died of skin cancer being from the human Y-Chromosome DNA haplogroup R-M198 family, none of their children ever experienced cancer. To be noted is that this skin cancer case is presented and discussed in detail in the following chapter 7 of this research work supported by medical imaging and medical reports including the health habits that the patient had, in order to provide vital information when discussing the topic of protective and prevention strategies important to prevent descendants of each human Y-Chromosome DNA haplogroup who live in geographic zones other than their sites of origin from getting gene mutations that cause cancer through keeping the environment around them as much as possible similar to the environments of their sites of origin.

6.6.6 Genetic testing for kit number 6

Similarly, the thyroid cancer case seen in generation III of the pedigree was investigated. Information gathered from her family sources also confirmed that

her husband is a member of an Arab tribe living in the Arabian Peninsula. The ancestry of the husband was also confirmed through DNA testing, and a genetic sample was obtained from his nephew. The genetic test results as given in following table (**Table 9**) revealed that his family is positive to the human Y-Chromosome DNA haplogroup J-M172.

Table 9. Single Nucleotide Polymorphism (SNP) test results of the DNA sample kit number 6.

SNP Name	Test Results	Test Type
M172	Positive (+)	Y-HAP-Backbone

Important to mention that up to now none of their children has experienced any type of cancer. These results also present evidence that the newly proposed concept is obvious in terms of different cancer cases have affected male and female members of this European family for being living in the Arabian Desert. However, when a female member of the family gets married to a native inhabitant, no cancer cases attack their children with the family being living in a geographic region different of their site of origin. Additionally, the thyroid cancer patient is still alive due to the fact that thyroid cancer can be treated, and this patient was treated through surgery (thyroidectomy). However, the patient has been put on continuous care after treatment in addition to annual breast cancer screening with mammography. Thyroid cancer affects the thyroid gland, and in most cases, it can be treated successfully. However, follow-up care is very essential due to the fact that thyroid cancer can come back after treatment (recurrent thyroid cancer). The main types of thyroid cancer are papillary and follicular carcinomas (differentiated thyroid cancers), medullary thyroid carcinoma and anaplastic thyroid carcinoma. Typically, thyroid cancer is treated through surgery (thyroidectomy) to remove part or all of the thyroid. Thyroid cancer is also treated through radioactive iodine treatment in which the patient swallows a radioactive substance which travels through the blood circulation to reach all the parts of the boy and to kill the cancer cells found anywhere in the body. Other treatments

used for treating thyroid cancer include external radiotherapy which uses beams of radiation to kill the cancer cells, as well as chemotherapy and targeted therapies to use medicines to kill the cancer cells. The following drugs are the main common drugs used to treat thyroid cancer including cabozantinib, lenvatinib and sorafenib.

6.6.7 Genetic testing for kit number 7

As it was the case with the previous cases, the case of the female member with breast cancer seen in generation III of the pedigree of the family was also investigated in this study, however it was not possible to get the medical reports and medical images of the breast cancer case from the hospitals where the patient was treated. Therefore, all the known health history and details of the patient and her breast cancer case were collected from her family members and relatives. Considering the family history of various cancer cases leading to fatalities in this study, it becomes apparent that cancer has attacked male and female members of this European family for being living in the geographical region of the Arabian Desert. Data and sources from the family confirmed that the breast cancer woman who died of the illness had married to a man from an Arab tribe living in the Arabian Peninsula. The ancestry of the Arab husband was confirmed through genetic testing and a DNA sample (kit number 7) was therefore obtained from a male relative and the results as presented in the following table (**Table 10**) confirmed that they are positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 10. Single Nucleotide Polymorphism (SNP) test results of the DNA sample kit number 5.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

The patient had married and lived together with her husband and their daughter and two sons in the Arabian Desert with a good quality of life (QOL) always maintained by the husband for his wife and children and up to date no cancer has attacked the children. This case study in addition to the previous cases provides some clear evidence that the newly proposed concept is valid in terms of that all these cancer cases affected the family investigated in this research because they are from Europe, and they have lived in the Arabian Peninsula. Furthermore, studying the health habits of this breast cancer patient is very important in relation to prevention strategies of cancer proposed in this research. The patient had breast cancer in her left breast, however the patient had the health habit of hiding her breast pain and discharge from her family. The patient used to use breast pads always kept in place to absorb and hide her left nipple discharge and she never revealed her breast condition to anyone until it was too late. Sources from the family reported that when the patient was taken to the emergency unit in her local hospital, doctors were shocked by seeing the changes of the size and shape of the affected breast compared to the healthy right breast and therefore, the patient had received urgent medical care, but her case was too late for any proper treatments and the patient later died at hospital. Therefore, and part of the protective and prevention strategies is that it is very important to inform family of any medical conditions and health issues to be reported to medical centres as soon as anything abnormal is noticed by patients. Family members of the human Y-Chromosome DNA haplogroups who live and reside in geographic regions that they genetically don't belong to are at a greater risk of getting cancer and therefore one of the effective protective strategy is to do regular health checks at home and health centres to keep an eye on any abnormality or health issue before they get out of control recommended in this research work.

6.7 Discussion and analysis

Generation IV of the pedigree of the family investigated in this work shows no cancer cases occurred among them. More than one scientific opinion is presented to explain this with the main opinion being based on the fact that the female members of the human Y-Chromosome DNA haplogroup R-M198 family

had married to members of the native tribes of the Arabian Peninsula. Likewise, other explanations include regular health checks and by keeping an environment with no exposure to the risk factors related to the tough climate conditions of the desert. However, one interesting pleuropulmonary blastoma (PPB) case was found in generation V. Therefore, and in support of the new genetic concept of cancer proposed in this work, the PPB case was very important to be investigated in detail and a scientific explanation is therefore presented which links the case to the human X-Chromosome recombination of the 23rd pair of chromosomes which is a process that occurs on the mother side throughout generations more than the father side. The PPB cancer case occurred in a child in generation V of the pedigree of the family investigated in this research and the child died of the illness. PPB is a very aggressive and rare type of cancer, which occurs mainly in children, however it may also affect adults. The cancer originates from the lung or the pleural cavity, and what causes the disease is unknown [215]. However, in this study a scientific explanation is presented to explain what might have caused this rare type of cancer to affect this child in this family and it is based on the new concept of cancer presented in this research which is based on understanding the human Y-Chromosome DNA haplogroups and the human population origins and migrations, environmental factors and gene mutations, and the development of cancer. Therefore, and based on studying the family history of this PPB case along with the genetic testing that was carried out in this family and also based on the details of the related cancer cases found among them throughout generations, specifically the mother sides. It can be seen that the mother of the child's mother and the mother of the child's father are sisters and members of the human Y-Chromosome DNA haplogroup R-M198 family. Importantly, the mother of the child's father's mother is also a member of the human Y-Chromosome DNA haplogroup R-M198 family as seen in the pedigree of the family. To understand X-Chromosome recombination, the following section explains the topic in detail.

6.7.1 X-Chromosome recombination

Variability of human hereditary is a result of a sexual reproduction. Normally, each individual receives half of their genetic material from each parent. As explained

previously, in each human cell there are 23 pairs of chromosomes inside the nucleus. 22 pairs of the chromosomes look the same in both males and females, however the 23rd pair of the chromosomes vary between males and females. Females have two copies of the X-Chromosome, while males have one X-Chromosome and one Y-Chromosome. A male gets his X-Chromosome from his mother and his Y-Chromosome from his father. The X-Chromosome, exactly as it is, is passed only to his daughter and his Y-Chromosome, exactly as it is, is passed only to his son. However, a female gets one X-Chromosome from her father, exactly as it is, and one X-Chromosome from her mother but after some combination of the two X-Chromosomes that her mother has. This is illustrated in the following image **Fig. 36**.

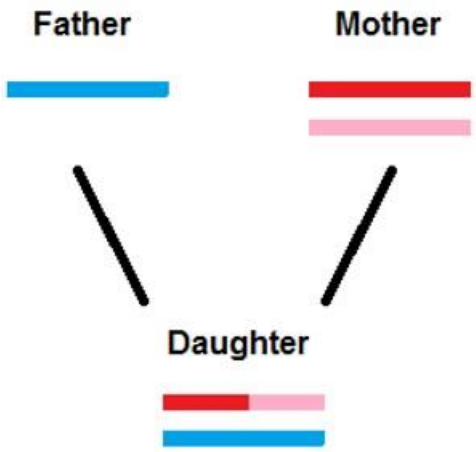

Figure 36 X-Chromosome recombination shows the father's X-Chromosome has the same share as two X-Chromosomes from the mother.

Likewise, when the daughter in **Fig. 36** gets married and she becomes the mother in **Fig. 37** X-Chromosome recombination in her daughter takes place as shown in **Fig. 37**.

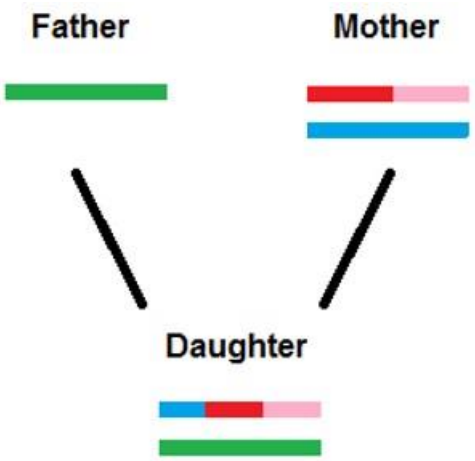

Figure 37 X-Chromosome recombination is further explained how the X-Chromosome from the father (in green colour) passed down exactly as it is. However, the X-Chromosomes from the mother are passed down after recombination.

The explanation of the X-Chromosome recombination of the 23rd pair of the human chromosomes is very important to understand the new genetic concept of cancer presented in this work, since it shows how the human Y-Chromosome undergoes almost no recombination when passed down from father to son, and the X-Chromosome from the father which also passed down to his daughter exactly as it is compared to the X-Chromosome that is passed down from the mother to her daughter but after X-Chromosome recombination. Therefore, the human Y-Chromosome DNA haplogroups play an important role in the genetic design and formation of populations. Likewise, in almost each population and almost in each culture, surnames are passed down in the same way as the Y-Chromosome passed down from father to son. Additionally, each population is formed according to each human Y-Chromosome DNA haplogroup that has a specific geographic zone that each population is genetically designed to live safely in that geographic region. Furthermore, it is explained in this work that in each generation, it is the father side that causes or prevents cancer to run in families, not the mother side. The pedigree of the family investigated in this study shows that when a daughter of a male from the human Y-Chromosome DNA haplogroup R-M198 gets married to a man from the human Y-Chromosome DNA haplogroup J, their children experience no cancer when they all live in the

geographic region of their human Y-Chromosome DNA haplogroup J. However, when the mother sides of an individual are sisters and belong to the human Y-Chromosome DNA haplogroup R-M198, a PPB cancer case was found in generation V of the pedigree of the family. According to the proposed new concept of cancer presented in this study the PPB cancer child had strong mother side human Y-Chromosome DNA haplogroup R-M198 genetic material as it was clearly noticed from the noted physical features of the child who had the physical features of similar to the common European white look, including light skin colour, causing the child this type of cancer due to the fact that the child was living in an environment forcing his body to change itself, especially the respiratory system to adapt to the desert climate conditions. This case is presented as case study in the following chapter 7 of clinical case studies.

6.7.2 Male chimerism in females

Following understanding the topic of X-Chromosome recombination, it is also very important to understand the topic of male chimerism in females as it further explains the role of the human Y-Chromosome DNA haplogroups in the population formation and shaping families and their branches generation after generation. It was apparent in the family that had cancer running among them investigated in this research that in each generation it was the father side causing or preventing the occurrence of the cancer cases found among their children. Past studies have confirmed that genetic material and cells can be exchanged from a male foetus or a female foetus and their mother during pregnancy in a process known as foe to-maternal microchimerism [216] [217]. Microchimerism is a bidirectional cross-placental trafficking that occurs during pregnancy, and michrochimeric cells can participate in the immune system development of the foetus [218]. However, past studies mostly carried out on foetal microchimerism and genetic material where cells left behind by a male foetus, due to the fact that his cells (searching for Y-Chromosome DNA) are easier to be distinguished from the cells of the mother (as females don’t have Y-Chromosome DNA). Each time a woman becomes pregnant she acquires foetal cells [217]. Genetic material and cells are detected at around week seven of pregnancy, and they steadily start to

increase up to week 24 and reach a peak at parturition [219]. These foetal cells may influence the biology and the health of the mother, and they may disappear sometime after pregnancy or settle in forever [220]. As explained in **Fig. 38**, second pregnancy allows rechimerism of foetal cells from first sibling to second sibling. Foetal cells are normally found in the breast tissue of the mother and in her milk. Rechimerism of foetal cells from first sibling to second sibling can also occur through breastfeeding and it can influence the biology and the health of the second sibling [221].

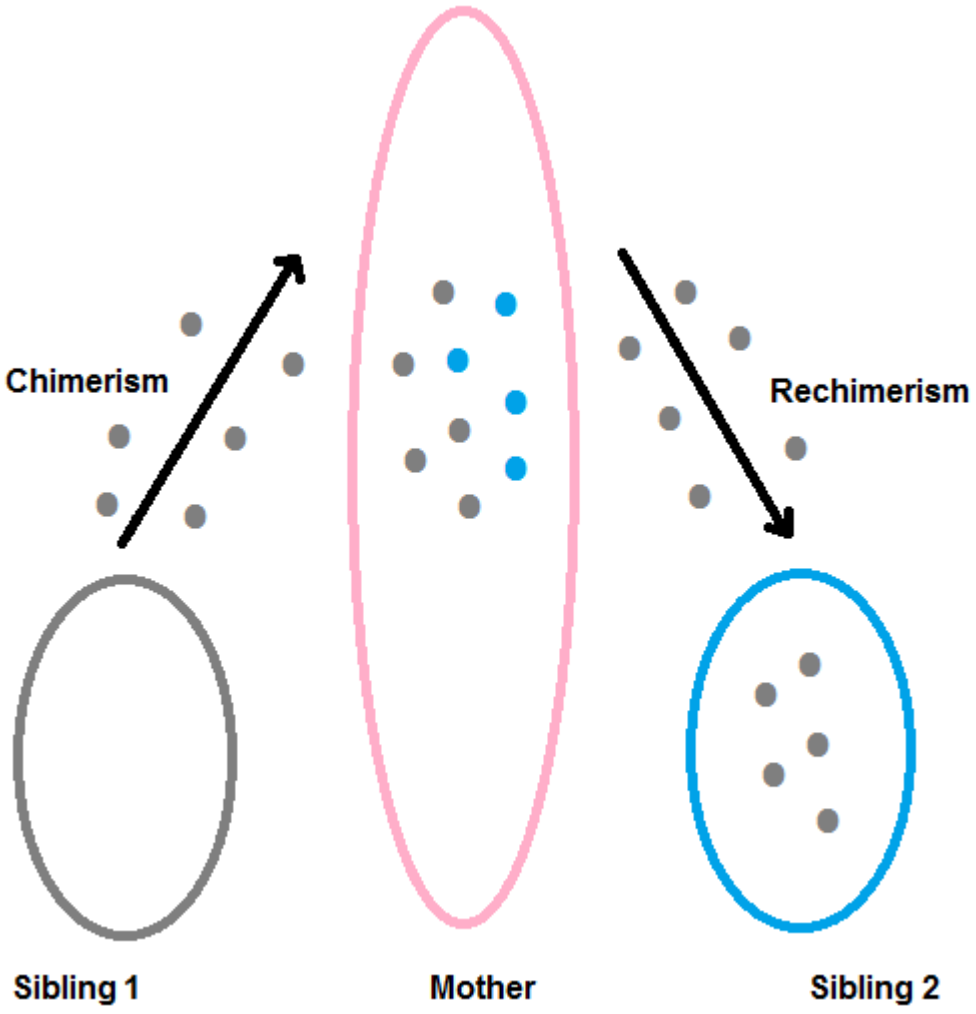

Figure 38 Chimerism and rechimerism explained.

The Y-Chromosome DNA found in a woman after pregnancy with a male foetus is not from that woman's father, as a woman has only XX chromosomes. This Y-

Chromosome DNA has come from her male foetus when genetic material and other cells exchanged between the male foetus and his mother during pregnancy. This Y-Chromosome DNA therefore belongs to the same human Y-Chromosome DNA haplogroup as the father of the foetus. Y-Chromosome DNA is found in various body organs such as the brain, the heart, the lungs, the liver, and the spleen of pregnant women with boys [222]. Likewise, the concentration of Y-Chromosome DNA in cancer-free women is found to be higher than in women with breast cancer [223]. In conclusion, studying the michrochimeric cells which participate in the development of the foetus is very significant to support the new genetic concept of cancer presented in this work, as it shows the influence of the human Y-Chromosome DNA haplogroups in the formation of populations and how the male genetic materials participate in the development of the foetus in each generation. The father side of the children has shown to be the main factor of causing or preventing cancer (whether cancer occurs or not) as explained with each marriage the children are reshaped to follow the father as the new concept genetic concept presented in this work suggests.

6.7.3 Genetic testing for hereditary cancer risk genes carried out in this work

While no cancer cases found in generation IV of the pedigree of the family investigated in this research, it was also important to carry out genetic testing for hereditary cancer risk genes to find out if there are any hereditary gene mutations that might have caused cancer to run in the family. A blood sample was therefore obtained from one of the daughters of the cancer patients of the family investigated in this study who died of the disease. A full BRCA gene test was carried out to see if she has any of the known hereditary cancer risk genes, BRCA1 and BRCA2. The results revealed that she is not affected and that she does not have any significant changes in the BRCA1 and BRCA2 genes. Consequently, receiving a negative BRCA1 and BRCA2 result is reassuring, since they are the two high breast and ovarian cancer risk genes that are known as discussed in detail in the literature review in chapter 3 of this thesis, in section 3.3.2 in family history and genetics. Likewise, as she was found to have no

changes in her BRCA genes, this has also decreased her risk of developing breast cancer and ovarian cancer, and the revised assessment has placed her cancer risk to that of other normal women. This result also means that her daughters as well as any of her future children will not be at risk of inheriting a BRCA gene change from her. However, the new genetic concept of cancer presented in this study uses the test results of the BRCA genes to explain that the cancer cases found running in the family is not because of hereditary cancer risk genes but for the reason that the family members are descendants of a human Y-Chromosome DNA haplogroup that has the site of origin of the Central and Eastern Europe and that they have been living in a geographic region that they do not belong to which is the Arabian peninsula. Therefore, the test results are very vital to support the new genetic concept of cancer presented in this work.

6.8 Further investigations carried out in this work

Likewise, it does not mean that all individuals of a human Y-Chromosome DNA haplogroup who live in a different geographic zone are likely to get cancer, especially if they keep the environment around them similar to the environment of their place of origin, hence it is likely that they will be at lower risk of getting cancer. Similarly, the same principal is true according to the new genetic concept of cancer presented in this study, which suggests that it does not mean that when individuals of a human Y-Chromosome DNA haplogroup who live in the geographic region of their human Y-Chromosome DNA haplogroup, will never get cancer. For example, heavy smokers are at higher risk of getting cancer even if they live in their sites of origin, and the reason behind this according to the new genetic concept of cancer proposed in this research, is that the lungs of a smoker are designed to take the fresh air of their place of origin and therefore, when smokers inhale toxic chemicals, they force their lungs to change itself to a different form of lungs that can cope with the toxic chemicals via smoking, which eventually leads to gene mutations that can cause cancer. This was supported by studying other participants in this research who live in the sites of origin of their human Y-Chromosome DNA haplogroups and have cancer found among them, in addition to participants from families who never had cancer running among

them, all supported by genetic testing for ancestry and clinical case studies along with historical evidence and data from various sources.

6.8.1 Genetic testing for kit number 8

Hence, five generations of a very big family (approximately 1000 family members) were investigated in this study. The family is known to be native inhabitants of the geographic region of Mesopotamia between the Tigris and Euphrates rivers of the Fertile Crescent where the major human Y-Chromosome DNA haplogroup J-M172 is believed to have evolved. A DNA sample from a male member of the family (kit number 8) was tested. The results as given in the following table (**Table 11**) showed that they are positive to the human Y-Chromosome DNA haplogroup J-M172.

Table 11. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 8.

SNP Name	Test Results	Test Type
M172	Positive (+)	Y-HAP-Backbone

However, it was vital to test the family for the big Y-700 test as the family represents the wider geographic region of the research conducted in this study and their DNA sample is a unique sample in this study with unique Y-Chromosome DNA variants that only their specific paternal line carries. The following table (**Table 12**) is the Y-Chromosome DNA standard STR markers Big Y-700 test results (only 4 panels are displayed) of the standard FTDNA panel 1 (1-12), panel 2 (13-25) and panel 3 (26-37) for the DNA sample (kit number 8).

Table 12. Y-Chromosome DNA standard Y-STR values for the DNA sample kit number 8.

PANEL 1 (1-12)											
Marker	DYS393	DYS390	DYS19	DYS391	DYS385	DYS426	DYS388	DYS439	DYS389I	DYS392	DYS389II
Value	12	23	14	10	13-17	11	15	12	13	11	29

PANEL 2 (13-25)									
Marker	DYS458	DYS459	DYS455	DYS454	DYS447	DYS437	DYS448	DYS449	DYS464
Value	16	9-9	11	11	25	14	21	35	13-13-15-16

PANEL 3 (26-37)										
Marker	DYS460	Y-GATA-H4	YCAII	DYS456	DYS607	DYS576	DYS570	CDY	DYS442	DYS438
Value	11	11	19-22	15	15	17	16	36-37	12	9

The human Y-Chromosome DNA haplogroup J2 or J-M172 is subdivided into the human Y-Chromosome DNA haplogroup J2a or J-M410, and the human Y-Chromosome DNA haplogroup J2b or J-M12. The analysis of the results of the family further revealed that the family is positive to the human Y-Chromosome DNA haplogroup J2a. To be noted is that the oldest J2a sample has ever been identified belongs to remains found in a cave known as the Hotu Cave which is located south of the Caspian Sea in northern Iran, dating from 9100 to 8600 BCE [224]. It was therefore very important to study this family due to the fact that the family has a huge number of family members in five generations, and according to data and sources from the family, only one type of cancer was found among the members of the family which is lung cancer and that it had affected six heavy smoker members of the family. To explain this, the lung cancer incidence in the family is simply due to the known risk factor for the disease which is heavy smoking as past studies have confirmed that lung cancer is caused by acquired gene mutations as a result of exposure to chemicals and toxins caused by smoking [225] [226]. Thus, the DNA test results of the family are crucial to support the new genetic concept of cancer presented in this research as it shows evidence that the family has lived safely in the geographic region of their human Y-Chromosome DNA haplogroup and that the lung cancer cases that occurred among the heavy smokers of the family is due to the fact that the affected

members of the family have themselves forced their body to get gene mutations through inhaling chemicals and toxins caused by tobacco smoke. It follows, therefore, that in line with the new genetic concept of cancer presented in this study the family has lived in the right geographic region of their human Y-Chromosome DNA haplogroup with their lungs and respiratory system being genetically designed for the air and climate system and the environment that they belong to and if it wasn't smoking, the six affected family members with lung cancer would never get the disease as it was the case with the rest of the unaffected members of the family. To support this explanation with more scientific evidence, past studies have confirmed that there are racial and ethnicity differences in lung cancer incidence [227] and that the White Ethnic group have different lung function and lung volumes in comparison to the Black race [228] [229]. Researchers have reported the highest annual lung cancer occurrence among the Blacks in the United States followed by the Whites, with the lowest rates of incidence reported among the American Indians/Alaska Natives, as well as the Asian/Pacific Islanders [230]. Very importantly, past studies have highlighted that there are occurrence of lung cancer among people who never smoked [231] [232] and that lung cancer is also caused by acquired gene mutations that take place inside the body cells with no known risk factors. Therefore, the explanation of the differences in the lung volume and lung function of each ethnic group according to the new genetic concept of cancer presented in this study is that each population is genetically designed specifically for the geographic regions that they belong to, and that the incidence of lung cancer in never smokers is therefore believed to be due to the fact that the affected individuals have lived in geographic regions that they don't belong to, in different environments from the climate conditions of sites of origin of their human Y-Chromosome DNA haplogroups.

6.8.2 Genetic testing for kit number 9

Similarly, another important DNA sample was tested (kit number 9) which was obtained from a male participant who is a member of a well-known family from the same geographic region (as kit number 8) of Mesopotamia. The analysis of

the results as given in the following table (**Table 13**) confirmed the ancestry of the family and that they are positive to the human Y-Chromosome DNA haplogroup J-M172.

Table 13. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 9.

SNP Name	Test Results	Test Type
M172	Positive (+)	Y-HAP-Backbone

Likewise, important data and information regarding the health history of five generations of the family was gathered and investigated. It was confirmed that the family had no cancer occurrence among them apart from one rare case of benign (non-cancerous) brain tumours in a child who eventually died of the disease. This paediatric case is presented as a detailed case study in the following chapter 7 of clinical case studies. These results are also very significant to support the new genetic concept of cancer presented in this research and they are evidence that the descendants of the human Y-Chromosome DNA haplogroup J-M172 are genetically designed to live safely and without developing unrelated health conditions in the geographic region of their human Y-Chromosome DNA haplogroup.

6.8.3 Genetic testing for kit number 10

Also, one more important genetic sample was obtained from a male participant (kit number 10) who is a member of a family from one of the known native tribes of the geographic region of the Arabian Peninsula where the human Y-Chromosome DNA haplogroup J-M267 is most frequent. The results as shown in the following table (**Table 14**) revealed that the family is positive to the human Y-Chromosome DNA haplogroup J- M267.

Table 14. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 10.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Very importantly, after the health history of five generations of the family was investigated, no cancer cases were found among them except one very rare high grade metaplastic breast carcinoma case in a female member of the family who had a long history of confirmed rheumatoid fever. In order to understand this breast cancer case in more detail, the case is presented as a detailed case study in the following chapter of clinical case studies, chapter 7. Likewise, studying this family was also very vital as the results additionally support the new genetic concept of cancer presented in this work and that the descendants of the human Y-Chromosome DNA haplogroup J-M267 are safe and that there is no possibility of gene mutations that cause cancer to occur among the members of the family as long as they remain within the site of origin of their human Y-Chromosome DNA haplogroup.

6.8.4 Genetic testing for kit number 11

In order to study additional native clans of the same geographic area of the Arabian Peninsula, another significant DNA sample was obtained from a male participant (kit number 11) who is a member of a family from another known native tribe of the southern part of the Arabian Peninsula. The results as presented in the following table (**Table 15**) confirmed that the tribe is a native tribe of the Arabian Peninsula and that they are positive to the human Y-Chromosome DNA haplogroup J- M267 which is the main human Y-Chromosome DNA haplogroup of the tribes of the Arabian Peninsula.

Table 15. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 11.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Following investigations regarding the health history of five generations of the family, it was found that no cancer cases ever affected the members of the family. Therefore, the results of this family are also very vital as this tested individual is from a family that has no known cancer cases, which is further proof of the new genetic concept of cancer presented in this work based on the explanation that because the family is positive to the human Y-Chromosome DNA haplogroup J-M267 and that they live in the geographic region where their haplogroup is originated from.

6.8.5 Genetic testing for kit number 12

Another DNA sample was obtained from another male participant in this study (kit number 12). The tested individual is again from a native tribe of the Arabian Peninsula. His results as given in the following table (**Table 16**) showed that he is positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 16. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 12.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Five generations of the tested individual's family were investigated, and data and information from various sources of the family as well as hospital records was gathered in as much as detail it could be obtained. It was found that there were no patterns of incidence of any type of cancer among the members of the family. These results again support the new genetic concept of cancer presented in this

study as it shows evidence how the family who are native inhabitants of the Arabian Desert members of a tribe that are Bedouin i.e., desert dwellers and have always lived in the desert under the known difficult desert climate conditions, however without developing gene mutations known for causing serious health complications. Additionally, the difficult environmental conditions of the Arabian desert with its limited resources to freshwater, include the desert sand and the desert dust in the air that can cause damage and injury to the lungs and the respiratory system as well as the kidneys. However, these indigenous people have survived and without developing renal or respiratory related health conditions. Evidence is therefore conclusive that the respiratory system as well as the renal system and the rest of the body organs of such native clans of the Arabian Desert are genetically designed specifically for the Arabian Desert to survive the hot desert climate conditions. To be noted is that the Arabian Desert is the largest area in Asia, and it has the largest area of continuous sand in the world with a very hot climate all year long [233].

6.8.6 Genetic testing for kit number 13

Genetic testing for ancestry was also carried out on another male participant in this study (kit number 13) to confirm his human Y-Chromosome DNA haplogroup. A DNA sample was therefore obtained from the participant who is also from the same geographic region of the southern part of Western Asia as the previous tested participant. The results as given in the following table (**Table 17**) which also showed that the individual is positive to the human Y-Chromosome DNA haplogroup J-M267 which is believed to have originated in the southern part of the geographic region of Western Asia.

Table 17. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 13.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Again, no patterns of any cancer types were ever found in five generations of the tested individual's family. However, one rare type of bone cancer known as dedifferentiated chondrosarcoma was recorded in a male member of the family. The causes of chondrosarcoma are not known; however, the illness may emerge from benign tumours and bone conditions. Likewise, this rare case of bone cancer is presented as a detailed case study in the following chapter 7 of this thesis. The test results of this family also support the new genetic concept of cancer presented in this research as it shows further evidence how the tested participant and his family who are native inhabitants of the Arabian Peninsula and positive to the human Y-Chromosome DNA haplogroup J-M267 have lived safely in the site of origin of their human Y-Chromosome DNA haplogroup.

6.8.7 Genetic testing for kit number 14

One more DNA sample was also obtained from another male individual (kit number 14) who is also from Western Asia. The Y-Chromosome DNA test results as given in the following table (**Table 18**) showed that he is positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 18. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 14.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

Similarly, five generations of the family of the tested individual were investigated and it was found that no occurrence of any type of cancer was ever recorded

among them. Over again, these results support the new genetic concept of cancer presented in this work through providing more evidence that the family of the tested individual who are native inhabitants of the site of origin of their human Y-Chromosome DNA haplogroup and have experienced no gene mutation among the members of the five generations investigated as they never needed to be forced by the environment of where they have lived to adapt to their environmental conditions.

6.8.8 Genetic testing for kit number 15

The tested individual is also a member of one of the native tribes of the Arabian Peninsula the results of his DNA sample (kit number 15) as given in the following table (**Table 19**) showed that he is positive to the human Y-Chromosome DNA haplogroup J-M267.

Table 19. Single Nucleotide Polymorphism (SNP) test results for the DNA sample kit number 15.

SNP Name	Test Results	Test Type
M267	Positive (+)	Y-HAP-Backbone

One more time no cancer cases were found among the investigated five generations of the family of the tested individual. The family is positive to the human Y-Chromosome DNA haplogroup J-M267 and has always lived in a geographic region which is the site of origin of their human Y-Chromosome DNA haplogroup, and they have developed no cancer among their members. These results are all over again evidence to support the new genetic concept of cancer presented in this research which links between human population origins and migrations, environmental factors and gene mutations, and the development of cancer.

6.9 Gene mutations causing cancer and the new genetic concept of cancer presented in this work

Cancer is caused by gene mutations inside cells. A normal human being has normal cells that function, grow and divide normally. Normal cells function by following normal genetic instructions from their normal DNA. However, if gene mutations (changes) occurred because of any factor such as radiation, toxicity, pollution, smoking, poor diet, environmental factors, etc., these mutated genes give new instructions to cells to function, grow and divide in a different abnormal way, which can lead to cancer [234] as shown schematically in the following image **Fig. 39**.

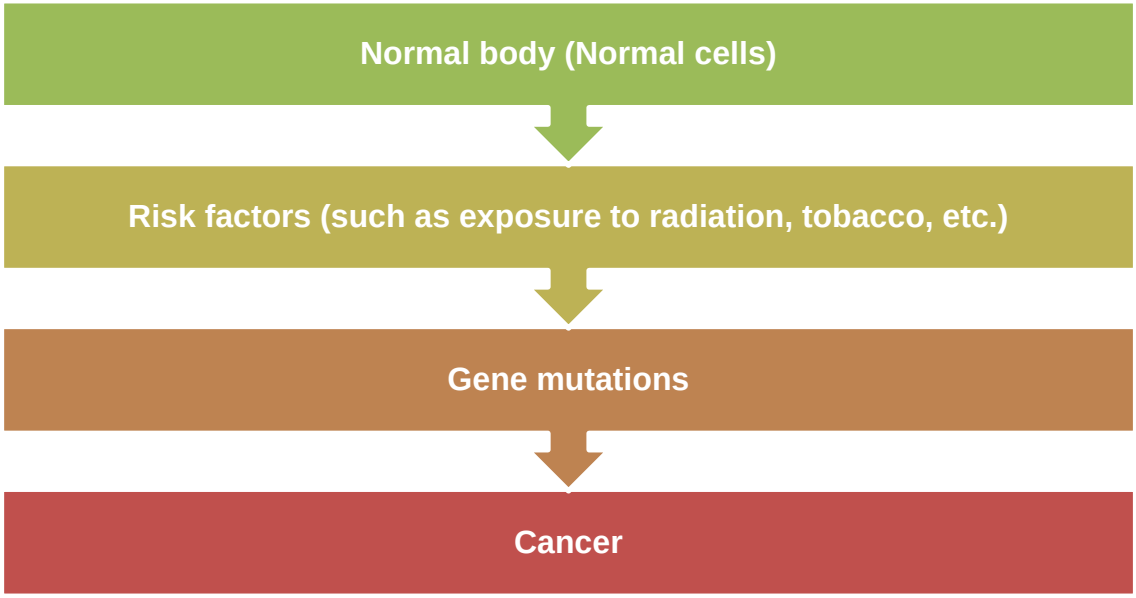

Figure 39 A simple schematic definition of cancer.

However, when studying the past migrations of our human ancestors, we realise that mutations occurred to their DNA after they reached new destinations, in order to adapt the new environments, leading to the formation of new populations, as shown schematically in the following image, **Fig. 40**.

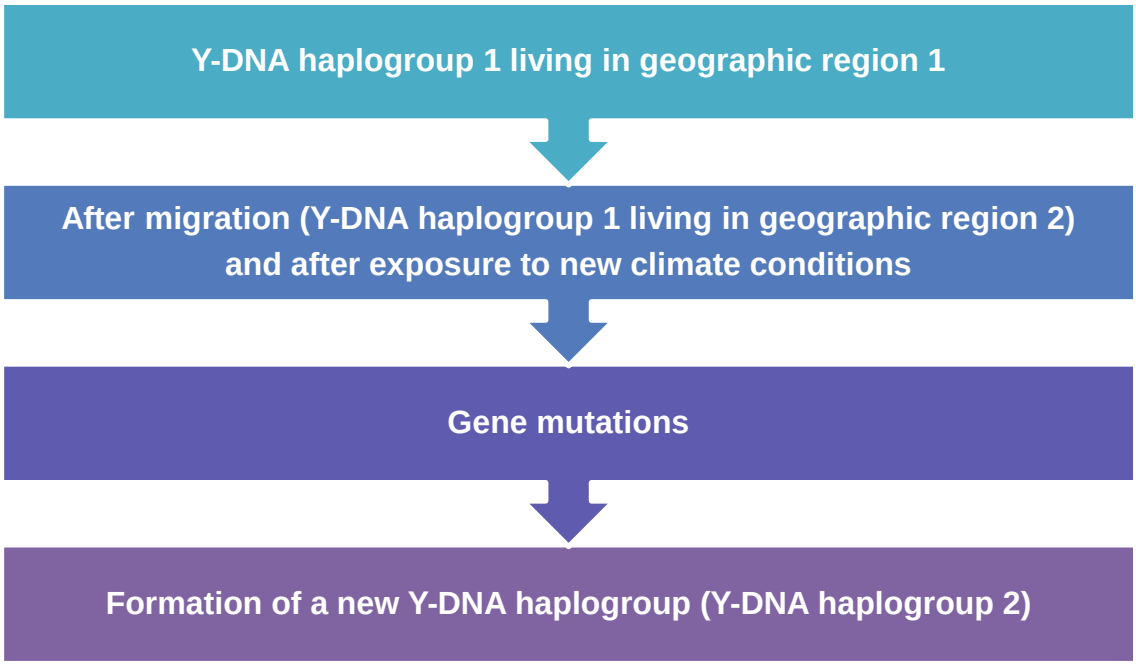

Figure 40 Past migrations and formation of new populations.

According to the new concept of cancer presented in this work and based on the research carried out in this study, when gene mutations occur in the human body due to any factors, the human body tries to change itself to form a different form of body cells in order to adapt the new factors as it was the case with our human ancestors when gene mutations occurred due to migrations from one geographic zone to another as shown in the following image, **Fig. 41**.

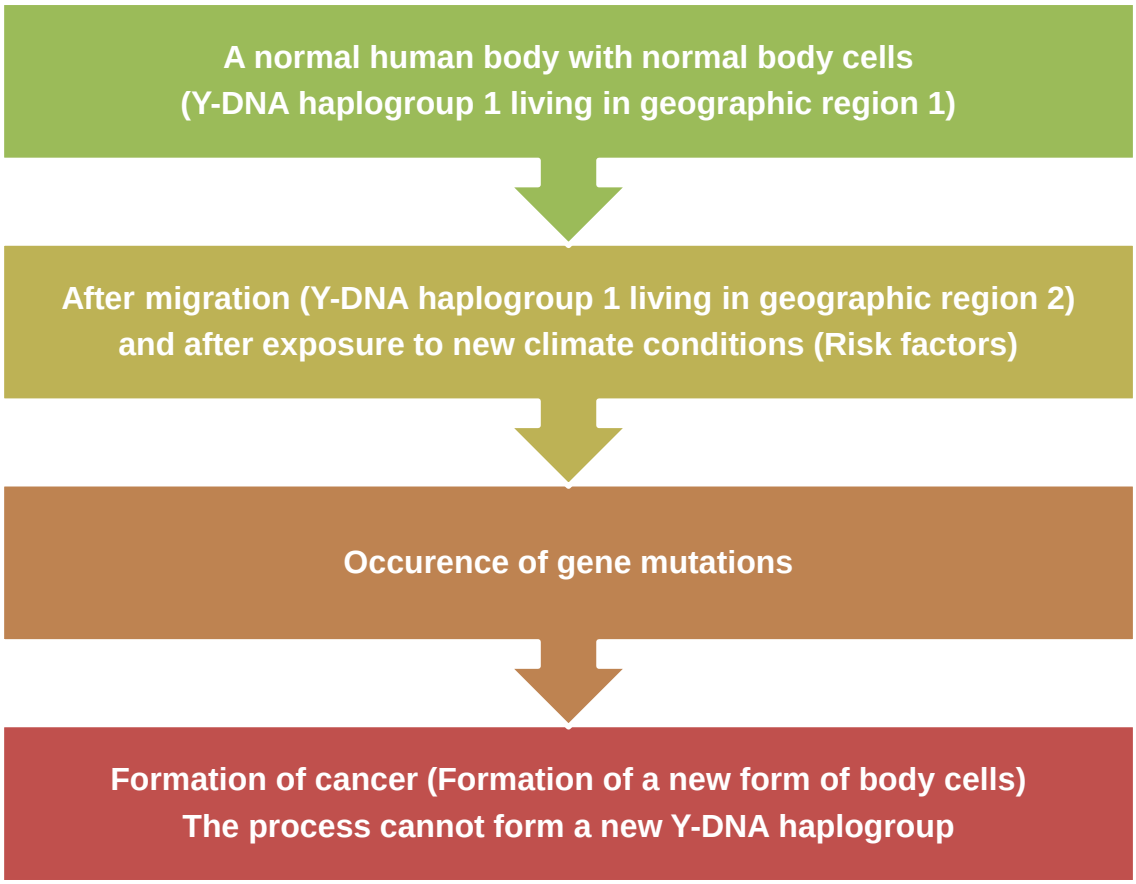

Figure 41 The new concept of cancer presented schematically.

At the same time, many other changes in the body have to occur when the body is in the process of producing a new form of body cells to adapt the new climate conditions or the risk factors. For example, gene mutations give instructions to tumour suppressor genes such as p53 to stop working (switch off), and that explains why the p53 gene is either missing or damaged in most cancer cases [235]. Another example is that gene mutations give wrong instructions to various genes in the body to stop the body cells from repairing themselves, so as not to go back to their normal state before they get exposed to the new environmental factors. The same process is true for all the other genes that allow cancer cells to form, and that again explains the reason behind why damaged DNA repair genes are found in some types of cancer [235]. The other important point is about the immune system and why cancer cells develop the ability to keep away from the body's immune system while they continue growing. In simple words, as the

body starts to change itself to another form of body and the cells start to change into cancer cells, i.e., the new form of cells that will form the new body, the mutated genes give new instructions to make the cancer cells develop mechanisms to avoid immune response and keep growing without getting detected by the body's immune system. This is how cancer cells are able to block the function of NLRC5 gene to evade the body's immune system and form tumours [236].

6.10 A new definition of cancer presented in this study

As a result of the research carried out in this work, a new definition of cancer is therefore presented in this study, and it is based on understanding the scientific facts of how the past migrations of our human ancestors led to the establishment of our present human populations due to gene mutations caused by environmental factors following reaching new destinations. The current international definition of cancer is that cancer is a term for a group of diseases, in which abnormal cells (cancer cells) of the body grow and divide uncontrollably and can spread (metastasis) to other parts of the body, with metastasis being a major cause of death from cancer [237]. However, the new definition of cancer presented in this study is that cancer refers to the process in which the normal body cells are changed to a new form of body cells (cancer cells) due to gene mutations caused by body's exposure to risk factors, starting in one part of the body such as the skin, the lungs, etc., and spreads to other body parts/organs (metastasis) to produce a new form of body parts/organs to adapt the new conditions (risk factors), however the process cannot be completed and a new full human body and organs cannot be produced which is subsequently leading to death.

6.11 A novel risk factor of cancer proposed in this research to be added to the existing list of cancer risk factors

The past studies have identified a number of risk factors that cause breast cancer and other types of cancer such as hereditary factors, and environmental factors

and lifestyle behaviours including obesity, smoking, drinking alcohol, exposure to chemicals, radiation, using hormones, infections, and etc. researchers have also highlighted other risk factors such as demographic factors including age, gender, and race and ethnicity. Likewise, past studies have discussed the topic of race and ethnicity as a cancer risk factor, but mainly as studying the diversity of one population in the country i.e., many studies have compared the incidence of cancer among the various groups of migrants all being in a host country with the native inhabitants of the country. For example, cancer incidence classified by race and ethnicity in the United States, in which the studies have compared the occurrence of cancer among the Whites, the Blacks, the Hispanics, the Asians, etc., in the United States i.e., while these racial populations all live in the United States. Similarly, variety of studies have discussed the incidence of cancer among the Whites, the Blacks, the Asians, etc., in the UK and at the time these ethnic groups all live in the UK. However, not many studies have compared the occurrence of cancer among one specific group of migrants to their population of origin. Likewise, only some studies have compared the incidence of cancer among the various populations around the world while each population being living in their country of origin. However, and based on the research carried out in this work, it is explained that the right methodology of studying and understanding the occurrence of cancer among the various racial groups around the world is as follows:

1. Studying the incidence of cancer among one specific ethnic group (such as ethnic group A) and they live in their home country (such as geographic region A) that they belong to, compared to the same ethnic group (i.e., ethnic population A) and they live in another country (such as geographic region B) that they don't belong to. In addition to considering all the known cancer risk factors for the population in their site of origin and in the country that they don't belong to.

2. Studying the incidence of cancer among one specific ethnic population (such as ethnic population A) and they live in their home country (such as geographic region A) that they belong to, compared to another specific ethnic population (such as ethnic population B) and they live in their home

country (such as geographic region B) that they belong to. In addition to considering all the known cancer risk factors for each population in their sites of origin.

According to the new genetic concept of cancer presented in this research it is explained that cancer is caused by gene mutations due to environmental factors following migration and that cancer appears to run in such families for being living in an environment of a geographic region that they don't belong to. Therefore, migration is proposed in this work as one important risk factor responsible for causing gene mutations that can lead to cancer, to be added to the current list of cancer risk factors.

6.12 The available rates of breast cancer and other types of cancer according to the WHO Cancer Country Profiles

The following tables (**Table 20** to **Table 30**) show the available data according to the WHO Cancer Country Profiles for the current status of breast cancer and other types of cancer globally, in addition to the UK, and Saudi Arabia. The data presented is the total population in each case as well as the total number of cancer cases in addition to the total number of cancer deaths, and the incidence and mortality percentages of the most common types of cancer, along with the population attributable fractions (PAFs) showing the contribution of select risk factors essential to understand the occurrence of cancer around the globe and to support the new genetic concept of cancer presented in this work.

6.12.1 Burden of cancer (Worldwide)

According to the data from the WHO, cancer is a leading cause of death worldwide. There was a total number of 18 million cancer cases globally recorded in 2018 with a total number of cancer deaths of almost 9.5 million (**Table 20**). The annual number of new cancer cases is expected to reach 21 million by 2030 [238].

Table 20. Burden of cancer (Worldwide)

Total population (2019)	Total number of cancer cases (2018)	Total number of cancer deaths (2018)
7,676,965,500	18,078,957	9,555,027

The most common types of cancer recorded globally (**Table 21**) include preventable cancers such as lung cancer and Colorectum cancer through avoiding the risk factors that are responsible for causing such cancers including the use of tobacco, diet and alcohol. Other common cancer types recorded globally are preventable through the early detection of the tumour as in the case of breast cancer.

Table 21. The most common cancer cases globally (2018)

Cancer type	Incidence	Mortality
Lung	5.6%	9%
Colorectum	4.4%	3.7%
Stomach	3.6%	4.9%
Breast	3%	1.5%
Liver	2.8%	4.9%
Oesophagus	1.9%	3.2%
Thyroid	1.5%	0.1%
Prostate	1.3%	0.8%
Pancreas	1%	1.7%
Non-Hodgkin lymphoma	0.8%	0.8%

The use of tobacco is recognised as the most avoidable cancer-causing risk factor worldwide (**Table 22**). Lung cancer is caused by acquired gene mutations mainly as a consequence of exposure to smoking related chemicals [225]. Lung cancer can be prevented through avoiding smoking tobacco as well as keeping a healthy diet and exercise [239]. Infections are also recognised as the second

most common cancer-causing risk factor globally such as infections caused by certain viruses which can be passed from one individual to another by way of blood or body fluids. Likewise, cancers caused by infectious agents can be prevented through vaccinations and protected sex [240].

Table 22. The population attributable fractions (PAFs) globally

Tobacco (2017)	25%
Infections (2012)	13%
Alcohol (2016)	4-5%
Obesity (2012)	3-4%
Occupational risk (2017)	2-8%
UV (2012)	1%

6.12.2 Burden of cancer (United Kingdom)

The total number of cancer cases in the UK was 446,942 in 2018 (**Table 23**). The incidence rates of prostate cancer along with breast cancer are recognised as the highest in the UK (**Table 24**), followed by lung cancer, and colorectal cancer. The data from the National Cancer Intelligence Network (NCIN) of the Public Health England on breast cancer, and the Breast Site Specific Clinical Reference Group (SSCRG) with the analytical support being provided by NCIN (Birmingham) shows breast cancer as the most common type of cancer in the UK affecting all the ethnicity groupings of White, Asian, Black, Chinese, Mixed and Other Ethnicity. The data from NCIN also shows that the number of breast cancer cases among women as well as prostate cancer cases both increased over the past years [241].

Table 23. Burden of cancer (UK)

Total population (2019)	**Total number of cancer cases (2018)**	**Total number of cancer deaths (2018)**
67,530,161	446,942	178,473

Table 24. The most common cancer cases in the UK (2018)

Cancer type	Incidence	Mortality
Prostate	12.6%	7.4%
Breast	12.4%	6.6%
Lung	11.7%	21.1%
Colorectum	10.7%	11.7%
Melanoma of skin	4%	1.5%
Non-Hodgkin lymphoma	3.6%	3.1%
Kidney	3.1%	2.5%
Bladder	2.7%	3.4%
Pancreas	2.5%	5.6%
Leukaemia	2.5%	2.8%

In the UK, UV radiation is recognised as the highest cancer-causing risk factor (**Table 25**). The topic of UV light is explained in section **6.15** of this thesis with detailed analysis of exposure to UV radiation including the UV radiation from the sun as a cancer risk factor, which is very important to support the new genetic concept of cancer presented in this study. Past studies have highlighted that overexposure to UV radiation can cause DNA damage which can develop cancer [242] [243]. Past studies have also highlighted the link between UV radiation and the natural synthesis of vitamin D which is essential for the functioning and health of the immune system [244]. Therefore, low UV radiation causes vitamin D deficiency which is also linked to increased risk of cancer as a strong immune system can better distinguish damaged and harmful cells and destroy them along with the recognised effects of vitamin D upon cell proliferation and differentiation [204]. According to the new genetic concept of cancer presented in this work it is explained that cancer caused by acquired gene mutations as a result of high or low UV radiation among the various ethnic groups in the UK is due to the fact that they are descendants of human Y-Chromosome DNA haplogroups that belong to other parts of the world than the UK and that each group are genetically designed to safely live in the geographic regions that they belong to. More

importantly, not all of the reported/recorded White ethnicity in the UK are native inhabitants of Britain. The genetic testing for ancestry has shown that many Whites in the UK are in fact descendants of human Y-Chromosome DNA haplogroups that have other sites of origin than the UK [245] and therefore it is a significant error when they are all amalgamated into one UK grouping of White ethnicity. The correct ethnic grouping according to the research conducted in this work is based on the human Y-Chromosome DNA haplogroups and that there is a group of UK White ethnicity that is genetically designed to safely live in Britain which is different from other Whites of other parts of the world who also look White, but they don't genetically belong to Britain and therefore it makes them of no difference from the known BAME communities in the UK when dealing with cancer research and other public health issues.

Table 25. The population attributable fractions (PAFs) in the UK

UV (2012)	89.3%
Tobacco (2017)	25%
Occupational risk (2017)	10.2%
Alcohol (2016)	8%
Obesity (2012)	6.3%
Infections (2012)	4.1%

6.12.3 Burden of cancer (Saudi Arabia)

In the Kingdom of Saudi Arabia, the total number of cancer cases was 24.485 in 2018 (**Table 26**). The incidence rates of breast cancer in addition to colorectum cancer followed by thyroid cancer are recognised as the highest in the country (**Table 27**). The analysis of the data shows that the total population of Saudi Arabia is half of the UK population, however the total number of cancer cases in the UK is much higher than that of Saudi Arabia. The total number of cancer cases per 100,000 population in 2018 was 659 in the UK compared to 71 in Saudi Arabia.

Table 26. Burden of cancer (Saudi Arabia)

Total population (2019)	Total number of cancer cases (2018)	Total number of cancer deaths (2018)
34,268,529	24,485	10,518

Table 27. The most common cancer cases in Saudi Arabia (2018)

Cancer type	Incidence	Mortality
Breast	14.8%	8.5%
Colorectum	14.6%	15.2%
Thyroid	10.1%	1.4%
Leukaemia	6.2%	8.7%
Non-Hodgkin lymphoma	5.5%	3.9%
Corpus uteri	4.4%	3%
Lung	3.8%	7.4%
Liver	3.7%	8.1%
Kidney	3.4%	2.4%
Bladder	3%	2%

Past studies have highlighted that cancer in Saudi Arabia is mainly caused by acquired gene mutations due to environmental factors and lifestyle behaviours in addition to inherited gene mutations which are passed down in families from generation to generation [246]. Infections in Saudi Arabia are recognised as the most common cancer-causing risk factor (**Table 28**). Infectious agents such as *Streptococcus bovis*, *Helicobacter pylori*, human papillomavirus, in addition to JC virus are linked to colorectal cancer which occurs in the colon or the rectum due to the high volume of viruses as well as bacteria that the intestine is exposed to [247]. Colorectal cancer is the second most common cancer type in Saudi Arabia (**Table 27**). Likewise, the use of tobacco is recognised as the second most avoidable cancer-causing risk factor responsible for lung cancer in the country. Moreover, Obesity is the third biggest preventable cause of cancer in the Saudi Arabia. Past studies have highlighted the link between obesity and breast cancer

[248]. Women experiencing obesity are at higher risk of both pre and postmenopausal breast cancer. Overweight women typically have higher insulin levels which is linked to breast cancer and other types of cancer. Past studies have also identified that obesity-associated inflammation is associated with a higher risk as well as progression of breast cancer. Furthermore, overweight women especially those consuming high animal fat diet have more fat tissue that increases estrogen levels which also increases the risk of breast cancer [249]. Importantly, obesity is one of the factors that can be modified by way of choosing a healthy lifestyle. The available data in regard to the ethnicity groupings in Saudi Arabia shows that around 60% of the Saudi population are the native-born Arabs of Saudi Arabia, and the remaining 40% are people from other parts of the world including mainly Syrians, Indians, Pakistanis, Bangladeshis, Filipinos, Indonesians and other Asians in addition to Africans [250]. However, the data from the Saudi Cancer Registry (SCR) of the Saudi Health Council (SHC) shows the registration of cancer as cancer cases among Saudis and non-Saudis. According to the SCR, the total number of the incidence of cancer in Saudi Arabia in 2016 was 17,602. A total of 13,562 cancer cases reported among Saudis and the remaining 4040 cancer cases were reported among the non-Saudis and unknown nationalities. The analysis of the data conducted by SCR demonstrates significant differences in the pattern of cancer among non-Saudis, however it is explained by SCR that the differences are due to the nature of the expatriates in the country with majority of them aged 25 to 44 years and mainly males [251].

Table 28. The population attributable fractions (PAFs) in Saudi Arabia

Infections (2012)	12%
Tobacco (2017)	10%
Obesity (2012)	6.8%
Occupational risk (2017)	1%
Alcohol (2016)	0.4%
UV (2012)	0%

6.13 The right methodology for analysing and studying the incidence of cancer among the various ethnic groups in the UK

One of the serious issues that the cancer incident data reports face is the handling of the unknown ethnicity rates reported by the patients in the assigning ethnic groups for the patients with cancer in the UK. The reports are therefore missing the actual data needed and therefore when such reports are produced, they are inaccurate and don't actually represent the facts on the ground. For example, a published report regarding breast cancer incidence rates by major ethnic groups among females in England from 2002 to 2006 (number of cases per 100,000 population) showed the highest incidence rate for White patients, a lower rate for Asian patients, and a significantly lower rate for Black patients. However, the report clearly states that 25% of the 187,620 breast cancer cases (46905 breast cancer cases) had no known ethnicity [252]. However, in another published report regarding the rates of breast cancer incidence by five largest ethnic groups (black African, black Caribbean, Indian, Pakistani and white) among females in England and Wales between 2013 and 2018 showed that ethnic minority patients are at greater breast cancers risk. Likewise, the report states that less than 10% of the 244,135 patients with breast cancer (22216 breast cancer cases) had no known ethnicity [253]. However, the rates for breast cancer patients with no recorded ethnicity went down from 25% to less than 10% due to significant improvements in ethnicity recording in national datasets. Therefore, the right methodology for studying the incidence of cancer by race and ethnicity in the UK is through having the lowest amount of missing data, with

considering all the risk factors known for causing gene mutations that lead to cancer. Secondly, in regard to the White ethnicity in the UK, it is not always accurate to consider all whites are the native inhabitants of Britain. This can only be confirmed by way of genetic testing for ancestry through verifying the human Y-Chromosome DNA haplogroup for the White ethnic population in the UK. To understand the human Y-Chromosome DNA of the native inhabitants of the UK, it starts with the major human Y-Chromosome DNA haplogroup R which has two major descendant lineages, the human Y-Chromosome DNA haplogroup R1 and the human Y-Chromosome DNA haplogroup R2. Likewise, the human Y-Chromosome DNA haplogroup R1 has two descendant subclades, the human Y-Chromosome DNA haplogroup R1a and the human Y-Chromosome DNA haplogroup R1b. The human Y-Chromosome DNA haplogroup R1b is dominant in Western Europe and its subclades the human Y-Chromosome DNA haplogroup R1b-M529 is the most common haplogroup in Britain and Ireland [254]. The human Y-Chromosome DNA haplogroup R1b-M529 (also known as R1b-L21) or (R1b1a2a1a2c) is a typical characteristic of the inhabitants of the British Isles, and it is found in highest frequencies among the Irish, Scottish, Welsh, and Bretons [208]. The available data regarding genetic testing and the genetic structure of the UK population has revealed that not all white ethnic individuals are native inhabitants of the UK. According to the data from the FTDNA public projects, the following human Y-Chromosome DNA haplogroups are also found among the white ethnic population in the UK: the human Y-Chromosome DNA haplogroup I which comes after the human Y-Chromosome DNA haplogroup R, the human Y-Chromosome DNA haplogroups E, G, and J are also found among the white ethnic population [245]. However, these human Y-Chromosome DNA haplogroups have sites of origin other than the British Isles. Therefore, and according to the genetic concept of cancer presented in this study it is explained that the incidence of cancer among the migrant is higher due to the fact that these various ethnic groups belong to other Y-Chromosome DNA haplogroups than haplogroup of the native inhabitants of Britain. Therefore, the right methodology of in addition to the collection of complete and accurate data regarding the incidence of cancer in the UK, is understanding the topic of the

human Y-Chromosome DNA haplogroups essential to help finding preventative measures to save lives in the UK and worldwide.

6.14 Data from the Million Women Study (MWS)

One of the vital sources of data in regard to breast cancer and other types of cancers obtained for this research was the cancer incidence rates by ethnicity from the Million Women Study (MWS). The MWS list of ethnicity groups used in the study is as follows: Whites, Blacks, South Asians, other Asians, other specified, in addition to ethnicity not available. The following table (**Table 29**) shows the current numbers available for women in the MWS study with incident breast cancer by ethnic group.

Table 29. Ethnicity and breast cancer incidence in the UK

Ethnicity	Breast cancer incidence
White	73,204
Black	297
South Asian	374
Other Asian	129
Other specified	523
Ethnicity not available	2463
Total	76,990

The analysis of the above rates of cancer incidence in MWS study shows that the total number of the known non-white ethnic group is 1323 breast cancer cases (about 1.8%). However, a large number (2463) of the breast cancer cases recorded with missing data on ethnicity (about 3.4%). Therefore, caution must be exercised when interpretating cancer incidence rates in the MWS study. For example, if the 2463 breast cases recorded were of Non-White ethnicity, that would clearly make the breast cancer incidence rate higher among the migrant population in the UK which is more likely as evidence was presented in the

previous section which showed that the 2002 to 2006 published report regarding breast cancer incidence rates had 25% of the data missing and therefore it showed the highest incidence rate for the White ethnicity. However, the 2013 to 2018 published report had less than 10% of the data missing regarding ethnicity and therefore it showed the highest incidence rate for the none-white ethnicity. Likewise, the following table (**Table 30**) shows the data for all incident cancers to end 2017 available for women in the MWS study by ethnic group.

Table 30. Ethnicity and cancer incidence in the UK

Ethnicity	Cancer incidence
White	227,263
Black	1,019
South Asian	989
Other Asian	403
Other specified	1,639
Ethnicity not available	10,241
Total	241,554

The analysis of the above rates of cancer incidence in the MWS study shows that the total number of the cancer cases of the known Non-White Ethnic group is 4,050 cancer cases (about 1.68%). However, once again a significant number (10,241) of the cases of cancer recorded with missing data on ethnicity (about 4.24%). It is therefore important to use scientific methodologies for studying and understanding the various cancer cases in the UK when dealing with missing crucial data regarding the race and ethnicity of the cancer patients. To be noted is that the data and information from the MWS study is very useful for studying and understanding the incidence of breast cancer and other types of cancer among the women population in the UK, especially the detailed information about the affected women such as the risk factors that are known to put women at a higher risk of getting cancer, including the lifestyle factors, the reproductive

factors, and other factors, needed for better understanding the incidence of breast cancer and all incident cancers when the MWS cases are investigated.

6.15 Analysis of exposure to ultraviolet (UV) radiation including the UV radiation from the sun as a cancer risk factor

Additionally, and according to the cancer research agency of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), physical carcinogens such as exposure to ultraviolet (UV) radiation including the UV radiation from the sun, are classified as one of the main cancer-causing agents [195]. However, this cancer risk factor is understandable for a light skin colour individual such as a native European who has less melanin pigmentation in their skin and had travelled and exposed to the UV radiation of a hot/sunny country such as the hot/sunny parts of Africa, then they would be at a higher risk of getting gene mutations that can lead to different types of cancer such as skin cancer. Importantly, past studies have confirmed that skin cancer is rare among Africans as native inhabitants of Africa [255]. However, the key question is that why a dark skin colour individual with a skin that is rich in melanin pigments be at a higher risk of getting cancer if they migrated to a low UV radiation country. There is no such a high exposure to UV radiation in a low UV country, however and according to past studies, dark-skinned individuals who live in low UV countries are at a higher risk of getting gene mutations that will cause various cancer types [205]. Therefore, and based on the research conducted in this work it is explained that the cancer risk factor of prolonged exposure to UV radiation is true for light skin colour individuals who went to hot/sunny countries, but it is due to the fact that they went to a geographic region they don’t belong to. Since the indigenous people of the hot/sunny countries do get exposed to UV radiation from the sun all their lifetime, yet they have low rates of incidence of cancer, otherwise no native inhabitants would exist in the hot desert climate conditions countries due to exposure to radiation.

6.16 Cancer prevention strategies proposed in this work

Based on the novel genetic concept of cancer presented in this work, important cancer protection and prevention strategies are proposed in this study to help prevent people from getting the gene mutations responsible for causing cancer through understanding the various cancer risk factors. Consequently, to control and prevent cancer through avoiding and controlling the key risk factors and save lives. According to the advice from the world health organisation (WHO) the risk of cancer can be reduced through avoiding various factors including, using tobacco, getting overweight, unhealthy food and diet, infections, and exposure to UV radiation in addition to other risk factors [195]. However, and as a result of the new genetic concept of cancer presented in this work which links the development of cancer with the human population origins and migrations, and the environmental factors and gene mutations, evidence-based protection and prevention strategies have been recommended in this research. First of all, the main prevention strategy proposed in this work is based on the fact that human gene mutations are more likely to occur after some time following leaving the site of origin and start living in other geographic regions that have significantly different climate conditions such as being from a cold European country and relocate to a hot/sunny country of desert climate conditions. Therefore, it is highly essential for people to stay within the geographic zones of their human Y-Chromosome DNA haplogroups. It follows that with the increased availability of DNA testing and for a reasonable price, it is therefore highly recommended for people to get their DNA tested to know their human Y-Chromosome DNA haplogroups. In general, one sample from one male member of the family is enough to be tested for their whole family or their bigger family and clan. Evidence was presented in this work that the White ethnic population in the UK belong to more than one human Y-Chromosome DNA haplogroup some of which belong geographical regions to Asia and Africa. In other words, the White ethnic population in the UK is a mixture of various races although they all look white and classified as one major ethnic group in many research studies regarding race and ethnicity. According to the research conducted in this work this inaccurate recording of ethnic group is one of the major issues when studying the cancer

incidence rates in the UK. Secondly, in regard to individuals who live in environments other than their place of origin it is critical to keep the environment around them similar to the environment of their place of origin. From the cancer cases investigated in this work, certain health habits were noticed such as that of the skin cancer patient found in generation III of the pedigree of the family investigated in this work (see **Fig. 35**). It was noticed that the patient had the habit of not willing to stay within an environment cool enough to prevent as investigated in this work at least some of the health conditions that she suffered from (this health habit is discussed in more detail in the following chapter 7 of this thesis). Thirdly, and based on the cancer cases investigated in this work supported by genetic testing, it was repeatedly observed that when a female member of a migrant family gets married to a male from the host population (a native inhabitant) no cancer cases affect their children with the family being living in a geographical region of their site of origin as the children follow the human Y-Chromosome DNA haplogroup of their father. Therefore, it is proposed in this study and as a prevention strategy that if the female members of a migrant population married to the male members of the host population and remained in the host country, then that will bring their children to a lower risk of getting gene mutations responsible for cancer. Thirdly, one important natural protection strategy is through the body's own immune system. The immune system is capable of recognising and killing abnormal cells. The human body produces abnormal cells on daily bases however they are destroyed by the body's immune system before they cause harm to the body. Therefore, having a strong immunity through diet, exercise, sleeping well and etc., can dramatically protect and prevent the body from the produced abnormal and damaged cells before developing into tumours. The immune system also protects the body from infections and illnesses. Certain viral and bacterial infections are known cancer risk factors. Similarly, some poor diet and lifestyle activities can weaken the immune system such as too much sugar intake, not only causes blood sugar to rise leading to weight gain, but also weakens the immune system. Sugar can deplete our body from essential immune-supporting nutrients such as zinc, vitamin C, and glutathione. It also feeds parasites in our body and may lead to abnormal tissue and cancerous growth. Furthermore, our body needs regular

sleep to rest, repair and regenerate. Sleep deprivation on a regular basis will surely lead to fatigue, exhaustion, and low concentration. Sleep deprivation also leads to reduced immune protection and increased inflammatory processes and this can increase the risk to infections and illness. Drinking plenty of water and proper hydration is essential for the immune system, circulation, nervous system, and normal body function. Chronic dehydration can result in too much histamine in the body and elevated histamine may also increase inflammation, chronic pain, headaches, allergic reactions, digestive and immune system problems. The consequence of chronic dehydration may also increase the risk of infections, illness, and disease. Prolonged staying indoors and too much indoor time/activities also increase body's exposure to indoor pollutants in addition to not getting sufficient fresh air and vitamin D from the sun. To protect our immune system, it is essential to spend time outdoors regularly. People with optimal vitamin D levels during winter have lower rates of flu than people who receive flu vaccines, whereas people with vitamin D deficiency are 11 times more likely to get a cold or flu. On the other hand, supplementing with vitamin D reduces colds and flu by up to 42%. Vitamin D is naturally made by the body when the skin is exposed to direct sunlight. It is therefore critical for people to get the vitamin D levels tested and making sure the level stays at least 30 ng/mL [256]. A daily dose of at least 400 international units (IU) of vitamin D3 for adults is recommended especially for people who do not get a 30-minute daily dose of direct sunlight. The active hormone made by the kidneys (via vitamin D intake) increases calcium absorption in the gut ensuring strong bones (and muscle) free from osteoporosis. Vitamin D supports/boosts the immune system via immune pathways involved in fighting against viral infections, therefore, reducing serious complications. Additionally, nutrient deficiencies cause impaired immune function, thus eating a variety of foods rich in phytochemicals will boost the immune system. Such plant foods include green vegetables rich in folate, calcium and antioxidants (lutein and zeaxanthin). Folate produces antibodies which destroy antigens. Beans, lentils and peas have plenty fibre and improve gut microbiome. Onions have quercetin fighting against bacteria and produce prebiotic fibre in large intestine. Mushrooms enhance immunity with anti-cancer effects and increase IgA (antibody produced in mucus membranes) which has an

important role in immune function (eaten cooked mushrooms for avoiding any carcinogens). Berries are rich in antioxidants, lower inflammation and fight disease. Seeds and nuts (walnuts, almonds) are rich in fibre, healthy omega3 fats, vitamin E, iron, zinc and calcium. Zinc is known as the gatekeeper of the immune function and is high in sesame, hemp and pumpkin seeds. Beets high in nitrates (nitric oxide as vasodilator) which lower blood pressure and heart rate, beets also contain betalains which reduces inflammation hence prevents various diseases. Purple vegetables (carrots, cauliflower, red onion, cabbage) are rich in antioxidants (anthocyanins) heal damaged cells hence may prevent cancer, promote healthy hearts and boost memory. After all, and part of the protective and prevention strategies suggested in this study is that it is very important to make sure of regular health checks at home and at medical centres through to keep a healthy body in addition to reporting any abnormalities or health issues to family and family doctors and hospitals before it is too late. Thus, the topic of cancer prevention strategies is of utmost importance for the public and authorities worldwide specially in countries where large numbers of migrated people are found, therefore the proposed protocols in this work will most likely lower the cancer rates amongst such populations, hence decrease the mortality rates and save more lives with huge cost savings for the national healthcare providers.

CHAPTER 7

CLINICAL CASE STUDIES

7.1 Clinical case studies carried out in this work

In this chapter a number of cancer cases related to the families investigated in this work are discussed based on the medical reports and medical images obtained from the various hospitals where the cancer patients attended and received treatments. The clinical case studies provide detailed analyses and discussion of various types of cancer as detailed investigation of each patient's full medical history was carried out including information regarding any illnesses, screenings, and treatments including surgeries in addition to other information related to their health habits/diets and prescribed medications. The investigations also included the analysis of various medical images for each cancer case produced via different medical imaging modalities. The analysis of the medical images of the clinical cases also presented comparisons between the medical images and highlighted how a medical imaging modality could be superior to another medical imaging technique in demonstrating the affected part of the body of the patient. The main objective for studying these cancer cases was to support the newly genetic concept of cancer presented in this work as well as the protection and prevention strategies to help and avoid people from getting affected with the disease. To be noted is that there was a personal (physical) presence and engagement and direct communication with patients and families of each cancer case discussed in this chapter some of which from the very beginning of when the cases started and how they were diagnosed, treated, progressed and ended including all the relevant details, however there was no involvement in any form of decision making in regard to any management or treatment of the cancer cases. Importantly, the clinical case studies carried out in this research and presented in this chapter have been peer-reviewed and published and submitted for publication. The first two cancer case studies (case study of Squamous cell carcinoma and malignant otitis externa of the left external auditory canal, and pleuropulmonary blastoma (PPB) in a 3-year-old boy) are from one family that have European ancestry and have lived in the geographic region of the Arabian Desert, important to understand what types of cancer affected the family throughout five generations investigated in this work. The third case study (case study with analysis of paediatric optic nerve glioma and

craniopharyngioma) is a case found in a native family from the geographic region of Mesopotamia and that they have lived there all their life. The fourth case study (dedifferentiated chondrosarcoma of the right chest wall: case study of a deceased middle-aged male subject) is a rare cancer case found in a native family from the geographic region of the Arabian Desert and that they have lived there all their life. Likewise, the fifth cancer case study (case study of a 50-year-old woman with high grade (G3) triple-negative metaplastic breast cancer) is a rare breast cancer case found in a native family from the geographic region of the Arabian Desert and that they have lived there all their life. The last three cancer cases discussed in this chapter are not from families that are related to each other; however, the importance of investigating these cancer cases was to support the newly genetic concept of cancer presented in this research.

7.2 Cancer diagnosis overview

In this section the common tests and procedures as well as the imaging scans that are used for the diagnosis of the various types of cancer discussed in this work in addition to the tests generally carried out to find out if cancer has spread to other parts of the body (metastasis). Typically, medical imaging tests play an important role in the diagnosis of most types of cancer; however, a tissue biopsy is required to confirm the diagnosis. Imaging tests are performed when an abnormality is detected to learn more about the abnormality and to find out whether or not cancer has spread to other parts of the body for which various imaging modalities are used such as X-rays, CT scan, mammography, bone scan, PET scan, MRI, and PET/CT scan. A biopsy is used to determine whether or not cancer is present, to find out if the tumour is benign or malignant, and to check if the disease has spread to other parts of the body. A biopsy is the procedure of removing a small sample of the body tissue for examination in the laboratory. A biopsy can determine the grade of the tumour which refers to how abnormal the cancer cells appear under the microscope compared to normal cells, in addition to looking at how fast or slow they grow. Low grade tumours (grade 1) grow slowly, and the cancer cells appear similar to the normal cells. However, high-grade tumours (grade 3) grow and spread faster, and the cancer

cells don’t look like the normal tissue. Low grade tumours have better prognosis i.e., it will respond to treatments better. High grade tumours are expected to come back following treatments as either primary tumours or secondary tumours. Likewise, using information from a biopsy along with information from medical imaging tests as well as information from physical examinations all together are used for staging breast cancer and other types of cancer. Stage describes the size of the primary cancer and whether it has spread to other parts of the body. The tumour node metastasis (TNM) classification is used in the patient’s pathology report for staging the patient’s cancer. Most types of cancer have 4 stages. The stages of cancer are the numbers 1 to 4. In stage 1, cancer is small and hasn’t spread, while in stage 4, cancer has spread to other parts of the body. There is also stage 0 or carcinoma in situ (CIS) which shows a group of abnormal cells in a certain part of the body, but they are too small to form a tumour. Following the surgical removal of a tumour, more information can be obtained to determine the surgical or pathological stage of the disease which is more accurate, and it can be different from the clinical stage. In general, a cancer stage remains the same following diagnosis, however sometimes cancer may be restaged following treatments or if there is cancer recurrence. There are different types of biopsies including fine needle aspiration biopsy, core needle biopsy, and image-guided biopsy during which a needle is guided to the location of the tumour using medical imaging such as ultrasound imaging and CT scan. Furthermore, the samples obtained from a biopsy can be analysed to reveal the genetic characterisation of the cancer cells. Normal cells have normal DNA, however the DNA of the cancer cells has acquired multiple genetic mutations leading to the development of the cancer. Genetic analysis of the cancer cells looks for unique gene mutations through sequencing which is important for cancer treatment to target the cancer cells using targeted therapy (biological therapy) [72]. Targeting therapy stops the growth and spread of the cancer cells by targeting specific gene mutations of the cancer cells. Finally, in rare cases needle seeding or tumour seeding may occur during which the inserted needle at the time of the biopsy causes the spread of cancer along the track of the needle [257].

7.3 Case study of Squamous cell carcinoma and malignant otitis externa of the left external auditory canal

Necrotizing or malignant external otitis (MEO) also known as malignant otitis externa (MOE) is a severe invasive infection of the external auditory canal (EAC) that invades the base of the skull and causes potentially life-threatening complications. MEO is often found in elderly patients with diabetes mellitus, chronic kidney disease (CKD) and kidney failure [258] [259] or other conditions that compromise the body's immune system such as in cancer patients receiving chemotherapy and radiotherapy [260]. This case study is for the skin cancer case found in generation III of the pedigree (see **Fig. 35**). It was important to study this case in more detail and provide full discussion and analysis of the related medical images of the case and to support the new genetic concept of cancer presented in this research in addition to understand what protection and prevention strategies could help people and prevent them from serious illnesses. The subject discussed here is an elderly deceased female with squamous cell carcinoma (SCC) and malignant external otitis of the left external auditory canal (EAC). The subject as confirmed (see kit number 1) has a European ancestry and has lived all her life in the Kingdom of Saudi Arabia, together with her husband and their children. Although a good quality of life (QOL) was always maintained for the patient, she suffered difficult health conditions from time to time throughout her life. In this case study, a detailed report of the patient's case is presented including a number of medical images (and analysis) via computed tomography (CT) scan and magnetic resonance imaging (MRI). It was found that the medical images from the CT scan and Brain MRI revealed detailed information of the patient's case of MEO and SCC. CT scan revealed osteomyelitis (and extension of infection) of the temporal bone, whereas MRI was superior to CT in estimating the anatomic extent including inflammation of fat, connective tissue, muscles, bone, and cartilage.

7.3.1 Medical history

The case of a 70-year-old deceased woman with squamous cell carcinoma and malignant external otitis of the left external auditory canal is discussed in this case study. The patient had a longstanding history of chronic ear infection with pain and discharge from the left ear, sometimes bloody, in addition to hearing loss in left ear and normal hearing in the right ear. The following image **Fig. 42** is a clinical image of the outside look of the patient's affected left side, which shows the extension of inflammation much more around the ear.

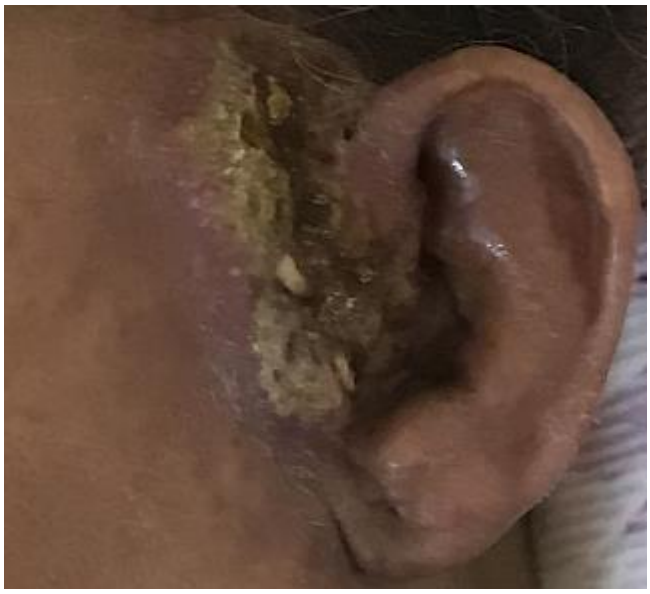

Figure 42 Image of the left ear showing extended inflammation around the ear.

The patient also had a history of diabetes mellitus and hypertension, for which she was prescribed the regular medication. However, at a later age she developed kidney failure, and had to have a kidney transplant. Not long enough after her kidney transplant, she started experiencing severe pelvic pain, frequent urination, and excessive menstrual bleeding, and later she was diagnosed with benign tumours in her uterus for which she had to have hysterectomy to surgically remove her uterus. The patient was also diagnosed later in life with squamous cell carcinoma of the left ear canal, possibly as a result of a cumulative, unprotected sun exposure, which later spread beyond the ear skin. Biopsy from the patient revealed squamous cell carcinoma of the left external auditory canal.

Squamous cell carcinoma is the most common histological type of cancer in the head-and-neck region [261], it affects the squamous cells of the epidermis of the ear. Surgery is usually the primary treatment, but in this case, it would have been hard to operate in order achieve a full recovery. Therefore, radiotherapy was the recommended option for this patient who was unable to have surgery. To be noted, chemotherapy is not widely used for the treatment of squamous cell carcinoma [262]. This patient was unable to be treated with surgery or chemotherapy due to the existing illnesses in addition to the location of the cancer, therefore, she received only radiotherapy treatment. However, after radiotherapy, she developed malignant external otitis, for which, she received the standard antibiotic therapy. Malignant external otitis and squamous cell carcinoma are characteristically seen in elderly patients. However, when these two diseases exist at the same time, usually in rare cases, they are associated with substantial morbidity and mortality [263]. Malignant external otitis can be very painful, which was the case with this patient, for which she received strong painkillers such as morphine. The patient also developed facial nerve palsy which is considered as a sign of progression of malignant external otitis [264]. The aim of this case study was to discuss vital details with concluding remarks about the medical history of a deceased female member of the family studied in this work. The patient is a member of a family from the human Y-Chromosome DNA haplogroup R-M198, which is believed to have originated in the geographic region of the Central and Eastern Europe. The patient was born and raised in the Arabian Peninsula and had lived there all her life. The noted physical features of the patient show clearly the common European white look, including light skin colour, which is logical due to the genetic haplogroup they belong to which was confirmed through testing the DNA sample taken from the patient's brother to determine their paternal ancestry, as her father had passed away. Original people of the Arabian Peninsula are known to be dark skinned, for being in the sunny hot climate conditions of the Arabian Desert as it was the case with the patient's husband who is a native Arab from a well-known Arab tribe in the Arabian Peninsula, and he is dark skinned. The husband's tribe has a large number of genetic samples in the database of the approved genetic testing company used for this research, i.e., the FTDNA. The analysis of these DNA samples all showed

that they are positive to the human Y-Chromosome DNA haplogroup J-M267 which is found at its highest frequencies in all of the Arabian Peninsula. To determine the paternal ancestry for this patient's husband, a genetic sample was obtained from his son (see kit number 5), and the analysis of the results showed that they are positive for the human Y-Chromosome DNA haplogroup J-M267. Studying the health habits of this patient is significant as it can be used for setting up prevention strategies for the new concept of cancer presented in this study.

7.3.2 Medical imaging results and discussion

CT scan and MRI imaging techniques were used for this patient to evaluate her medical status. The following medical images were obtained from the radiology department, King Faisal Specialist Hospital and Research Centre, in Jeddah, KSA. The image in **Fig. 43** (CT Topogram of the brain) shows this patient's condition with malignant external otitis in the presence of squamous cell carcinoma in the left external auditory canal.

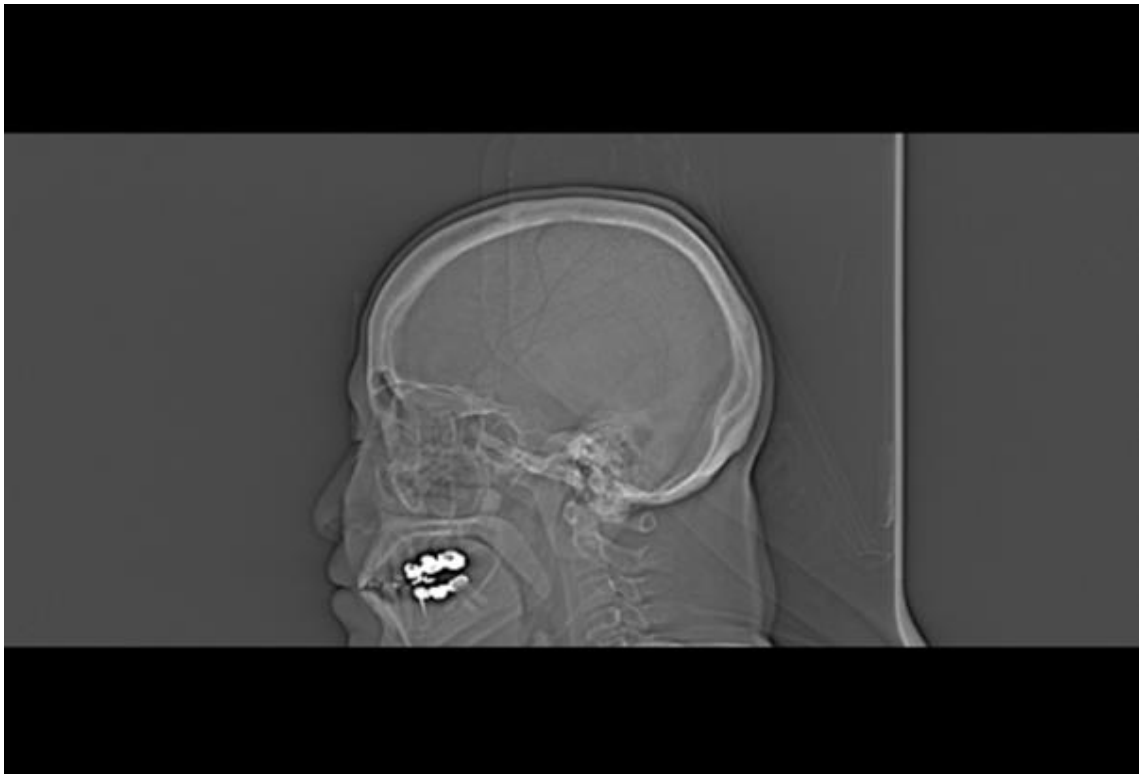

Figure 43 CT scan of the brain (Topogram 0.6 T20s).

To be noted is that the CT Topogram is a two-dimensional digital radiograph used to plan the scan field of view (SFOV) which is a view from the top and it can reveal useful information discovered only in this view [265]. Topogram 0.6 T20s is related to the series description in the scan protocols. The following image **Fig. 44** is the axial non-contrast CT of the brain. The brain consists of white matter and grey matter structures. On CT scans, white matter appears gray, and grey matter appears white. Anything seen darker than brain has lower density (see **Fig. 45**), such as air and cerebrospinal fluid (CSF) [266].

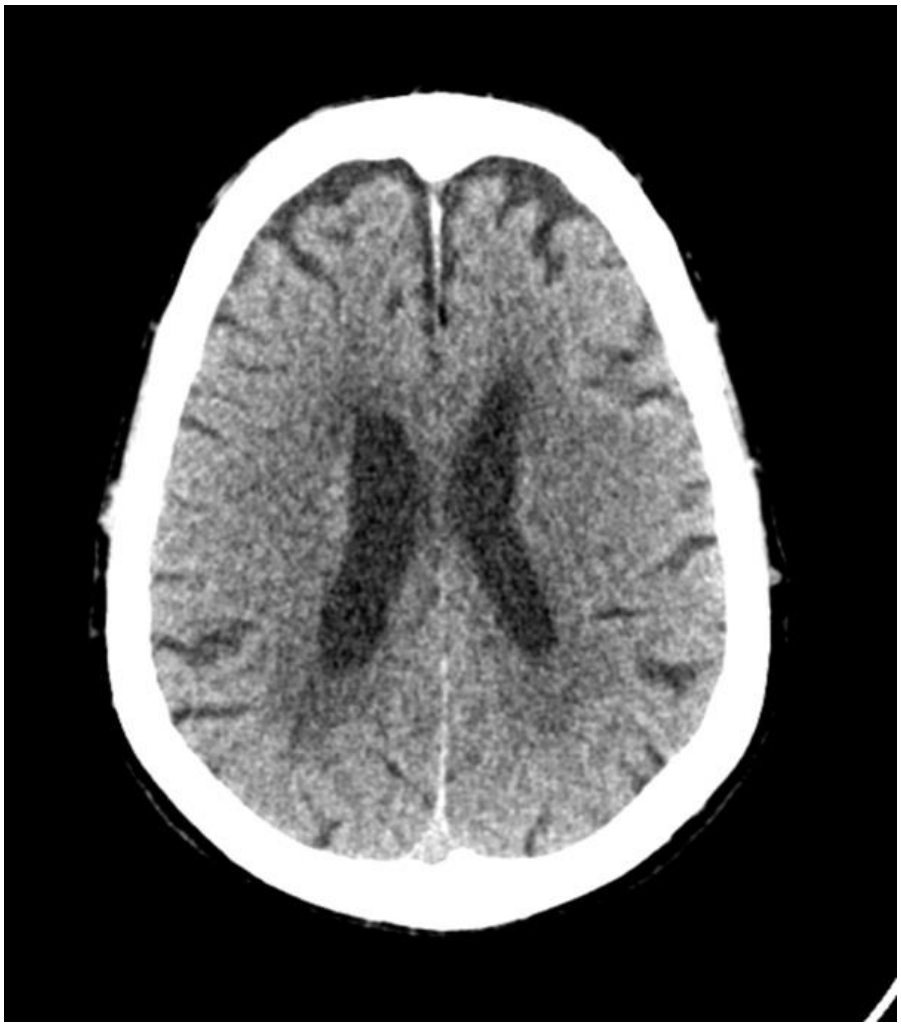

Figure 44 Axial non-contrast CT scan of the brain.

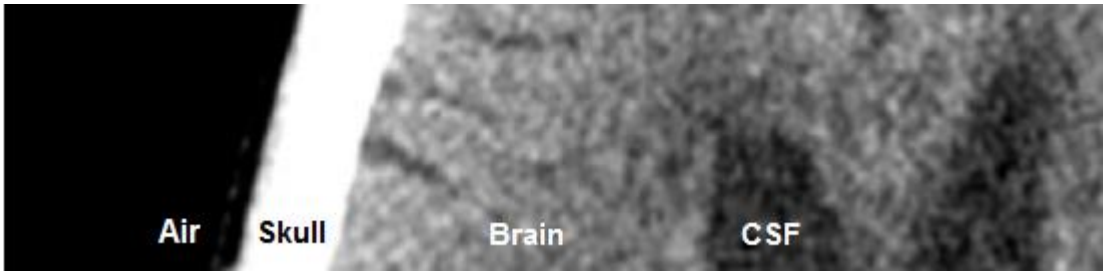

Figure 45 CT brain densities showing different appearances.

When reading an axial image, the right side of the image is the left side of the patient. The top of the image is the anterior (the front) surface of the patient. The slices on CT are at an angle, unlike MRI which has true axial slices. The following image **Fig. 46** is the axial non-contrast head CT scan at a different slice.

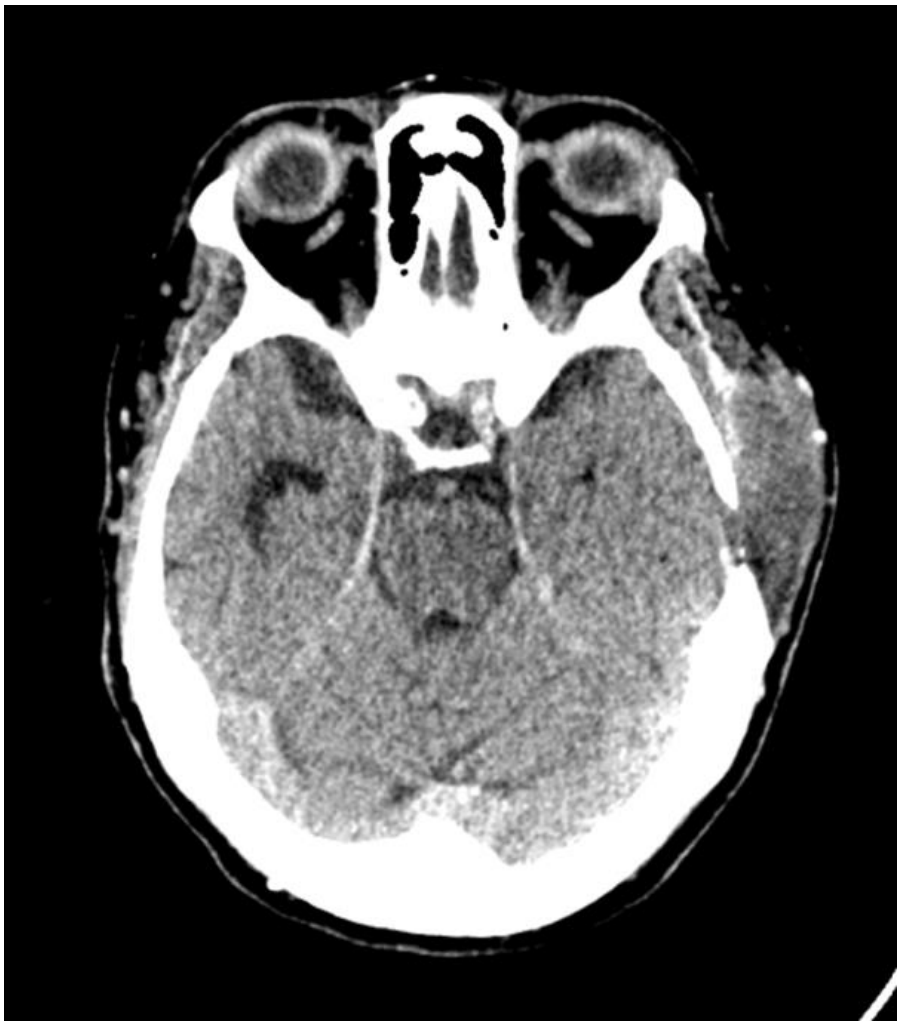

Figure 46 CT Brain axial non-contrast scan.

For this patient, re-demonstration of huge left malignant otitis externa associated with aggressive looking large peripheral adjacent fatty stranding is also noted in soft tissue window suggesting an infectious process and possible intracranial involvement of left temporal bone. The following image **Fig. 47** is another slice of the axial non-contrast head CT scan.

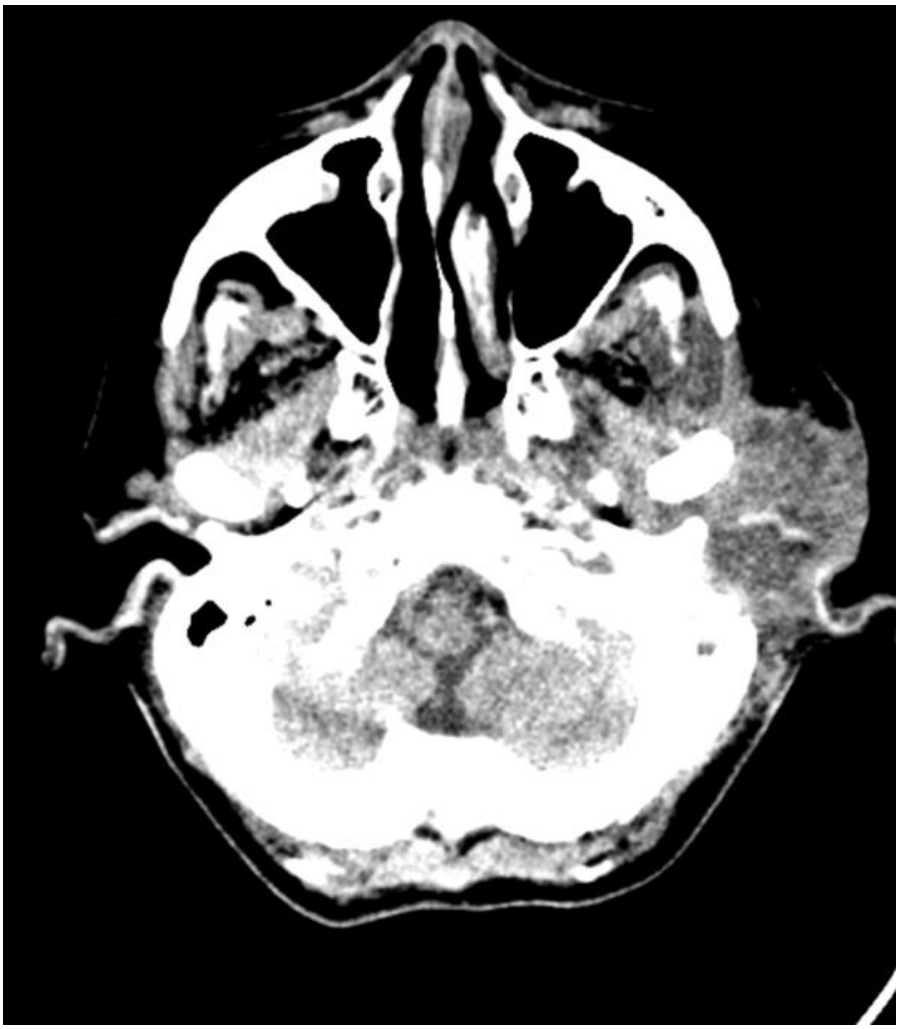

Figure 47 Axial non-contrast CT brain (another slice) scan.

MRI imaging was also recommended for this patient which is superior to CT in estimating the anatomic extent of MEO [267] and being able to detect flowing blood. Brain MRI is safe, painlessit and demonstartes the anatomy and detailed images of the soft tissue. The posterior fossa is more easily visualised on MRI than CT. MRI can visualise the anatomy in all three planes, i.e. axial, sagittal and coronal. Abnormalities such as tumour and infection can be detected using MRI.

There are two basic types of MRI images, T1 weighted and T2 weighted images. T1-weighted is the longitudinal relaxation time and T2 is the transverse relaxation time. CSF is dark on T1-weighted images and bright on T2-weighted images [268]. The following image **Fig. 48** is the midline brain sagittal T1 weighted image of the patient.

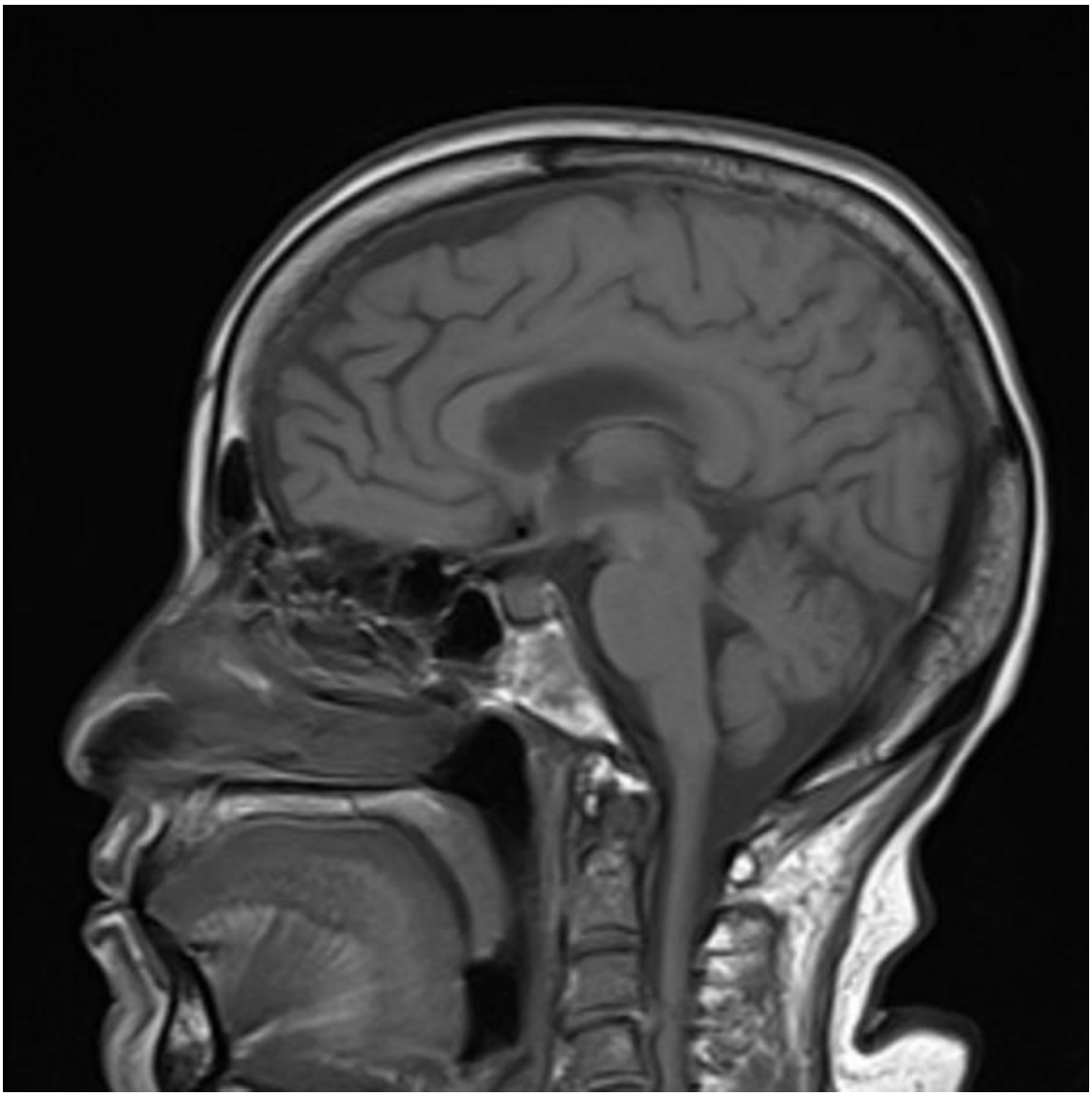

Figure 48 T1 SE (spin eco) sag MRI brain scan image.

SE or spin echo is a T1 weighted sequence. Sagittal plane MRI is very useful for assessing the details of the midline structures. For this patient, the brain parenchyma demonstrates preserved Gray-white matter differentiation.

Prominent ventricular system and sulci in keeping with atrophic changes, i.e., the loss of brain cells. The following image **Fig. 49** is the axial T1-weighted brain image of the patient.

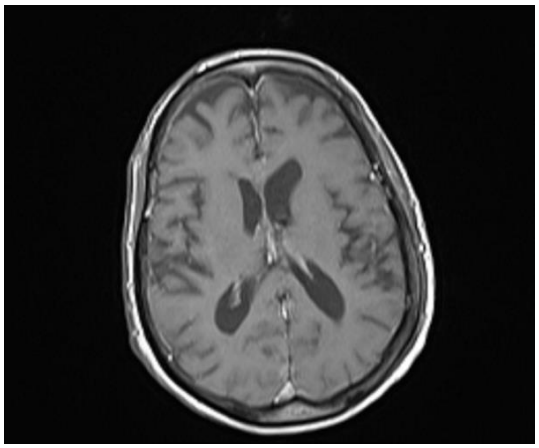

Figure 49 T1 Turbo spin echo (TSE) MRI brain scan image.

Turbo spin echo (TSE) or fast spin echo (FSE) is an adaptation of conventional spin echo (SE) acquisition technique [194] and TSE reduces imaging time. The following image **Fig. 50** is a different slice of the axial T1-weighted brain image of the patient.

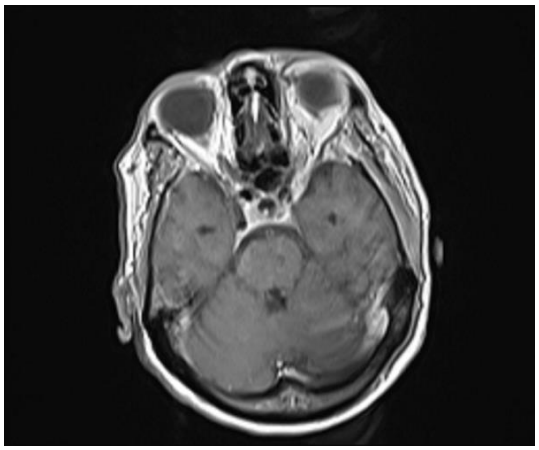

Figure 50 T1 TSE MRI scan of the temporal bones.

Posterior fossa structures appear unremarkable in this case and paranasal sinuses demonstrate circumferential wall thickening of the bilateral maxillary

sinus and ethmoid opacification of bilateral mastoid air cells. The following image **Fig. 51** is another slice of the axial T1-weighted brain image of the patient. The above-mentioned condition is clearly visible.

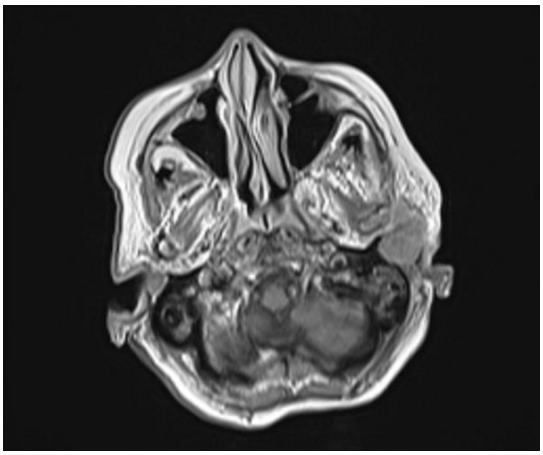

Figure 51 T1 TSE MRI image of the temporal bones.

The following image **Fig. 52** is the coronal T2-weighted brain image of the patient. Comparing the affected left side with the unaffected right side, it clearly shows this patient's abnormal conditions of the left ear as described earlier.

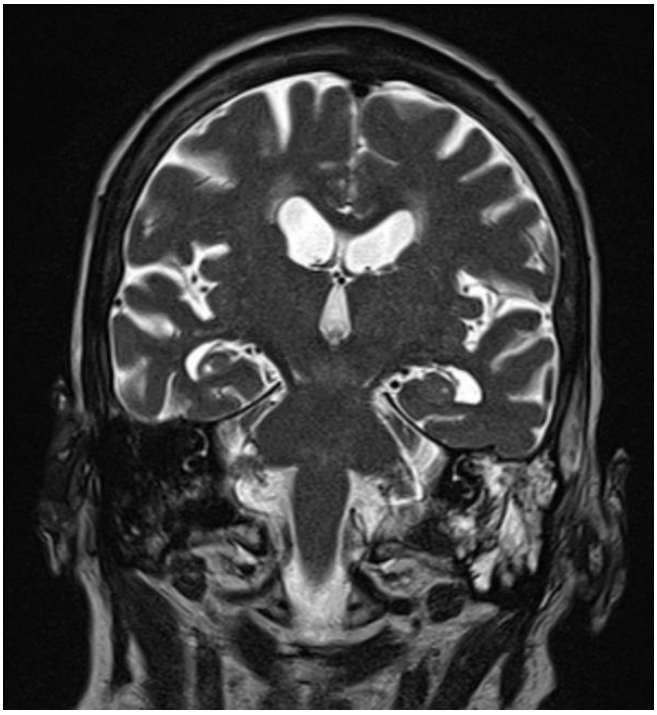

Figure 52 T2 TSE coronal MRI image of the brain and temporal bones.

Coronal plane divides the brain into an anterior and posterior portion. The brain is sliced parallel to the long axis of the body, i.e., perpendicular to the floor. On T2-weighted MRI images, CSF is bright as well as tumour, oedema, and inflammation which also appear bright. Fat is light, white matter is dark Gray and air is very dark. The following image **Fig. 53** is the axial T2-weighted brain image of the patient.

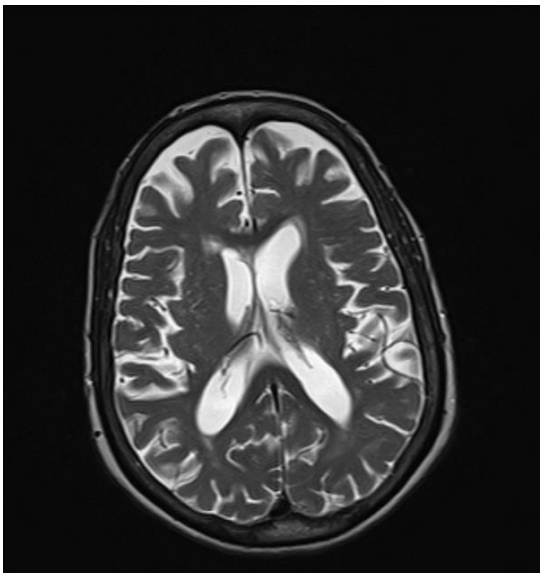

Figure 53 T2 TSE MRI image of the brain and temporal bones.

The following image **Fig. 54** is a different slice of the axial T2-weighted brain image of the patient demonstrating the affected left side.

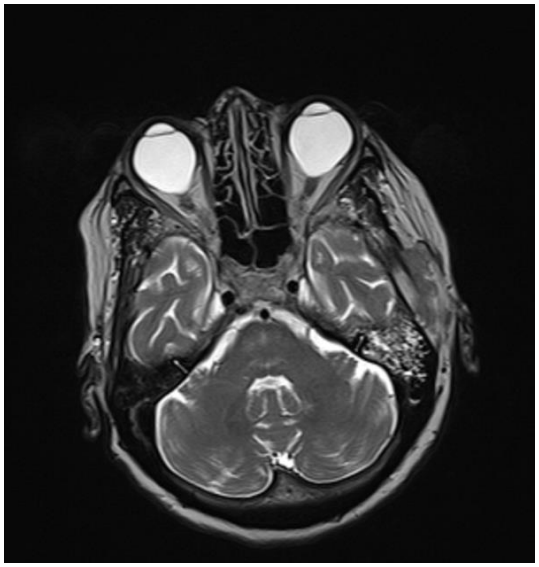

Figure 54 T2 TSE MRI image of the brain.

The following image **Fig. 55** is another slice of the axial T2-weighted brain image of the patient. Comparing with the unaffected right side, it can be seen that there is abnormal brightness confirming the presence of disease in this case and as expected.

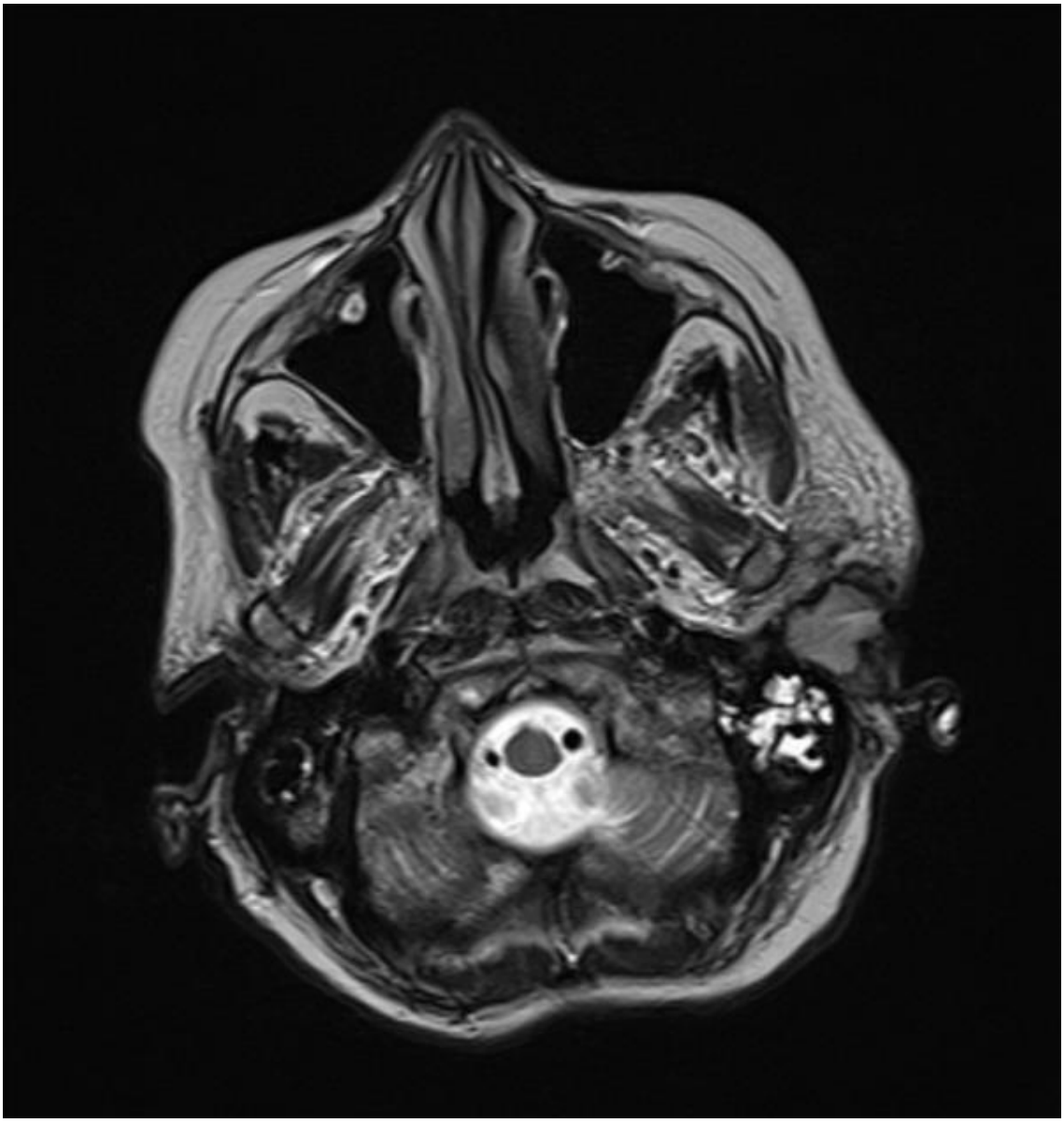

Figure 55 T2 TSE MRI image of the temporal bones.

The following image **Fig. 56** shows the coronal T1-weighted brain images of the patient, (**A**) is T1 SE MRI brain, (**B**) is T1 SE MRI brain with contrast, and (**C**) is T1 SE MRI brain with contrast and fat saturated, demonstrating extensive inflammation and enhancement of the affected left ear side.

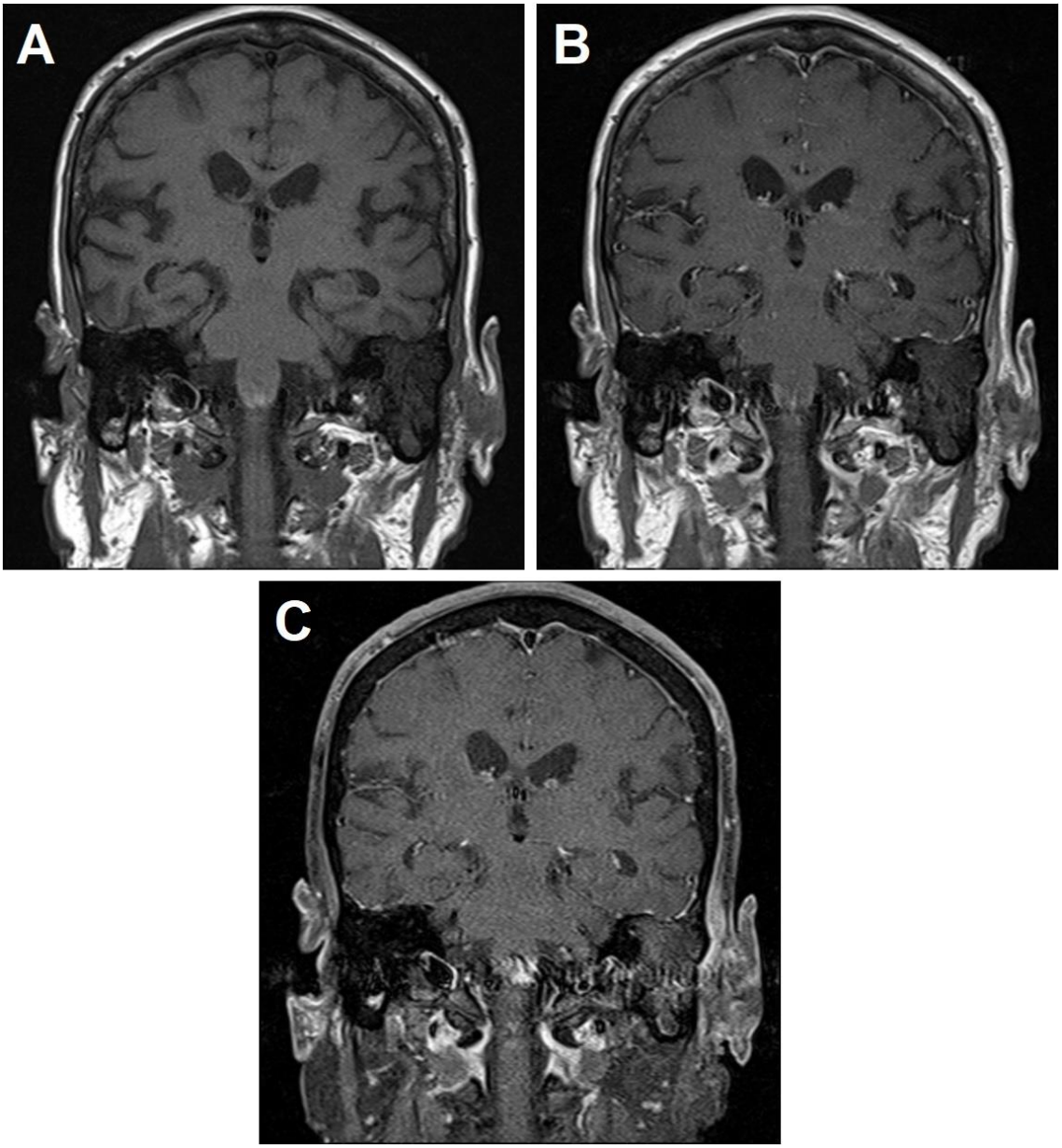

Figure 56 Coronal T1-weighted brain images of the patient showing extensive inflammation of the affected left ear side, (**A**) is T1 SE MRI image of the brain, (**B**) is T1 SE MRI image of the brain with contrast, and (**C**) is T1 SE MRI image of the brain with contrast and fat saturated.

7.3.3 Discussion

This work has shared vital details about malignant external otitis of the left external auditory canal in the presence of squamous cell carcinoma in a deceased female. The patient had a confirmed European ancestry, she was born

and raised in Saudi Arabia and had lived most of her life in the sunny hot climate conditions of the Arabian Desert. Various CT scans and MRI image analyses in addition to genetic testing for ancestry, with detailed population genetic analysis have also been carried out. Sufficient evidence has, therefore, been provided conforming that this patient suffered difficult health conditions most likely due to living in an adopted environment, i.e., the Arabian Desert, that was different from the climate conditions of her place of origin, i.e., Europe. The patient's genetic testing results for ancestry showed that the patient's parental ancestry is positive to the human Y-DNA haplogroup R-M198, which is found at its highest frequencies in the Central and Eastern Europe. Genetic testing also revealed the paternal ancestry for the patient's husband, which showed that they are positive to the human Y-DNA haplogroup JM267 which is found at its highest frequencies in the Arabian Peninsula. The patient's husband who is a native Arab has lived all his life in the Arabian Desert and without developing the above-mentioned health conditions related to his wife. CT scan images showed huge left necrotizing external otitis associated with aggressive and large peripheral adjacent fatty stranding in soft tissue window. MRI showed superior images than CT scans in demonstrating the anatomy and detailed images of the soft tissue for detecting abnormalities such as tumour and infection in all three planes (axial, sagittal and coronal). As a prevention strategy, it is suggested that people who live in other places than their place of origin, it is essential to keep the environment around them similar to the climate conditions of their place of origin. One of the health habits noted about this patient is that she did not try to make her environment cool enough to avoid some of the health conditions. A good internal air-conditioning system is essential to drive the heat absorbed by the body from the hot climate of the desert and the heat generated by metabolism, away from the body. The patient was known in the family for not keeping herself hydrated and she never liked the air-conditioning in the house, hence she later started to suffer serious health issues. It is worth mentioning that this patient also used to hide her health issues from her family, every time, until it was too late. It is therefore essential for people to let their family and friends know as soon as they notice any health issues, when the disease is easiest to treat. Other forms of prevention strategy would certainly be the genetic genealogy, so as to get vital

information about family roots and the site of origin, in order to keep similar environments around them and avoid a totally different climate.

7.3.4 Conclusions

Necrotizing external otitis is a severe infection of the external auditory canal, which is also known as malignant external otitis due to its aggressive clinical course as it does not remain limited to the external auditory canal as evidenced in this study. The disease affects elderly patients, immunocompromised patients, and patients suffering from diabetes and kidney disease. Malignant external otitis can exist at the same time with squamous cell carcinoma typically in elderly patients and they are usually associated with substantial morbidity and mortality. However, complete healing is possible for which an early diagnosis plays an important role. Strong painkillers are needed for relieving the severe pain caused by malignant external otitis in addition to prolonged antibiotic therapy. CT scan can expose the disease and help in the early diagnosis of the disease and before developing facial palsy, and MRI can reveal more anatomic details. Treatment of such cases is usually managed by a team of specialists including those treating diabetes, haematology, and oncology.

7.4 Pleuropulmonary blastoma (PPB) in a 3-year-old boy: A case study

Pleuropulmonary blastoma (PPB) is a very aggressive and rare type of cancer that occurs mainly in children; however, it may also affect adults. PPB originates from the lung or the pleural cavity, but its cause is still unknown. PPB has four different subtypes based on whether it involves cysts and/or cancerous nodules, as well as considering the age at diagnosis and prognosis. Medical imaging plays an important role in the diagnosis of PPB to quantify the extent of metastasis of the tumour, such as in type II and type III, and to titrate the treatment strategy accordingly. In this case study, the case of a deceased 3-year-old boy found in generation V of the pedigree (see **Fig. 35**), who was diagnosed with type II and III PPB, is presented, including an analysis on related medical images involving both ionising (chest X-ray and computed tomography) and non-ionising

techniques (ultrasound), as well as the treatments that the child underwent. The patient received surgical resection of the tumour, followed by chemotherapy; however, local tumour relapse occurred, a second resection was not possible, and the relapsed tumour did not respond to chemotherapy leading to the death of the child. The medical reports and the medical images discussed in this case study were obtained from the radiology departments of Madina Maternity Children Hospital in Madina, KSA and King Faisal Specialist Hospital and Research Centre in Jeddah, KSA.

7.4.1 Case study

Pleuropulmonary blastoma (PPB) has four different sub-types based on whether it involves cysts and/or cancerous nodules and considering the age at diagnosis and prognosis: cystic (type I), type I regressed (type Ir), cystic and solid (type II), and solid (type III) [269] [270]. PPB is mainly found in children younger than 7 or 8 years; it occurs rarely in older children, and more rarely in adults [271]. In general, type II and type III involve a larger metastatic cancer [272] [273], which has, therefore, grown more deeply into the nearby tissue. Patients with PPB are usually treated with complete surgical resection, followed by neoadjuvant chemotherapy [274] [275] [276] [277]. The health history of the 3-year-old child discussed in this case study confirmed that he was born healthy, and he was healthy up to the end of his first year of age. However, after that, the child had started to experience symptoms, such as shortness of breath, as well as occasional coughing. At the beginning of age 2, the child started experiencing repeated cold with symptoms every 3 to 4 weeks, for which he was receiving antibiotics and painkillers in addition to antihistamines. Nevertheless, these treatments were helpful only for short periods and the symptoms were re-appearing. The medical record revealed that the child used to be seen every time by the same medical doctor and it was noted that the child had not undergone any medical imaging tests. At the end of his second year of age, he was admitted to a general hospital, where he underwent his first chest X-ray, which showed the presence of a huge mass in the left side of his chest. The child was urgently assigned to be visited by a multidisciplinary team (MDT) of consultants. The

patient had to undergo a tracheostomy to allow air to enter his lungs, which was booked on the same day he was admitted to the hospital. It was a necessary medical procedure wherein an opening in the neck was made below the vocal cords for a tube to be placed into the child's windpipe. The following image **Fig. 57** shows the chest X-ray of the child undergoing tracheostomy in supine view having a huge mass occupying the left side of the chest.

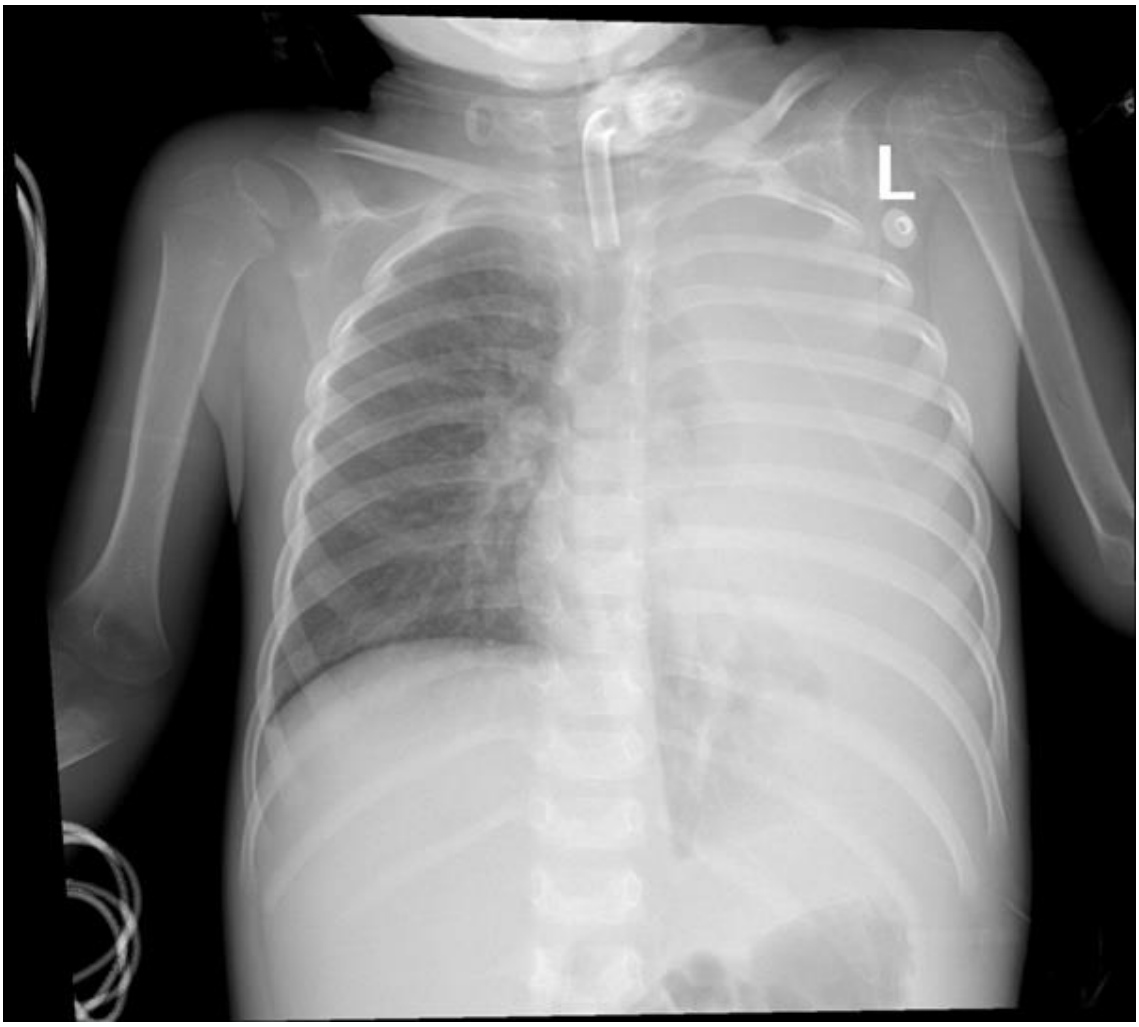

Figure 57 Chest X-ray of the 3-year-old child (supine view CXR) showing a huge mass on the left side of his chest.

7.4.2 Diagnostic tests

To confirm the presence of cancerous cells, a diagnostic biopsy test was initially carried out, which was followed by various imaging scans, involving both ionising

(computed tomography (CT)) and non-ionising radiation (ultrasound) to obtain detailed images of the lungs and his thoracic cavity. Based on such morphological imaging scans, the patient presented a huge mass of both cystic and solid areas and, therefore, his PPB was classified as type II (cystic) and III (solid). The following image **Fig. 58** shows the coronal (**A**), sagittal (**B**), and axial (**C**) views of the CT scan of the child's chest.

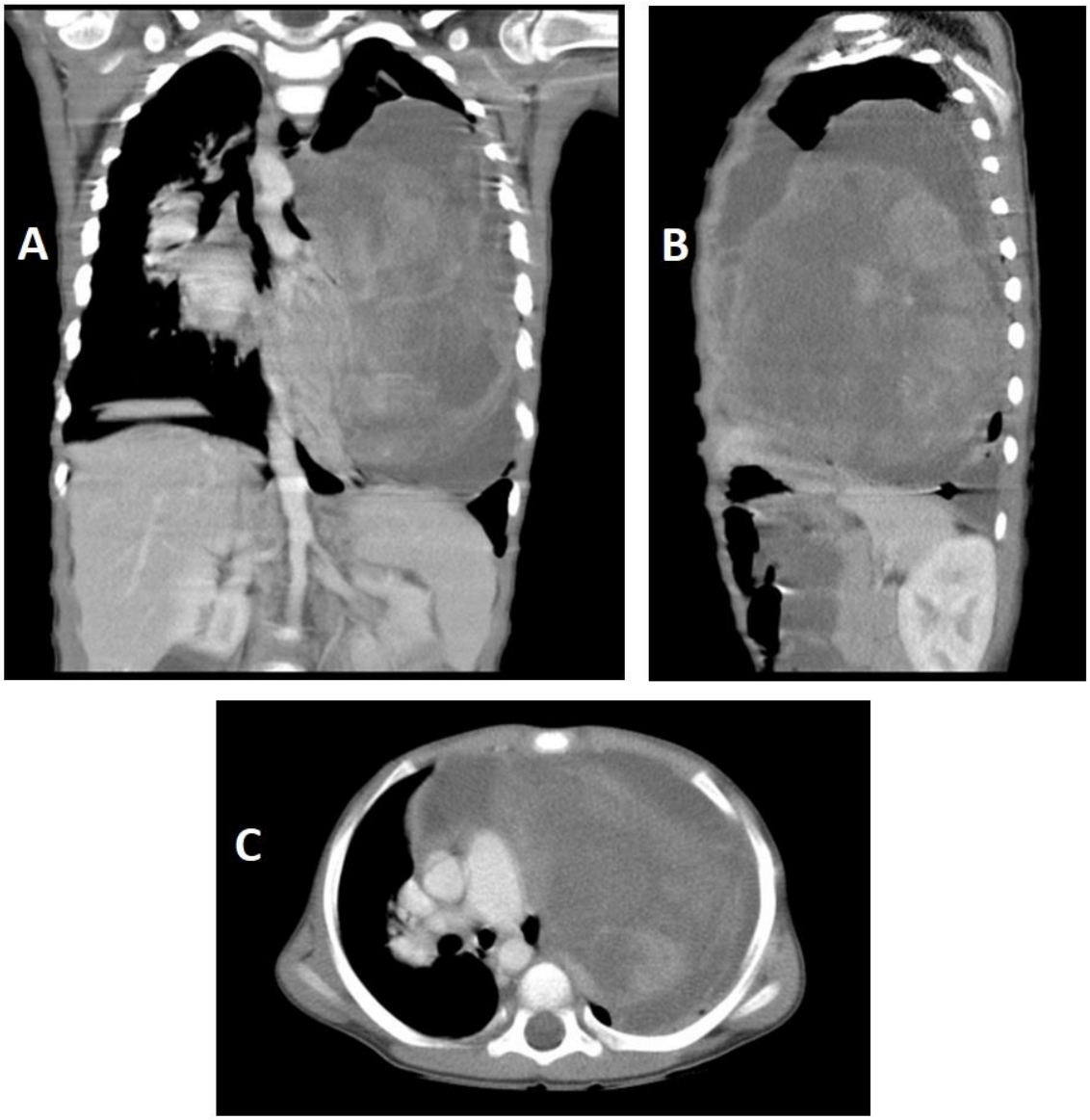

Figure 58 Chest CT scans with (**A**) coronal, (**B**) sagittal and (**C**) axial views confirming the presence of PPB of type II (cystic, see coronal view as an example) and III (solid, see sagittal and axial views) in the child. A large mass can be seen occupying almost the entire left hemithorax.

The following image **Fig. 59** is the axial view of the chest CT scan with contrast (hand injection) which shows a large mass occupying almost the entire left hemithorax. The intravenous (iv) contrast media is used in CT examinations for diagnostic accuracy improvements.

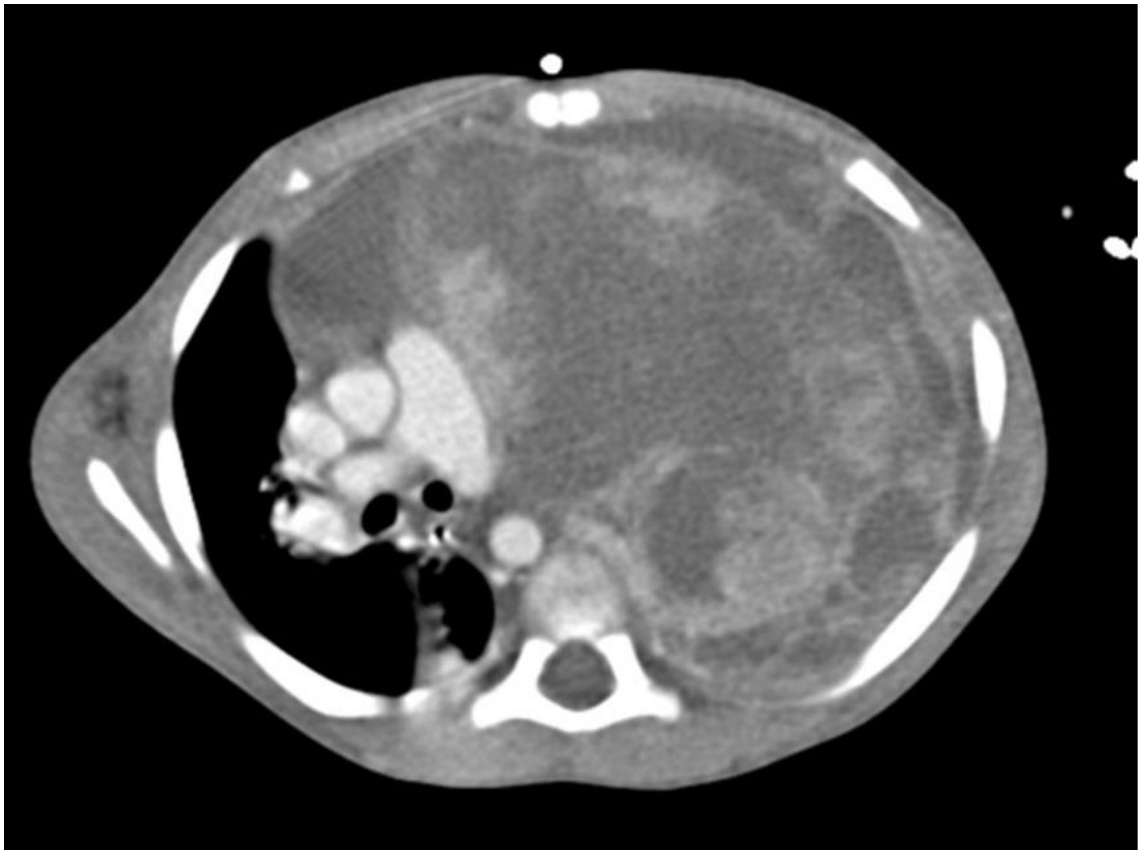

Figure 59 Axial view chest CT with contrast

7.4.3 Ultrasound imaging

Medical imaging techniques that are safe and painless are used to examine paediatric patients. Thus, in this case, both ultrasound (non-ionising technique) and X-rays were recommended. A chest ultrasound is used to assess the structures and organs within the chest, such as the lung's pleural space, i.e., the space between the lungs, the chest wall, and the mediastinum, i.e., the area of the chest that separates the lungs. Chest ultrasound allows real-time and mobile assessment of conditions involving the chest in addition to other advantages, such as lack of radiation (being non-ionising) and a short examination time. The

following image **Fig. 60** shows the chest ultrasound of the child, presenting a huge mediastinal mass in the area surrounded by the breastbone at the front, the spine at the back, and the lungs on each side.

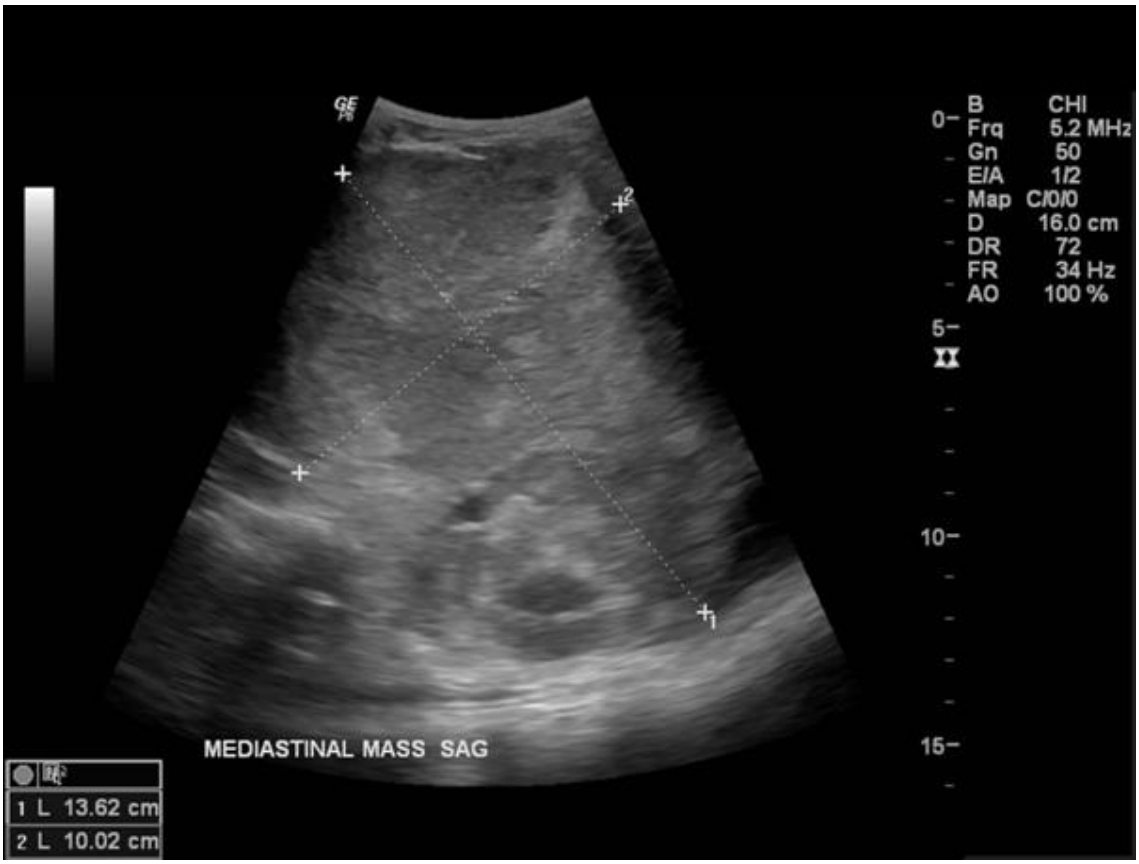

Figure 60 Chest ultrasound of the child presenting a huge mediastinal mass.

The mediastinum contains the heart and great vessels, thymus gland, trachea, oesophagus, nerves, and the anterior and posterior lymph nodes. In this case, chest ultrasound was performed easily and quickly showed a giant mass occupying his left hemithorax. The mass visualised on chest ultrasound correlated well with findings from the child's CT scan illustrated in **Fig. 58**.

7.4.4 Treatment Strategy

Following the biopsy and further to undergoing appropriate imaging diagnostic tests, the MDT decided to perform a surgical resection of the tumour, but the child

had to undergo chemotherapy initially to shrink the tumour prior to undergoing a complete surgical resection.

7.4.4.1 Chemotherapy

Chemotherapy was recommended prior to undergoing surgical resection to shrink the tumour; however, the child did not respond to chemotherapy and the tumour continued growing. Following chemotherapy, the child experienced severe complications and suffered more due to chemotherapy-related side effects leading to physical deterioration. Chemotherapy caused further negative impact on the child and his family, especially when the child started getting very weak, becoming unable to walk and started losing weight, hair, and appetite. The child also experienced a stroke after chemotherapy, which was due to the direct tumour compression of blood vessels, the toxicity of chemotherapy and the damage it causes to blood vessels [278] [279].

7.4.4.2 Surgery

Although the tumour was huge and it was in an area that was too difficult to be surgically removed, the cancerous mass was successfully resected, along with some of the surrounding healthy tissue to eradicate as many cancer cells as possible. The MDT was unable to anticipate if the cancer could recur further to the tumour resection. Nevertheless, the cancer was resurfaced after a few weeks post-resection. The MDT explained to the child's family that the cancer may have recurred because small areas of cancerous cells had remained in the surrounding area of the primary tumour following the surgery and as it was difficult to remove too much tissue around the tumour. In about three weeks, the cancer cells multiplied and grew further to form another tumour in the same area of the body as the primary tumour (local recurrence). The MDT planned to carry out another surgery to remove the new recurred tumour; nonetheless, the child died prior to the planned day of the second surgery.

7.4.5 Discussion and concluding remarks

This case study discussed the case of a deceased 3-year-old boy found in generation V of the pedigree (**Fig. 35**) in chapter 6 of this thesis. According to the new concept of cancer presented in this work and based on the health history of the patient and the human population origins and migrations, environmental factors and gene mutations, and the development of cancer, it is explained that the child was born healthy, and up to the end of the first year of the child's age, he remained healthy. However, understanding that the child in that year was staying in the bedroom sleeping 12-18 hours a day and sometimes in the living room with sufficient air-conditioning, i.e., the environment around the child was always kept cool during this period. The air-conditioning system was important for the child to survive the hot climate of the desert. However, when the child started to walk from the end of age 1 to the beginning of age 2, he started to get exposed to the hot weather environment as the air-conditioning system is only available inside the rooms, not outside, where the child was spending more time with his family and playing with other children and other outdoor activities. The child consequently stared to have difficulties with his respiratory system. As presented in chapter 6 of this work, the child had a clear common European look including light skin colour and it is therefore explained that he was in and environment i.e., the hot desert climate conditions that his body as it showed not to be belonging to. Specifically, the respiratory system of the child where the disease started, and in this regard, it is once again very important for people to consider the environment around them. The child later developed gene mutations that lead to his case of PPB. PPB is a rare, highly aggressive and malignant type of cancer. PPB originates from either the lung parenchyma or pleural surfaces. As with most childhood cancers, the cause for PPB is not known, and like many other cancers, PPB needs to be diagnosed early, since there is no metastasis in type I PPB and the recurrence rate of type I PPB is lower as compared to types II and III PPB. Therefore, when PPB is diagnosed at late stage, it may lead to death, due to the natural progression of PPB from type I to type II (cystic) or type III (solid). Importantly, death occurs only after type I PPB progression to type II or III [280]. Nevertheless, diagnosis of PPB needs the attention of MDT to perform

an accurate diagnosis via both ionising and non-ionising medical imaging techniques, besides a biopsy test. Medical imaging should be appropriate to the age of children, and it is safer if no ionising radiation is involved, especially if repetitive scanning is required. Nevertheless, whilst X-rays involves the use of ionising radiation, it uses fewer doses than other imaging techniques, such as CT. With CT scans, children receive higher effective radiation doses to their organs than those of adults, because children have a smaller body size, smaller cross-sectional area, and related attenuation [281]. Furthermore, CT requires patients to lie still on the scanning table, which is often difficult for children to achieve [282] [283]. X-ray, CT, and ultrasound imaging techniques were used for this child to assess the presence of cancer due to PPB. Further to the diagnosis, treating PPB of types II and III was mainly performed via chemotherapy and surgical resection. However, this child had to stop receiving chemotherapy because of the related complications and serious side effects. Chemotherapy was also stopped as the body was not responding to the treatment and the tumour did not stop growing. Chemotherapy may sometimes cause more harm than good to cancer patients, especially in patients near the end of their life [283] [215]. Eventually the child had to receive palliative care to improve his quality of life through a pharmacological treatment provided by the hospital to give him greater control over pain in addition to symptomatic relief.

7.5 Case study with analysis of paediatric optic nerve glioma and craniopharyngioma

This case study is for a child with benign (non-cancerous) tumours found in the family of kit number 9 investigated in chapter 6 of this work. No cancer cases were found in the family of this child and according to the new genetic concept of cancer this family was living in the geographic region of their human Y-Chromosome DNA haplogroup. The family therefore showed no patterns of cancer running among them as according to this research they were living in the right environment. However, one benign brain tumour case was found and to understand the case it was essential to be presented as a case study. Brain and spinal cord tumours are the second most common tumours that occur in children.

Brain tumours are mainly two types, benign brain tumours and malignant brain tumours. What exactly causes brain tumours in children is not known, however it is believed that there may be genetic and environmental causes. Brain tumours are either primary tumours which start in the brain or secondary tumours that spread into the brain from other parts of the body. While most optic nerve gliomas are benign and slow-growing brain tumours which grow in or around the optic nerve, craniopharyngiomas form near the base of the brain close to the pituitary gland and are non-cancerous tumours. The common signs and symptoms caused by brain tumours include seizures, headaches, weakness, and vision problems. Medical imaging tests such as magnetic resonance imaging (MRI) can give detailed pictures to investigate brain tumours. Paediatric brain tumours are usually misdiagnosed with the common headache and a delay in the diagnosis is known on and on. This case study presents the case of a deceased male child with optic nerve glioma and craniopharyngioma, including analysis of his medical history and medical imaging as well as the treatments that he had. However, the child died due to delay in the diagnosis and treatments were therefore too late to be effective.

7.5.1 Introduction

The most frequent tumours that affect children after leukaemia are the brain and central nervous system tumours [284] [285] and around 6% of all brain tumours occur in the paediatric population [286]. Brain tumours are mainly two types; benign (non-cancerous) brain tumours which are low grade tumours that grow slowly (grade 1 or 2 tumours), and malignant (cancerous) brain tumours which are high grade tumours (grade 3 or 4 tumours). The exact causes of paediatric brain cancers are not known, however various factors may increase the risk of developing brain tumours including environmental factors, in addition to family history. However, only 5% of brain tumours are believed to be linked to genetic conditions [287]. High grade brain tumours are likely to come back after treatments and are either primary tumours which start in the brain, or secondary tumours which spread into the brain from other parts of the body. The common signs and symptoms caused by brain tumours include severe headaches,

seizures, fatigue, nausea, vomiting, changes in sleep, vision problems, and changes in memory and behaviour. Brain tumours are frequently misdiagnosed with the common headache and therefore a late diagnosis of brain tumours is well known, and this delay means it is too late to save the life of the patient. In general, children with brain tumours get a combination of treatments such as surgery, radiotherapy, and chemotherapy, based on the types of tumours and other factors, and weather treatment options outweigh the risks of side effects and any other possible risks.

7.5.2 Medical history

The medical history of the child shows that he was born healthy without medical problems. However, the child was only 40 days old when suddenly started screaming and constantly. The child was taken to hospital and following numerous reasons from a number of doctors as to the reason for the continuous screaming. The child had urine tests and results showed that the child had sand in his urine, and it was decided that the child may have a urinary tract infection for which he received treatments and medications for pain in addition to medications that help the child stop screaming and help him sleep. However, weeks passed, and the child was still screaming continuously. Sometimes the child would cry himself to sleep in the arms of his parents and then wake a short time afterwards and start screaming again. Parents noticed when the child was screaming it was more like as if the child had pain in his head, it was noticed the child was constantly arching back and throwing his head back showing an uncomfortable feeling with his hand muscles tightened and contracted uncontrollably. The child also had full blood tests, but results showed nothing above or below the normal range.

7.5.3 Medical imaging

The child was first referred to get a computed tomography (CT) scan, as CT scan is a fast and painless imaging modality, and it can create detailed images of the body’s internal organs. However, the results showed no abnormalities. At the age

of 3 months the child had a nasogastric tube (NG tube), to carry food and medications through his nose to his stomach to feed him and also to help him get the medicines needed to relief any pain and help him to sleep. Later the child was noticed to start developing eye problems and therefore he was referred to get an MRI. MRI can give more detailed pictures than CT scan, however MRI is noisy, and it can be very scary for children, and it takes much more time than CT scan as well. MRI is more claustrophobic too and it requires children to keep still and therefore paediatric patients usually have MRI under general anaesthetic.

7.5.3.1 MRI

The child was referred to get an MRI, and the results showed that there is a tumour in the brain. The child's parents were informed that it would not be possible to treat the tumour and that no treatments would be given to the child. Moreover, the child was given 6-12 months to live. The following image **Fig. 61** illustrates the T1-weighted and T2-weighted sagittal brain MRI images of the child, showing a huge suprasellar mass.

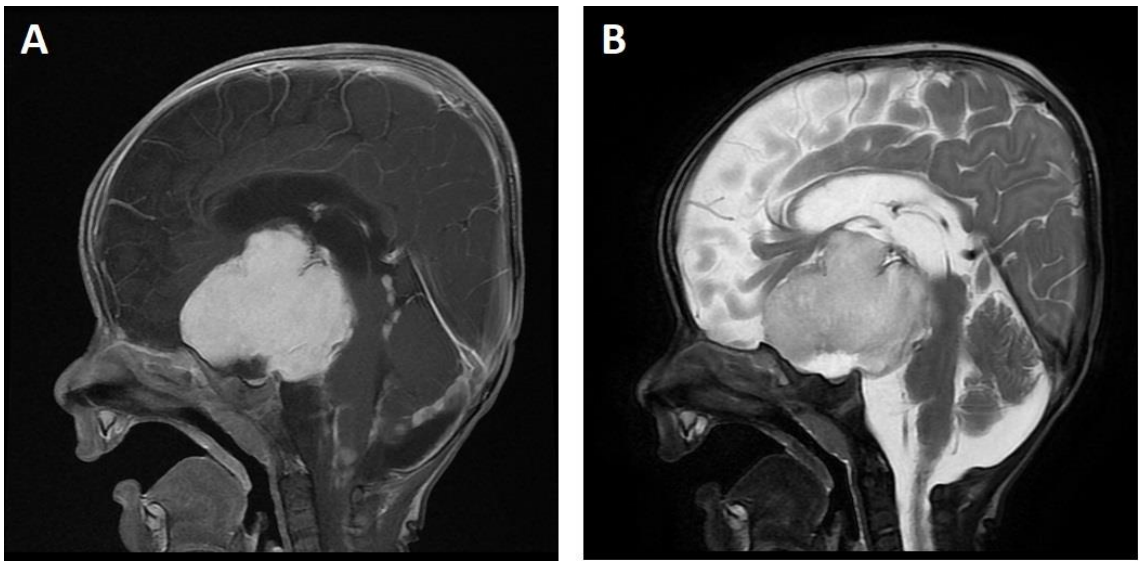

Figure 61 T1-weighted sagittal spin echo (SE) acquisition technique with contrast (+C) (**A**) and T2-weighted sagittal fast recovery fast spin-echo (FRFSE) (**B**) magnetic resonance imaging of the patient demonstrating a huge brain tumour, which could not be removed.

The MRI images demonstrated a large mass in the superior part of the suprasellar cistern, filling the optic chiasm hypothalamic region, creating significant pressure on the adjacent cerebral parenchyma and the brain stem. The following image **Fig. 62** Demonstrates the axial, sagittal, and coronal T2-weighted brain MRI of the patient.

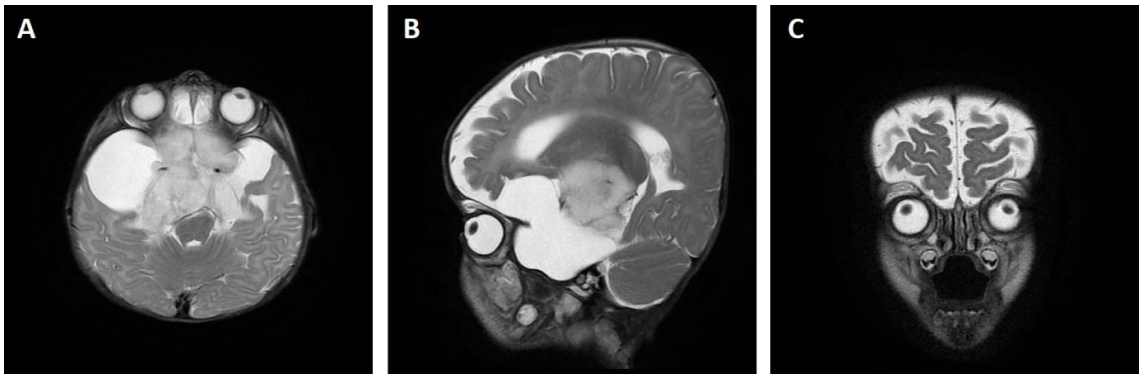

Figure 62 T2-weighted axial FSE (**A**), T2-weighted sagittal FRFSE (**B**) and T2-weighted coronal FRFSE (**C**) magnetic resonance images confirm the brain tumour. The images also show the upward deviation of the eyes.

7.5.4 Discussion

In this case study the case of a deceased child with optic nerve glioma and craniopharyngioma was discussed with analysis of the medical history and medical imaging. Optic nerve glioma is a benign and slow-growing brain tumour that usually grows in and around the optic nerve. Craniopharyngioma on the other hand is formed near the base of the brain and near the pituitary gland. Optic nerve glioma and craniopharyngioma cause seizures, headaches, weakness, and vision problems. Early diagnosis of brain tumours is very important, and treatments depend on the type, location, and size of the tumour, in addition to how far the tumour has spread and how abnormal the cancer cells are. Brain tumours are treated using surgery, radiotherapy, chemotherapy, steroids, in addition to other treatments needed to help the child with the symptoms. Medical imaging tests such as MRI can create detailed images. Other medical imaging techniques such as regular X-rays are not useful for paediatric brain tumours. The MRI images of this child showed a huge mass in the superior part of the

suprasellar cistern, filling the optic chiasm hypothalamic region, creating significant compression on both cerebral hemispheres, and extending below the tentorium and infiltrating the infundibulum. The child could not be treated due to the late diagnosis of the illness and therefore he eventually died. The exact causes of brain tumours in children are not known and according to the past studies it is believed that there might be genetic as well as environmental causes, with only 5% of brain tumours thought to be connected with genetic conditions [287]. However, according to the new genetic concept of cancer presented in this work and based on investigating five generations of the child's family to understand the case of the child and to find out if there any other similar cancer cases running in the family, it is explained that as no cancer cases ever occurred in the child's family, it is therefore more likely that the cause of the illness not to be related to any gene mutations running in the family. Furthermore, and according to the new genetic concept of cancer presented in this research and based on the genetic test results of a male member of the family (kit number 9) as presented in chapter 6 of this work, it is explained that the family of the child has lived in the site of origin of the human Y-Chromosome DNA haplogroup that they belong to and therefore the environmental causes are also less likely as the child's case was found to be a rare benign tumour case, and the only case found in his family. Importantly, the child died due to delay in the diagnosis of his brain tumour case and treatments were therefore too late to be given to child. Therefore, if the case of the child was diagnosed early, the child would have a better chance to survive with the availability of treatments as his case was benign (non-cancerous) brain tumours which are possible to be removed successfully through surgery and without coming back again [288]. However, researchers have presented that only 33% of brain tumours are diagnosed within one month of appearing the signs and symptoms [289]. The overall survival rate of children with brain tumours is linked to improvements in the diagnosis for the early diagnosis and also to improvements in treatments of paediatric brain tumours. However, visual impairment and the forward displacement of the eyes are common among children and survivors of brain tumours [290].

7.6 Dedifferentiated chondrosarcoma of the right chest wall: Case study of a deceased middle-aged male subject

Chondrosarcoma (CS) is a type of bone cancer that arises from the malignant transformation of chondrocytes and spreads metastatically to the surrounding bone tissue. CSs tend to grow and spread slowly, dedifferentiating into high-grade tumours; however, the cancer may grow rapidly too. What causes chondrosarcoma is not known, though it may arise from a benign tumour or bone conditions. Typically, CS tumours originate from the bones of the axial skeleton, but they may also occur in other parts of the body. CS patients usually experience aching pain around the tumour, especially at night or during physical activity, and it slowly deteriorates. Medical imaging tests play an important role in the diagnosis of CS; nevertheless, a tissue biopsy is required to confirm its diagnosis. The role of medical imaging is also vital in guiding and monitoring treatments. Surgical resection of the tumour is commonly the primary treatment for most types of CS due to its resistance to chemotherapy and radiation therapy. In this case study, the case of a deceased middle-aged male subject with dedifferentiated CS of the right chest wall is discussed, including analysis of medical images involving both ionising (computed tomography) and non-ionising techniques (ultrasound and magnetic resonance imaging), in addition to treatments the subject received, along with their outcomes. This CS case was found in the family of kit number 13 presented in the previous chapter, chapter 6 of this research. Five generations of the subject's family were investigated in detail and the subject was found to be the only cancer case in his family. Furthermore, the subject did not benefit from any treatments he underwent, and he died within two years from the diagnosis.

7.6.1 Introduction

Chondrosarcoma (CS) is the third most common type of primary bone cancer, and its onset lies in chondrocytes [291] [292]. Chondrocytes are the only cells found in healthy cartilage and they secrete the extracellular matrix to maintain the cartilage [293] [294]. Despite the aetiology of CS being unknown, the tumour may

grow out of bone conditions and benign tumours, or due to radiotherapy (RT) [295]. RT has been widely used to treat certain benign bone tumours and other bone diseases; however, RT may cause CS [291]. CSs account for about 20% of all primary malignant bone tumours, mainly affecting adults between the age of 40 and 75 years, with a slight male predominance [292]. Diagnostic procedures for CS include medical imaging and biopsy tests. Based on their histopathology, CSs are divided into three histologic grades: grade I (low), grade II (medium), and grade III (high) [296]. Furthermore, dedifferentiated CSs are considered as grade IV [293]. Typically, dedifferentiated CS occurs in middle-aged or older subjects. Dedifferentiated CSs are rare, but extremely aggressive tumours, which make up about 11% of all CSs [294]. CSs of the chest wall tend to grow slowly and they recur locally [297]. Common treatments involve a wide surgical resection of the tumour; however, local recurrence may occur post-operatively. Chemotherapy is often ineffective, and RT is used mainly as a palliative tool. The five-year survival rates among adult subjects with CS are at 90% for grade I tumours, 81% for grade II tumours, and 29% for grade III tumours [298] [296]. However, the five-year survival rate for dedifferentiated CS is between 7% to 24% [298].

7.6.2 Medical history

The case of a 54-year-old deceased male subject with CS is presented and discussed in this study. The subject was first admitted to the hospital because of chest and back pain, in addition to swelling around the area where back pain was perceived. Diagnostic tests were carried out and included both ionising (computed tomography (CT)) and non-ionising medical imaging techniques (ultrasound and magnetic resonance imaging (MRI)), besides open biopsy. Based on the findings from these tests, the subject was diagnosed with CS of paravertebral localisation and intra-thoracic and extra-thoracic regions. The subject received a combination of treatments involving surgical resection, chemotherapy, and RT; nevertheless, the subject did not survive for more than two years post-diagnosis.

7.6.3 Diagnosis

In general, CSs do not make people feel weak or ill; however, most subjects with CS will eventually experience swelling and/or pain due to various activities [299]. Pain and swelling may imply active growth of a tumour when other bone problems are excluded. Therefore, CSs are usually huge masses at the time of diagnosis [293]. Medical imaging has a major role to play in the diagnosis and treatment planning of CS. Each imaging modality plays an independent role in the diagnosis, assessment of local complications, as well as preoperative evaluation and preparation. Ultrasound can assist in determining the texture of the mass and the commonly associated calcifications, i.e., accumulation of calcium salts; however, the site of the origin of CS is often not determined using ultrasound due to its reduced contrast and resolution [300] [301]. The following image **Fig. 63** is the ultrasound image of the chest of the subject, presenting a well-defined large mass with a cystic component and calcifications.

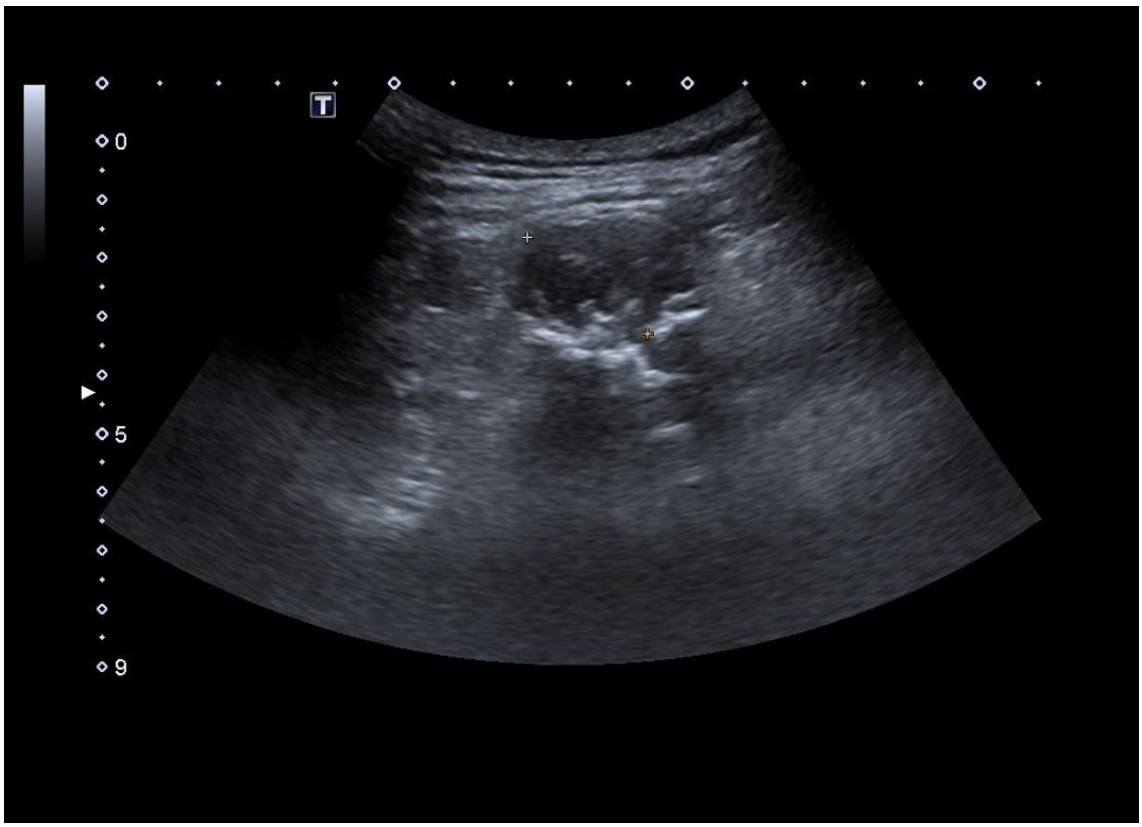

Figure 63 Right thorax ultrasound of the subject presenting a large mass.

Despite the use of ionising radiation, CT is leveraged to obtain high-contrast and high-resolution images and to provide further information about the morphology of the tumour to perform a more accurate diagnosis [302]. CT can show the extent of metastasis of a tumour, in addition to its origin [301]. The bony destruction caused by CS, as well as the associated small calcifications, can also be observed via CT. CT is helpful to assess any related structural cues, such as pathological fractures associated with CS, and it can provide a confident pre-operative diagnosis. The following image **Fig. 64** illustrates the three views of a CT scan of the chest of the same subject in **Fig. 63**, with IV contrast (C+) demonstrating a large tumour in the right hemi-thorax around the lower thoracic spine.

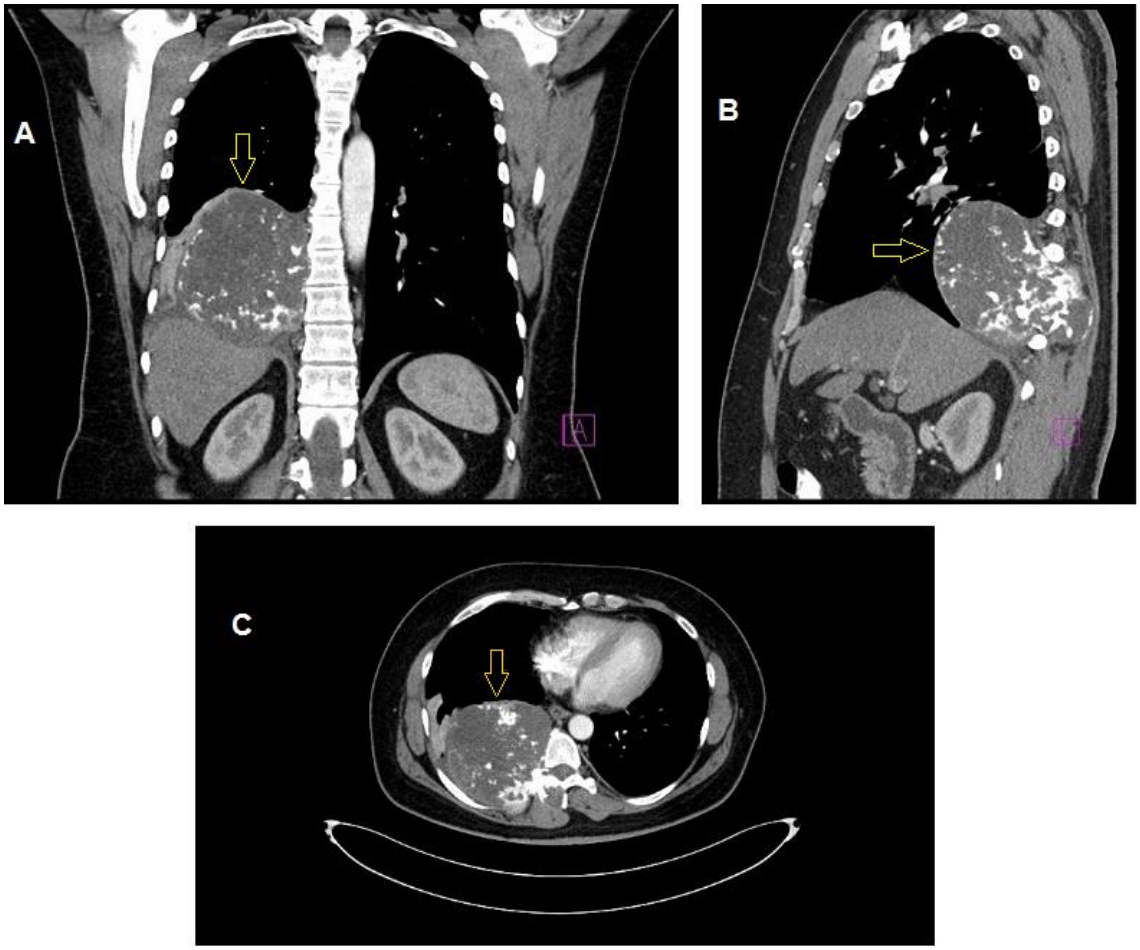

Figure 64 Coronal (**A**), sagittal (**B**), and axial (**C**) views of the chest imaged via CT with IV contrast (C+) arterial phase, identifying a huge tumour (see the arrows), localisation paravertebral with intra-thoracic and extra-thoracic regions.

Open biopsy of the known cancer was performed, and the histological examination of its tissue confirmed the tumour of chondroid origin. CT is a useful imaging modality in a subject who cannot take MRI due to, for example, having a pacemaker or claustrophobia. CT with IV contrast (C+) is the gold standard structural imaging modality for the diagnosis and treatment planning of CS [303]. However, MRI can produce clearer images when compared to CT for further functional assessments [304], such as in evaluating the involvement of soft tissue. The following image **Fig. 65** is the T2-weighted MRI of the thoracic spine of the same subject in **Fig. 63** and **Fig. 64**, showing a large tumour (marked by arrows).

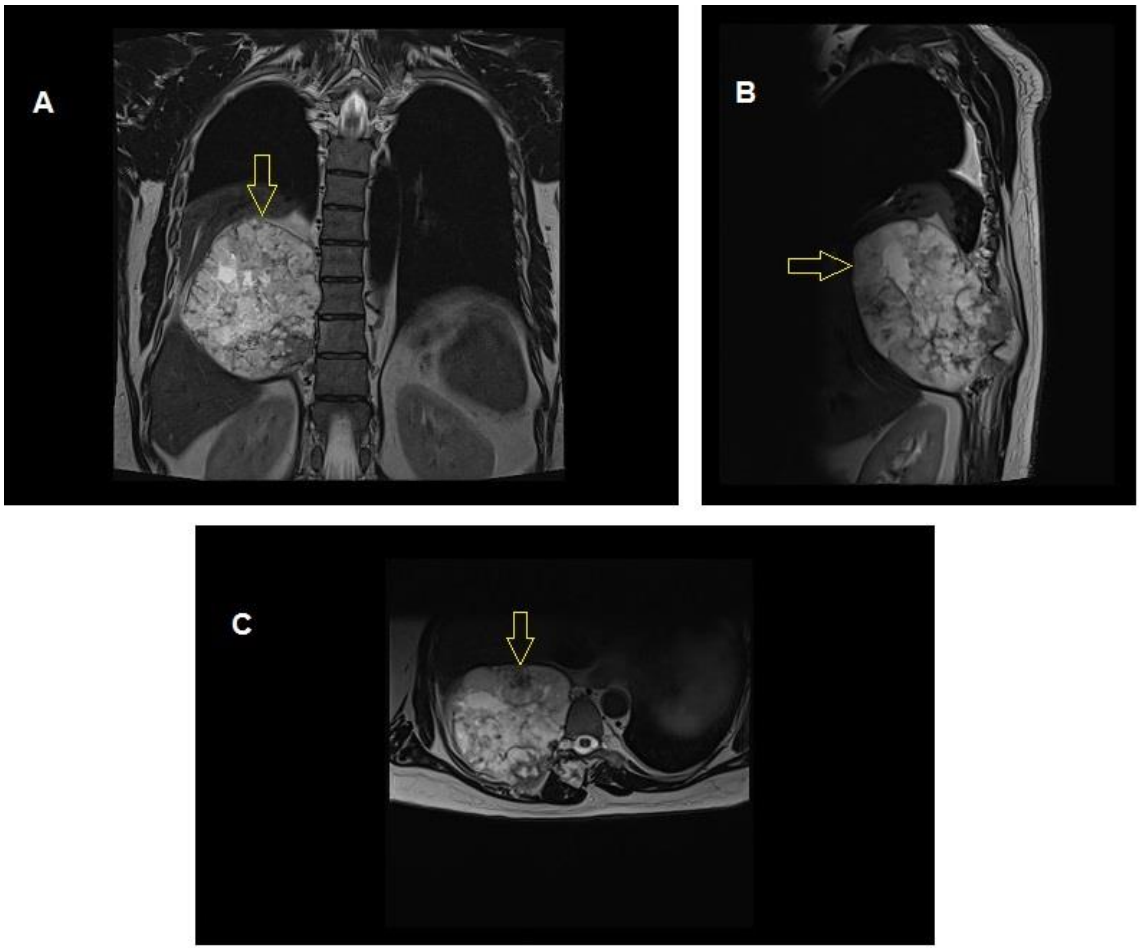

Figure 65 Coronal (**A**), sagittal (**B**), and transverse (**C**) T2-weighted MRI TSPINE demonstrating a huge tumour of chondroid origin (see the arrows) intra-thoracic and extra-thoracic and paravertebral at the lower thoracic spine, also highlighting how the neighbouring soft tissue was also affected.

7.6.4 Treatment options

Typically, CS subjects undergo a combination of surgery and adjuvant therapy, such as chemotherapy and RT. A wide margin of healthy tissue is typically removed with the complete surgical resection of the tumour. However, most CSs do not respond to chemotherapy or RT. These therapies have been ineffective, except for palliative purposes.

7.6.4.1 Surgery

Following the open biopsy and the diagnosis after one month, the subject received surgical treatment. Tumour resection was performed by thoracotomy on the right side of the chest. Moreover, a partial resection of the chest wall and ribs 9–11 was performed, as well as mediastinal pleurectomy (part of the pleura was removed to help in preventing fluid from collecting in the affected area), and the removal of the autochthonous back muscles. The aim of the resection margin around the removed tumour was to prevent the extension of the malignant growth. The resection margin for the subject was classified RX-resection (RX means the presence of residual tumour (R) cannot be assessed).

7.6.4.2 Radiotherapy

Further to the RX-resection after four months, the subject received RT. The target volume was the right paravertebral region using the technique of carbon ion therapy (C12) with active raster scanning, in addition to orthogonal X-rays for image guidance. RT is curative when undergone following incomplete resection for maximal local control; however, RT is palliative when resection is not possible. The subject received surgical intervention for the second time after about one month from the first date of undergoing RT, including right re-thoracotomy, partial resection of chest wall, back muscles and *processus spinosus* T7/T8, as well as mediastinal and paracardial tumour resection. Tumour recurrence paracardial and paravertebral occurred after about six months from the date of the second

surgery. Nevertheless, another resection was not possible; alternatively, the subject was evaluated for re-RT or chemotherapy.

7.6.4.3 Chemotherapy

Chemotherapy was recommended according to the EUROpean Bone Over 40 Sarcoma Study (EURO-B.O.S.S.) protocol [305]; however, following the first cycle of cisplatin (CIS) / doxorubicin (DOX), the subject experienced acute kidney failure (AKF) as a complication. CIS is a class of platinum-based anti-cancer chemotherapy drugs, and it works by forming platinum complexes when binding to DNA, causing cross-linking of the DNA strands leading to apoptosis. Instead, DOX is a class of anti-cancer chemotherapy drug known as ‘anthracycline’ and it acts by blocking the enzyme required by cancer cells to divide and grow known as type II topoisomerase, causing slowing, or stopping the growth of cancer cells. To avoid re-exposition of CIS, the subject received ifosfamide (IFO) / DOX according to EURO-B.O.S.S.; nonetheless, the subject experienced the same complication of AKF, in addition to exsiccosis, i.e., bodily dehydration due to insufficient intake of fluids. IFO is a class of anti-cancer chemotherapy drugs called ‘alkylating’ agents and it reduces or prevents the growth of cancer cells.

7.6.5 Progressive disease

In comparison to the time when the disease was first diagnosed, imaging tests confirmed progressive disease with growth of recurring CS of the back, in addition to constant lymph-nodal and progressed pulmonal and pleural metastases. The subject started to receive Carboplatin and Etoposide (Carbo / Etop) chemotherapy (salvage chemotherapy) according to the protocol of the Cooperative Osteosarcoma Study Group 96 (COSS-96) [306]. The term salvage chemotherapy refers to chemotherapy administered if none of the treatment strategies were effective. After the subject received the first cycle of salvage chemotherapy, he experienced complications of fever during neutropenia. Neutopenic fever is a chemotherapy side effect, and it involves a temperature of or greater than 100.4°F (38.0°C). Following the second cycle of salvage

chemotherapy, the subject experienced complications of fever during neutropenia, in addition to detection of *streptococcus sanguinis* in blood culture. The subject received the third and the fourth cycle of salvage chemotherapy. However, imaging tests confirmed constant sizes of the recurring CS in the autochthonous back muscles, as well as paracardial lymphnodal metastasis. The subject received the fifth cycle and the sixth cycle salvage chemotherapy Carboplatin and Etoposide (Carbo / Etop) with dose reduction to 66%. Imaging tests confirmed stable oncological findings with no evidence of significant cancer change within the diagnosed tumour relapse of the back.

7.6.6 Summary

This case study discussed the CS case found in the family of kit number 13 presented in chapter 6 of this thesis in detail. The family are native inhabitants of the southern part of Western Asia which was confirmed through DNA testing. Five generations of the family were investigated, and it was found that there were no censers running among them. The causes of chondrosarcoma are not known; however, it may arise from a benign tumour or a bone condition or radiotherapy. According to the new genetic concept of cancer presented in this research, it is explained that as the family of this CS case has always lived in the geographic region of their human Y-Chromosome DNA haplogroup safely and without developing gene mutations causing cancer and other difficult health conditions. Therefore, the case of this affected family member is not linked to genetic or environmental factors but to a known risk factor of bone conditions that the subject had before they get developed to such a rare malignant cancer case. The subject was later diagnosed with a CS paravertebral with intra-thoracic and extra-thoracic parts. Following resection and RT with carbon ions, there was a progressive disease with an extended tumour mass 9 cm x 3.5 cm with infiltration of the right vertebral body, right ventricular myocardial after nearly two years from the first time of diagnosis, which could not be respected. Chemotherapy was recommended according to the EURO-B.O.S.S. protocol. However, after each cycle, the subject developed AKF and he presented a progressive tumour via imaging tests; thus, it was not possible to continue with the chemotherapy.

Further to the required evaluation, the subject was recommended an adjustment to the COSS-96 protocol with Carboplatin and Etoposide. The therapy was tolerated well with supportive medication and further antiemesis, except for fever in neutropenia and therapy-induced anaemia/thrombocytopenia subject to transfusion. Staging analysis after the sixth cycle showed a stable disease. However, further surgery was not possible due to reaching a stable condition.

7.6.7 Conclusion

The case of a 54-year-old deceased male subject diagnosed with recurrent progressive CS was presented and discussed in this report. The subject first underwent surgical resection and received post-operative RT to the paravertebral region. The subject also received multiple lines of salvage chemotherapy. The subject was not found suitable for surgical intervention due to extensive tumour with multiple metastatic lesions. RT was carried out as a palliative treatment and had no therapeutic benefits; the subject also showed toxicity. The subject was not suitable for any further systemic anti-cancer treatments due to poor clinical status. The subject underwent palliative care to minimise the symptoms, improve quality of life and for symptomatic management (pain, vomiting, shortness of breath and other side effects) until he died.

7.7 Case study of a 50-year-old woman with high grade (G3) triple-negative metaplastic breast cancer

Metaplastic breast cancer (MpBC) is an extremely rare and aggressive subtype of breast cancer that has a poorer clinical outcome in comparison to other breast malignancies. MpBC is typically a triple-negative breast cancer (TNBC) however MpBC is known to have a worse prognosis and lower survival when compared to the common forms of TNBC. MpBCs are usually present high grade and larger in size when they are initially diagnosed, and it is still not understood what exactly causes MpBC. Surgery is typically used for MpBC treatment, along with radiation therapy and chemotherapy. However, MpBCs are more likely to come back after treatment and spread outside the breast to other parts of the body. In this case

study, the case of a 50-year-old woman with high grade triple-negative metaplastic breast cancer is presented. This case was found in the family of kit number 10 discussed in chapter 6 of this research. This very rare high grade metaplastic breast carcinoma case was the only cancer case found among five generations of the patient's family investigated in this research. This case study also includes analysis of a number of medical images of the patient obtained through ultrasound imaging, computed tomography (CT) scan, and mammography, in addition to the treatments that the patient has had up to the date of authoring this article including surgery and chemotherapy.

7.7.1 Introduction

Metaplastic breast cancer (MpBC) is very rare, comprising 1% or less of all the cases of breast cancer [307]. However, MpBC is an extremely aggressive subtype of breast cancer, and it is known to be difficult to treat. MpBCs are typically triple-negative breast cancers which mean that they are oestrogen-receptor-negative (ER-negative), progesterone-receptor-negative (PR-negative), and HER2-negative. However, when MpBC is compared to the common TNBC types, MpBCs tend to have a poorer prognosis and less disease-free survival [308] [309]. What exactly causes MpBC is still not understood, and MpBCs are typically present as high-grade tumours, at a higher tumour stage, and the original tumour is often found larger in size than in other types of breast cancer when they are initially diagnosed due to their rapid growth [310]. Grade is how abnormal the cancer cells look under the microscope and stage is how big the primary cancer is and whether it has spread to other body parts and organs. MpBC is often spread to other parts of the body via the bloodstream and therefore MpBC is less often found in the lymph nodes [311]. The lungs in addition to the bone and the brain are the most common sites of distant metastasis of MpBC [312]. An appropriate combination of surgery, radiation therapy and chemotherapy may be used for MpBC treatment. However, some MpBC patients who are initially eligible for surgery may become ineligible due to the progression of the illness before treatment. MpBC patients especially those with triple-negative have had a worse response rate to chemotherapy and radiotherapy, and the illness is more likely to

come back after treatment and spread outside the breast to the other parts of the body [310] [313]. However, MpBC patients without triple-negative may have survival benefit from chemotherapy and radiation therapy [314].

7.7.2 Medical history

This paper, discusses the case of a 50-year-old woman with high grade (G3) triple-negative metaplastic breast cancer, including medical history, medical imaging, treatments, and the outcomes of the treatments. The medical history of patient was studied in detail to investigate the causes of her MpBC. The information regarding the patient's medical conditions prior to her MpBC diagnosis included the history of 9 years of acute rheumatic fever. The symptoms of the patient's rheumatic fever included fevers, weakness, and painful joints especially her elbow joints, wrist joints, the knees and ankles. At times, the patient had to be carried and turned over due to being unable to even move or stand. The patient had lengthy hospital stays each time, and received treatments to control inflammation as well as the symptoms, including antibiotics and painkillers. To be noted is that the patient was on long term Penicillin injections. Monthly Penicillin injections are advised in rheumatic fever [315] [316], however it has been reported that using Penicillin and antibiotics may increase the risk of cancer [317] [318] and that using antibiotics is linked to increased risk of breast cancer [319]. Important to mention, studies have also indicated links between rheumatic diseases and cancer and that there is a risk of getting cancer among patients with rheumatic diseases [320] [321].

7.7.3 The patient's family history of cancer

Familial risks of cancer are measured by looking at the medical history of the patient's family members and relatives and investigate if there are cancer occurrences among them. Families usually share similar environments and lifestyle behaviours, in addition to the fact that families have similar genetic backgrounds. Majority of cancer cases (up to 90%) are caused by acquired gene mutations that are caused by environmental factors and lifestyle behaviours (non-

inherited). About 3% to 10% of all cancers are caused by inherited gene mutations which are passed down in families from generation to generation [322]. Cancers caused by non-inherited gene mutations may also appear to run in families when a common environment is shared by them or similar lifestyles. Women from families that have a history of breast cancer and other related types of cancer are at a higher risk of getting the illness. Predictive genetic testing is used to identify if an individual has inherited one of the known cancer risk genes. There are more than 100 cancer risk genes that have been identified linked with an increased risk of breast cancer and other types of cancer [27]. Mutations in BRCA1 and BRCA2 genes are associated with the common inherited breast cancer cases. Typically, it is considered a strong family history if there are two family members who are close relatives of the same family side a patient and that they were diagnosed with the disease before they reach the age of 50 years. According to the new genetic concept of cancer presented in this thesis, it is explained that due to the fact that the family of this rare breast cancer case has always lived in the place of origin of their human Y-Chromosome DNA haplogroup safely and without unrelated health conditions. Additionally, and based on findings of the investigations carried out in this study to investigate five generations of the patient's family to find out if other cancer cases found in her family. It was found that no family members of the patient ever had cancer, and that the patient is the only member of her family that has ever been affected with breast cancer. These results are vital to understand that the patient is not from a family that has cancer running among them and therefore it is less likely that her breast cancer case was caused by inherited gene mutations or gene mutations caused by environmental factors or lifestyles. Therefore, it is suggested that the causes of her rare type of breast cancer are linked to the rheumatic fever and the penicillin treatment that the patient had.

7.7.4 Diagnostic tests

The patient was first admitted to the hospital because of pain and swelling in the right breast, where she had a physical breast examination, and an abnormality was noticed in the upper inner quadrant of the right breast. The patient was then

referred to the radiology department for breast imaging. The patient had ultrasound imaging, and a 0.9 cm breast mass was found at 2 o'clock in the upper inner quadrant of the right breast. The following image **Fig. 66** is the ultrasound image of the patient demonstrating the mass.

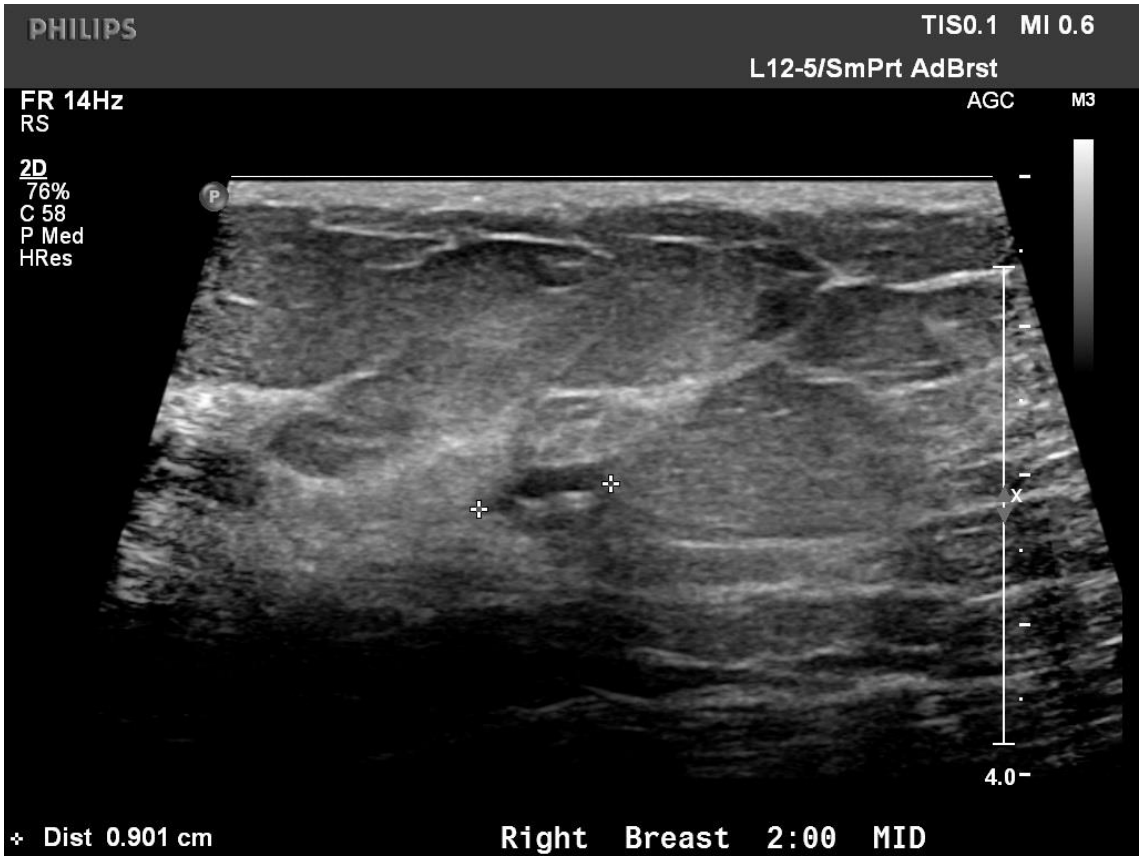

Figure 66 Ultrasound image of the patient showing a 0.9 cm hypoechoic mass seen at 2:00 in the right breast.

Following ultrasound imaging, the patient was referred for computed tomography (CT) scan to obtain detailed images. CT scans are often used to clarify the location of a tumour and to find out if cancer has spread to other parts of the body. The following image **Fig. 67** is the CT scan of the chest (axial lung window) of the patient showing a mass in the right breast (see the arrow).

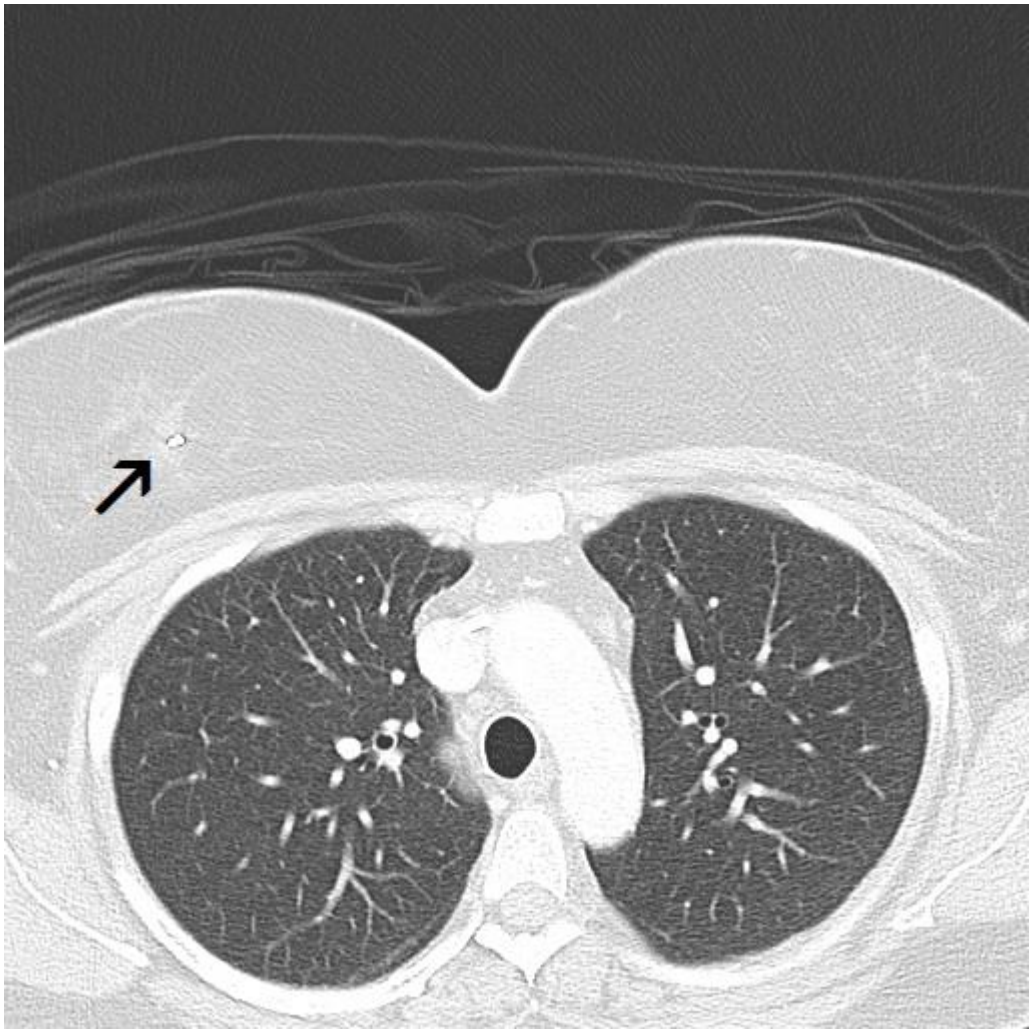

Figure 67 CT image (axial lung window) of the chest of the patient demonstrating a mass in the right breast (arrow).

The following image **Fig. 68** is the CT scan of the chest of the patient in coronal (**A**), sagittal (**B**), and axial (**C**) views with IV contrast (C+) demonstrating a mass in the right breast.

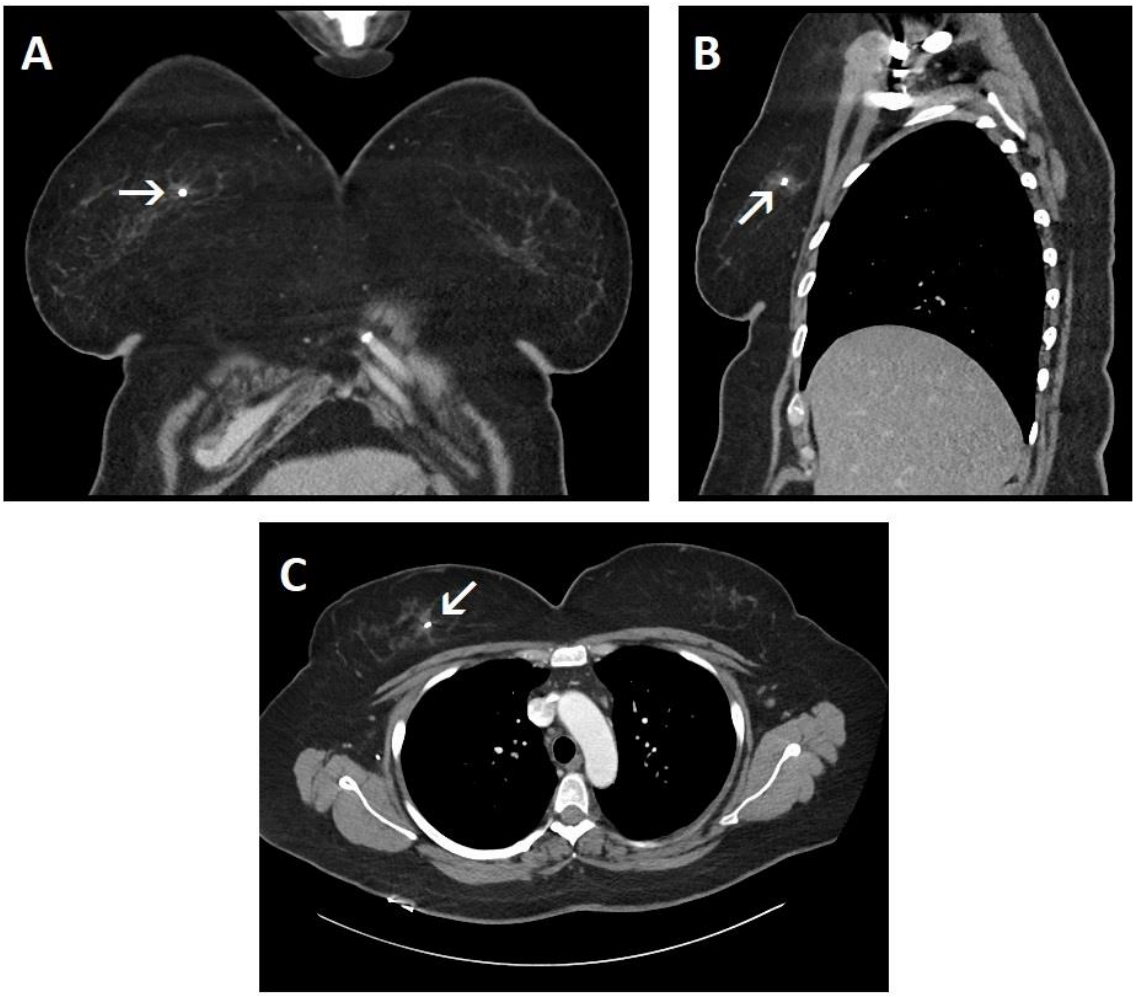

Figure 68 Coronal (**A**), sagittal (**B**), and axial (**C**) views of the chest CT with IV contrast (C+) of the patient, identifying a mass in the right breast (see the arrows).

Following the medical imaging tests, the patient was referred for a breast biopsy to take a small sample of the breast mass and examine it under the microscope. The mass was biopsied under the guidance of ultrasound imaging. A small metallic clip was placed inside the breast in order to mark the biopsy site. The following image **Fig. 69** is the mammography of the affected right breast of the patient showing the small metallic clip (see the arrows).

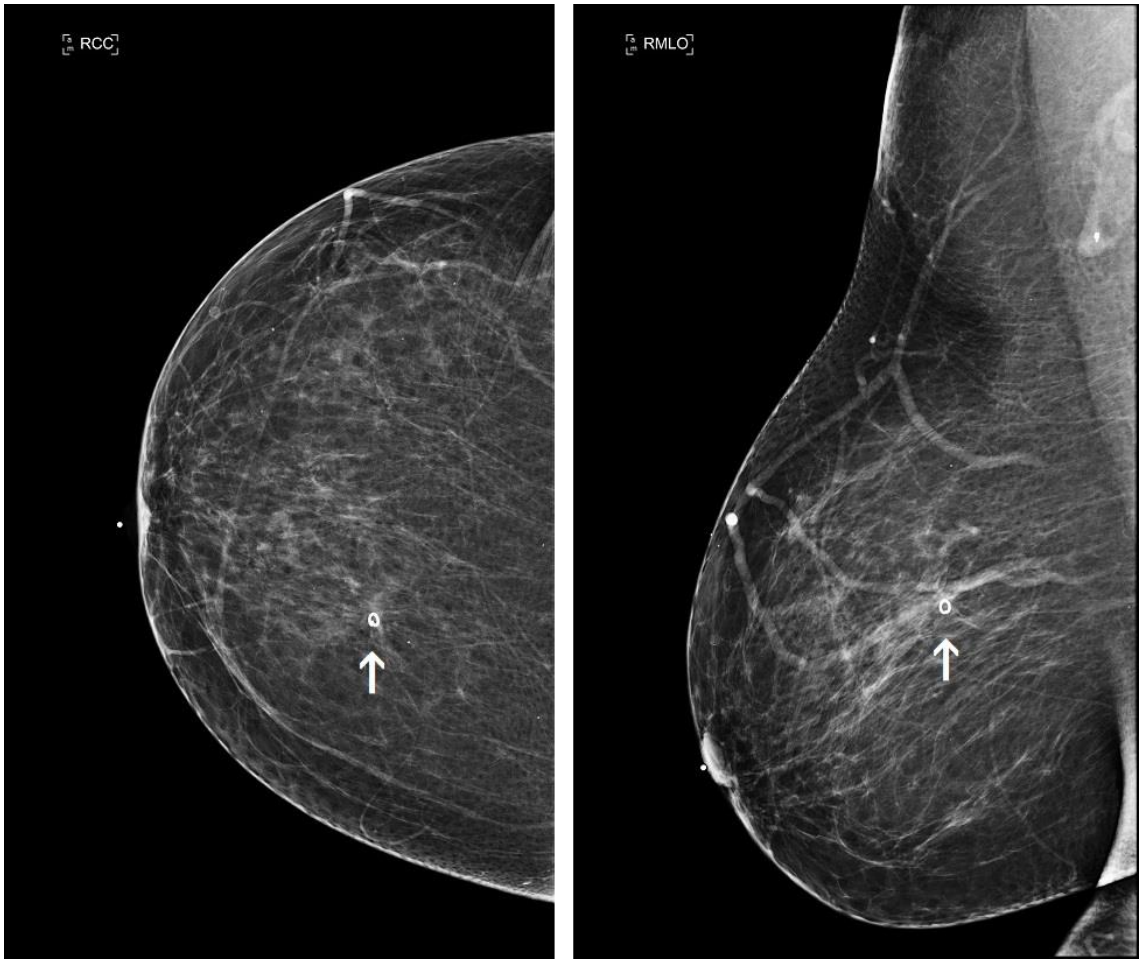

Figure 69 Mammograms in the right craniocaudal (RCC) and the right mediolateral oblique (RMLO) views of the patient showing a small metallic clip (see the arrows).

Breast metal clips (titanium clips) are not harmful to the body and typically they are removed at the time of breast surgery. However, it is important to discuss implanting titanium markers with patients beforehand, as titanium can cause allergic reactions and complications [323] [324]. The patient received her biopsy results, and the final diagnosis was breast cancer metaplastic carcinoma grade 3 (G3) triple negative. G3 means that the cancer cells look very abnormal when compared to normal cells and grow more aggressively (high grade cancer).

7.7.5 Treatment

The treatments that the patient has had up to the date of authoring this article include surgery and chemotherapy. Following the diagnosis, the patient started to receive neoadjuvant chemotherapy (NAC) regimen for her MpBC, Dose-dense Doxorubicin (Adriamycin) – Dose-dense Cyclophosphamide (Cytoxan) (DDAC) for 4 cycles in addition to DD Paclitaxel (Taxol). Dose-dense (DD) means treatment is given every 2 weeks. One cycle is a 2-week period. Taxol is an effective chemotherapy, and it is commonly used for breast cancer and other types of cancer including ovarian cancer. Taxol is a mitotic inhibitor, and it works by targeting the cancer cells which grow rapidly by mitosis (cell division) and stops them from dividing [325]. Following the NAC, the patient had breast conserving surgery (BCS) in addition to sentinel lymph node biopsy (SLNB). The tumour was surgically removed along with a clear margin or normal tissue around the tumour. SLNB was also carried out as a day case procedure to identify if the first lymph node or nodes are containing cancer cells. The following image **Fig. 70** is the specimen mammograms of the affected right breast of the patient. Mammography was used for intraoperative margin detection for breast conserving surgery.

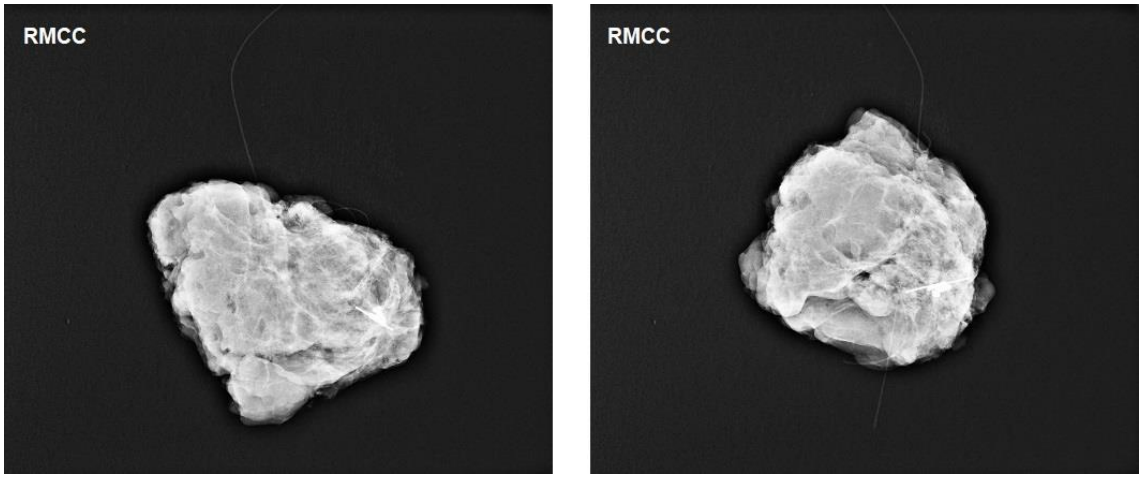

Figure 70 Specimen mammograms in the right craniocaudal (RCC) views of the right breast of the patient. The mass was visualised using mammography for intraoperative margin detection for BCS.

Following the surgery, pathology information from the breast tissue that was removed during the surgery was used for staging the patient's breast cancer after her neoadjuvant chemotherapy. The tumour node metastasis (TNM) classification in the patient's pathology report was recorded as ypT1a pN(sn)0. The y prefix is used for staging following NAC. The patient's y-pathological stage ypT1a means tumour size is more than 0.1 cm but not larger than 0.5 cm. The pathological staging for the patient's regional lymph nodes pN(sn)0 means no cancer cells are found in any nearby nodes. (sn) is confirmed by sentinel node biopsy [326]. The patient was put on adjuvant chemotherapy (adj) to start on adj Capecitabine for 6 months. Important to mention is that breast cancer patients with residual focus of metaplastic carcinoma on pathological testing following NAC, are at a higher risk of cancer relapse. Capecitabine is a chemotherapy drug used for breast cancer and other types of cancer. Capecitabine (Xeloda) is a type of chemotherapy that belongs to a class of chemotherapy known as anti-metabolites. Capecitabine is taken as a tablet (orally) and once in the body it is converted to fluorouracil (5-FU) which stops the body cells from DNA synthesis causing the cancer cells unable to divide leading to imbalanced cell growth and eventually cell death.

7.7.6 Discussion

This work discussed the high-grade triple-negative metaplastic breast cancer (MpBC) case of a 50-year-old woman. MpBC is very rare but very aggressive subtype of breast cancer, and it has a very poor clinical outcome. It is still not known what causes MpBC however this patient had a 9-year history of rheumatic fever for which she was put-on long-term Penicillin injections prior to her MpBC. The symptoms of MpBC are similar to the common symptoms of breast cancer including changes to the skin of the breast, swelling, pain, etc. however MpBC may not cause any symptoms. It is therefore very important to report any abnormality when noticed, as the early diagnosis of the disease can have more treatment options with better chances of a cure. The patient in this case study had pain and swelling and imaging tests demonstrated a mass in the inner upper quadrant of her right breast. The biopsy of the patient was carried out under the

guidance of ultrasound imaging and the final diagnosis was metaplastic carcinoma G3 TNBC. Past studies have shown that MpBC typically present high grade and larger in size at the initial time of diagnosis. The patient had NAC prior to her BCS and following her BCS the patient has been put on adjuvant chemotherapy. The pathology report of the breast tissue removed during her BCS showed a tumour size is more than 0.1 cm but not larger than 0.5 cm and no cancer cells are found in any nearby nodes.

CHAPTER 8

DISCUSSIONS

8.1 Discussions regarding breast cancer and imaging modalities

The research methodology selected for conducting the systematic review of the topics of breast cancer and medical imaging in this work presented an extensive review regarding all the aspects of breast cancer and medical imaging. In regard to breast cancer, it included the breast anatomy (important to understand which parts of the breast are usually affected by breast cancer), the breast cancer stages, the risk factors of breast cancer such as family history and genetics, reproductive factors, as well as dietary and lifestyle behaviours. The current worldwide used breast cancer prevention strategies by healthcare providers are also presented in this study in addition to the breast cancer symptoms, the types of breast cancer, breast cancer incidence in men, in addition to the current breast cancer treatments provided around the globe for the treatment of patients with breast cancer including surgery, chemotherapy, radiotherapy and immunotherapy as part of biological therapy. Likewise, the systematic review also covered the topic of breast cancer recurrence and the available blood tests used for breast cancer recurrence prediction. Importantly, systematic review of the topic of using complementary and alternative medicine for breast cancer and other types of cancer which is believed to be mainly working through boosting the body's natural immune system to kill the body's abnormal cells including the cancer cells. Similarly, this work also provided an extensive review regarding the medical imaging modalities used for the overall assessment of breast cancer such X-rays, mammograms, CT scan, USI, MRI, RI including PET and SPECT. The systematic review of the past studies carried out in this work highlighted several examples of how hybrid modalities and their characteristics are integrated to improve and enhance combined medical images. The fusion of hybrid imaging techniques has been used as a way towards the improvement in the specificity and sensitivity of these modalities to target the medical images of breast cancer patients. The combination of different modalities has been subjected to address biological processes for better characterisation of the biology of tumours as well as for assessing cancer treatments and tumour responses and resistance. Among the significant fusion methods, PET scan combined with CT scan, PET scan combined with MRI, and SPECT scan combined with CT scan, all are known

for their advantages and combined benefits. This research has revealed that the integration of imaging modalities for breast cancer, has helped in assessing the importance of certain therapies in line with treatment planning and protocols. These improvements have further helped in sourcing the hard and soft tissues. Cancer diagnosis is the most critical step in the clinical process as oncologic assessments give significant importance to tumour detection and identifying the suspected as well as evident lesion areas. The cancer diagnosis process is divided into different sub-processes such as detection at an early stage, detection of malignancies at an advanced stage, and detection at the progressive stage. However, most effective diagnosing technique should be capable of responding to the range of risk factors, symptoms, stages of breast cancer, and other variables associated with different cases. It can be depicted from the findings that breast cancer prevalence is associated with male and female genders although the severity and intensity of the prevalence may vary. Evidence also highlighted the importance of age as an independent factor affecting the prevalence of breast cancer in women across the globe, however the effective diagnosing technique should be capable of identifying the risk factors in the women population suffering from breast cancer, especially the young women population. This study has highlighted in addition to the age, the family history and genetics, hormone replacement therapy, birth control pills and alcohol consumption as significant risk factors associated with the higher prevalence of breast cancer. The analysis and critical review of recent studies has proved that mammography alone cannot be used as an effective modality in all populations of woman, especially in women with dense breast tissue. Therefore, other modalities such as PET/CT, PET/MRI have been developed as improved methods for breast cancer imaging along with the traditional methods of X-rays, ultrasound, etc. When PET scan technique is combined with other modalities such as MRI, it can produce remarkable results in the diagnosis phase of breast cancer assessment. Such assessment is highly necessary for the identification of the effective treatments subsequently needed to deal with issues regarding patients with breast cancer. The outcome of this research programme has clearly concluded that the diagnostic stage must be capable of identifying all the underlying factors, i.e., not only the medical factors but also the sociodemographic and lifestyle factors. The diagnostic technique

must also be capable of identifying the associated gene mutations responsible for the higher prevalence of breast cancer in women as highlighted in this study. The literature and the present study have identified some gene mutations as one of the high risk's factors associated with breast cancer. Also as explained in this work, diagnosis should also be based and focused on deeper factors including differences in lifestyle such as obesity, alcohol consumption, diet, breast size and the associated risks. The image acquisition processing of some modalities such as PET makes it highly significant, specific, and sensitive to the biologically active molecules and tissues found in the breast. Image acquisition protocol of PET scan which consists of the emission of gamma rays through a radionuclide tracer is highly effective and functional and also it has operationally safe outcomes. Besides PET, ultrasound is also identified as effective in the diagnosis stage of breast cancer assessment. Automated improvements made in the traditional ultrasound techniques has improved the efficiency of the image acquisition protocol and the image qualities. On the other hand, this investigation has also highlighted the overall sensitivity of MRI in producing breast cancer images. MRI has also been a popular method used for the diagnosis of breast cancer [327]. The importance of the imaging surveillance after primary breast cancer treatment is also considered as an effective parameter in examining the different imaging techniques. Primary breast cancer treatment is related to the types of treatment strategies available for breast cancer patients such as surgery, chemotherapy, radiotherapy, hormone treatment and targeted therapies. This study has investigated the side effects of such therapies to consider/reflect on the recurrence of breast cancer after such treatments along with the management of the side effects on patient's overall health. Imaging surveillance after treatment is more complex and it must be capable of discriminating between the risk associated with complexities faced by patients afterwards. For this purpose, imaging techniques used at the treatment stage need to ensure whether the cancer has spread to other body parts, and if yes, whether or not it can be treated effectively through the consumption of the cancer drugs. The results of the imaging technique must be capable of suggesting the treatment likely to result in long lasting positive impacts for patients. On the other hand, radionuclide imaging is identified as the most important technique for breast cancer imaging at the

treatment stage. Among the modern medical imaging techniques, radionuclide imaging was identified as effective due to higher resolution features associated with breast cancer lesions. The characteristics of resolution and sensitivity further make it highly remarkable to produce effective results in the treatment stage. Clinical studies have confirmed that radionuclide imaging is an effective technique for treatment stage as it is able to alter the treatment protocols developed in the initial assessment of breast cancer lesions [328]. The radionuclide imaging technique is not only capable of identifying the biological features but also is effective in detecting the functional features of the regions in the treatment stage. Researchers have also confirmed the significance of the radionuclide technique in identification of the distant metastases staging for breast cancer patients, in context of locally advanced, recurrent and metastasis disease. Furthermore, radionuclide technique is highly effective in identifying the effects of breast cancer therapies. Both the first-time appearance and the relapse or recurrence of breast cancer are crucial for clinicians to deal with breast cancer patients. Breast cancer relapse can take place in two ways, local recurrence, and cancer recurrence in other body parts. In the process of making effective identification of the type of recurrence, it is highly necessary for breast imaging techniques to differentiate initially among the different stages of cancer associated with such recurrence. While showing its compatibility in detecting different recurrences, radionuclide imaging has ultimately confirmed its effectiveness relative to other imaging techniques. Radionuclide imaging has also been used for tumour response modification for understanding the effects of treatments on the disease resistance. In simple words, the technique has been in use for the protection of therapy responses as well as for controlling the progression of the disease in breast cancer patients [328]. Another medical imaging technique, mammography, has been identified in producing quality medical images. Mammography can easily target lesions such as mass, mass with microcalcification, microcalcification, architectural distortion, and local asymmetry. The effectiveness of digital mammography technique has been improved and it is identified as a gold standard for breast cancer diagnosis. Mammography has the ability of the provision of adequate visualisation of soft tissue abnormalities. Soft tissues can lead to the development of benign tumours,

which can occur at any part of the body. Effective imaging techniques, therefore, should be capable of identifying the appearance and behaviours of tumours in different body parts. Imaging techniques must be capable of understanding and differentiating the aggressive and non-aggressive behaviours. Both the literature review as well as analysis of the different medical imaging techniques have confirmed that nuclear medicine advances are paying important role in the detection of metastatic disease and support in the provision of complete information on soft tissue and bone metastases. It is also important to highlight that these techniques are capable of detecting information in a single scanning session without any need of a repetitive scanning [328]. Follow up surveillance should be more efficient compared to both the diagnosing and treatment stage-imaging techniques. Follow-up imaging needs to revaluate all the factors responsible for the primary occurrence of breast cancer in order to ensure that they cannot lead to the relapse of the disease or slowdown the process of treatment and interventions. Imaging modalities need to be responsive to the varying lengths and durations of the follow up stage and it should be capable of detecting early local recurrences or contralateral breast cancer, while of evaluating and treating therapy-related complications such as menopausal symptoms, osteoporosis and the likelihood of second cancers and to encourage breast cancer patients regarding the continuity of treatment [329]. The reviewed literature in this report has revealed that there are inadequate findings about the outcomes of medical imaging techniques, in particular due to lack of studies focusing on the long-term outcomes. Such limited findings can be ultimately associated with the emergence of novel screening modalities, which have subsequently reduced the duration of the follow-up stages. The systematic review highlighting the recent studies has confirmed that clinical researchers are placing more effort in assessing the effectiveness of follow-up techniques related with breast cancer imaging. Breast cancer imaging has been initially assumed to be a diagnosis stage process. However, due to the emergence of the fusion-based modalities, examining the effectiveness of the existing medical imaging as well as the new medical imaging techniques such as radionuclide imaging and medical image analysis modalities can be seen in recent studies. New nuclear imaging techniques are increasingly investigated for the assessment of cancer

patients including treatment response along with the traditional medical imaging techniques. Investigations have revealed that MRI has proved itself as one of the important imaging techniques especially in dealing with young breast cancer patients, and in cases of patients with dense breast tissue [330]. The use of ultrasound imaging technique is also regarded as an effective modality especially in dealing with invasive cancer types. Invasive cancers are highly complex and crucial due to varying level of symptoms associated behind their prevalence as well as their increased risk of spreading to other body parts and further worsening patients' situations. Follow-up imaging such as ultrasound can assist in identifying lobular invasive carcinomas. However, ultrasound is limited to local areas of the breast while detecting changes and recovery in the nipples, breast tissue, etc. while nuclear imaging techniques can detect tumours in other body parts too [328]. The current study has highlighted ultrasound as an effective diagnosing technique for breast cancer imaging used across the globe. Besides ultrasound, MRI combined with PET technique was also identified as the most used medical imaging modality in its robust and comprehensive assessment of the cause as well as image acquisition approach. Systematic review revealed that the most effective diagnosing technique is the modality that is capable of detecting evident as well as suspicious breast lesions with high-level of sensitivity. Most effective diagnosing techniques are not affected by the small size of breast lesions, unexpected metabolic activity, or changes in the microscopic tumour growth patterns. It is worthy to highlight that imaging techniques do not need only the result orienting abilities with respect to the specificity and sensitivity of medical images but also, they should be responsive to the health and safety of patients too. Safety considerations are mostly related to the ability of imaging techniques to utilise the contrast agents for addressing the cancer-specific molecular markers. Imaging techniques are only effective when they are capable of reducing their ionised radiations. The systematic review has highlighted that significant improvements have been made within the traditional ultrasound imaging technique, further making this imaging modality to be approved as the most popular as well as safest method to target the different sizes of breast cancer lesions, irrespective of the size and density of the breast. Ultrasound is a safe and non-invasive method requiring little procedural

preparations before conducting a diagnosis or follow-up examinations. Studies have also confirmed that the use of ultrasound in all the stages of breast cancer assessment is very effective. It can be analysed that the most significant element in identifying the effectiveness of the technique is associated with the independence of the technique in targeting breast cancer in the diverse breast cancer population. The investigation has further confirmed the significance of soundwave frequency in targeting specific problematic lesion areas through the use of multiple colours and movements of frequencies. The technical, as well as procedural features of ultrasound, make it viable still among the novel medical imaging techniques. The arrival of more sensitive colour doppler and powerful machines have increased the efficiency of ultrasound in relation to the reduction of flowing solid masses and for the differentiation of flow. Ultrasound in comparison to the other techniques is effective in identifying when the management issues as well as normal tissues associated with breast lesions. It is also capable of detecting the surrounding stiffness [331]. Positron emission tomography combined with magnetic resonance imaging is a hybrid imaging technology that has also confirmed the potential of finding soft tissue and functional imaging aspects related to breast cancer assessment. Besides breast examination, PET/MRI was also identified as effective for the whole-body assessment. The functionality provided by the tracers of the PET technique is further, examination of molecular, functional, as well as anatomical information. Simultaneous acquisition of breast data using PET/MRI functionalities, preparations have also confirmed that it is an innovative technology which is able to produce exceptional quality images that are conclusive evidence with low variations. All assessment outcomes can be easily achieved in one single exam without the need of immediate measures [167]. The use of the qualitative, as well as quantitative information about the medical imaging techniques, has reported the significance and importance of this investigation. The literature review has reviewed recent studies describing the role of different modalities in the diagnosis, treatment, and follow-up stages of breast cancer. It can be examined that a large set of imaging modalities was reviewed in the current investigation including both the traditional ones as well as the novel techniques. There is a possibility that a wide range of studies is now available for the traditional methods

such as ultrasound, MRI, mammography while in comparison very few studies are initially conducted by researchers for the modern and normal imaging techniques such as CT, MRI, and radionuclide imaging. Other than the research methods, a sample size of the study selected for the current investigation was also one of the important factors affecting the findings. It can be discussed that for different modalities a different number of studies were used to assess their role at different stages of the breast cancer assessment. The variation in the sample sizes was due to the availability of the studies related to the imaging techniques. For the traditional techniques, the bulk of academic studies were available for the diagnosis stage while a small number of studies were found for the other stages. For this reason, sample size can be related to the differences in the weightage given to the discussion of the different medical imaging techniques. It is observed that some of the techniques were precisely discussed due to the small number of studies found for the assessment. In similar context, the examination and assessment of follow-up imaging techniques were quite low due to more focus by researchers being on the diagnostic and treatments stages. The current investigation has highlighted the most effective medical imaging technique for breast cancer imaging, and the findings are also helpful in suggesting the need to improve the functional as well as safety-related features for improving the effectiveness of breast cancer imaging modalities. Preference is given to those imaging techniques, which require to put fewer efforts and at the same time to produce better outcomes. Clinical experts have also changed their demands in relation to the effectiveness of medical imaging capable of producing high-quality images by protecting the health of their patients. It is realised that some of the medical imaging techniques are still able to produce harmful effects on the physical aspects of breast cancer lesions. Therefore, no matter how much improvements in the medical imaging modalities have been accomplished as in the case of hybrid approach, the effectiveness of the technique is still reliant on the ability to produce safe images.

8.2 Summary

It can be summarised based on the present evidence-based discussions that comparatively to the past studies in recent years, more improvements have been evidenced in the medical imaging field such as enhancement of the image acquisition protocols as well as increased safety of patients. The summary of the key insights gathered from this investigation on the role of medical imaging techniques in the overall assessment of breast cancer, the main points are related to the effective medical imaging modality that can be used effectively in the diagnosis, treatment, as well as in the follow-up stages for assessment of breast cancer as highlighted in this work. In this study, review of the traditional and modern medical imaging techniques has confirmed the improvements undertaken by healthcare professionals and clinicians in enhancing the ability of imaging techniques to diagnose, treat and to monitor the recurrences of breast cancer in the overall population of the breast cancer patients. However, such effectiveness of the imaging techniques cannot be assessed without relating it to the risk factors, symptoms, and patients' demographic attributes such as age, prevention strategies, treatment options, and the physical attributes of the breast. Socio-demographic variables of patients such as age, lifestyle, and genetics and hereditary conditions have to be considered while using any medical imaging technique. Multi-level factors are required to be considered while assessing the effectiveness of any modular approach. Deeper analysis of the physical changes appearing in the breasts and breast parts as well as the risk factors behind it, specifically the gene mutation involved also essential to be considered while assessing the effectiveness. Detailed overview of breast cancer, its various stages and different factors associated with such stages need to be considered for gaining classification of imaging techniques suitable for different stages of breast cancer imaging. Systematic review conducted in this study has confirmed the use of new technologies such as the fusion of different modalities in increasing the overall assessment and monitoring of the disease. A range of medical imaging modalities, for example X-ray, mammography, CT, ultrasound, MRI, PET, and radionuclide imaging, were reviewed in this study for assessing the effectiveness required to acquire an image. Besides reviewing the image

acquisition protocols for these medical imaging techniques, consideration was also made of their safety and health issues. The study has confirmed ultrasound as the most effective technique that can be used in all the three stages of breast cancer assessment. Image acquisition protocol of ultrasound imaging has helped in enhancing the ability to deal with breast cancer cases and in decreasing the mortality rate caused by breast cancer. The study has confirmed the focus on increasing the features of medical imaging techniques in order to make it crucial for the treatment planning and strategic purpose such as using many of fusion-based techniques, for example PET with CT and PET with MRI. Treatment of breast cancer requires a critical approach towards the technical as well as the functional and biological features to target the affected breast cells and to use the techniques which can help in altering the path of the treatment protocols according to the effects of the individual cases. Such alterations and modification are further required to be aligned with the severity of the risk factors and the side effects of treatments. The imaging techniques are contributing vitally to relating the patient-related factors with other medical factors in order to detect the appropriate imaging technique. These imaging techniques at different stages of breast cancer screening, when applied adequately, are capable of leading to an effective physical as well as psychological recovery. This study has critically discussed that researchers have mainly focused on the diagnosis and treatment stages, whereas follow-up stage is not given much significance and sufficient attention. This study has also informed that follow-up cannot be separated from the physical perspective. Long-term survivorship of breast cancer patients needs to be addressed through the responsiveness to the challenges faced by the researchers in the context of patients' expectations after the end of treatment. Follow-up screening is therefore crucial than diagnosis and treatment stages in order to investigate the side effects of the treatment as well as long-term implications of living with breast cancer. Therefore, effective screening technique needs to be concentrating on the follow-up care procedure along with the diagnosis and treatment. This study has highlighted that single screening method or dual screening technique must be used for routine stage evaluation at the early breast cancer phase and evaluation of the functional and anatomical information in the advanced stages. The study informed that different screening techniques

are capable of dealing with the issues at the pre as well as post-operative procedures and, therefore, screening procedure needs to be considered in the staging and management of the local recurrence and the loco-regional disease appearances. This study has also confirmed that the high-level effectiveness and the characteristics of all the imaging techniques are needed to be combined or integrated for new formation in all the stages of the assessment rather than only focusing on one specific imaging stage. The improved technique needs to be useful in the identification of the clear as well as suspected affected areas despite of the effects of their size, metabolic activity, subtype, growth of the tumour, and proliferation. The effective technique is also capable of providing information targeted by the medical experts along with the provision of additional information about the unsuspected distant metathesis. The sensitivity as well as specificity of the modality should be clearly directed towards the detection as well as assessment of breast lesions in dense breasts as well as in the upstages of the disease. The findings of the study have also highlighted towards a specific point related with the use of image acquisition protocols, i.e., the scanner, tracer, or any other instrument to be used for capturing the images of the cancerous tissues (active) or other body areas (non-active) should be user-friendly and security oriented for patients. It is therefore necessary to assess the effectiveness of medical imaging techniques after looking into the benefits and risks of each of the imaging techniques. Thus far, the overall aim and objectives of this research programme have been successfully accomplished with some useful concluding remarks. It is hoped that these findings will provide significant benefits in understanding the possible occurrence of cancer due to environmental gene mutations and preventive strategies, thus making huge difference to the wellbeing and avoidance of unhealthy conditions and as a whole to the related scientific communities including the medical imaging modalities. Irrespective of the availability of numerous studies of medical imaging techniques used for breast cancer screening, diagnosis and treatment monitoring, the way is still open for further development in order to identify one specific modality fulfilling all the purposes. This investigation has highlighted traditional as well as modern imaging techniques used by biomedical engineers and clinicians as well as other healthcare professionals for the effective assessment of breast cancer patients

at different stages of the disease, i.e., the early stages as well as the advanced stages. Through detailed descriptive and systematic assessment of different imaging techniques covered in this study, including their image composition protocols and their ability to contribute towards the human health and safety, this study has presented some improvements that have been made to the medical imaging techniques used for diagnosing patients with breast cancer, including the work that has been done on targeting dense breasts by improving the image quality as well as the size of various images. The role of effective imaging can therefore be attributed towards the decline in breast cancer mortality rates across the globe.

CHAPTER 9

CONCLUSIONS

9.1 Conclusions regarding the newly proposed concept of cancer

This work has introduced and presented a new genetic concept of cancer which links between the human population origins and migrations, environmental factors and gene mutations, and the development of cancer. Past studies have presented that up to 10% of all cancers are caused by inherited gene mutations and it can cause cancer to run in families. However, mainstream cases of cancer about up to 90% are caused by acquired gene mutations caused by environmental factors and lifestyle behaviours which can also appear to run in families when family members share certain exposures and environments. Therefore, the methodology used included understanding the topics of the human Y-Chromosome DNA extensively in addition to the human Y-Chromosome DNA haplogroups, the human Y-Chromosome DNA testing types and the geographic origins of the human Y-Chromosome DNA haplogroups. The new concept is also based on understanding the natural physical boundaries and the political boundaries important for analysing the genetic test results of the genetic samples that were obtained from the participant in this study and the detailed case studies of various cancers found among families investigated in this work to support the new genetic concept of cancer which links cancer to the human population origins and migrations. Therefore, evidence is presented from case studies, various image analyses and full-poof genetic test results that if family members of a human Y-Chromosome DNA haplogroup migrated to a geographic zone that they do not belong to, then they are at high risk of getting gene mutations that will eventually lead to cancer as a result of developing cellular abnormalities over time caused by such acquired gene mutations. This work presented a clear pedigree and in such a clear way it showed how cancer can look to run in families for being in a specific environment and a particular exposure of climate conditions of a geographic zone that they don’t belong to due to the fact that the whole body of the family members is forced by the new environment to adapt the new climate conditions. This was supported by the genetic test results of the genetic testing for cancer risk genes conducted in this work which showed that no inherited gene mutations were running among them. It is reported in this work that descendants of each human Y-Chromosome DNA haplogroup share a distinct gene mutation

which allows them to safely live in the geographic zones that they belong to, hence no gene mutations were seen in these individuals. The newly proposed concept in this work explains with clear evidence that cancer is a process in which the normal body cells are changed to a new form of cells, i.e., cancer cells, after they are exposed to various risk factors such as radiation, migration to different climates to the original environment, gene mutations, toxicity due to pollution, smoking, etc. The forced adaptation seems to cause adverse effects on certain body parts such as the respiratory system, starting in one part of the body and later on spreading to other body parts (metastasis), forming a complete new form of human body organs. This process of forced body adaptation is considered to lead to abnormal whole-body change which cannot be tolerated leading to fatalities. Similarly, a new definition of race and ethnicity was presented in this research crucial to give the actual race and ethnicity classification of populations that are composed of various races and ethnicities through classifying them according to the major human Y-Chromosome DNA haplogroups. This study also discussed important genetic topics such as the topics of the human X-Chromosome recombination and the male chimerism in females. It was essential to propose a powerful methodology needed for investigating the available rates of breast cancer and other types of cancer due to the fact that almost all of the past studies have presented inaccurate conclusions regarding the incidence of cancer among population composed of mixed ethnic groups leading to substandard results. Therefore, the right methodology for analysing and studying the incidence of cancer among the various ethnic groups in the UK and other parts of the world was suggested in this work. Migration was therefore proposed as a cancer risk factor suggested in this work, which works through the analysis of comparing the incidence of cancer among for example the Black Africans in Africa, and the White ethnic group in the UK. Additionally, the proposed cancer risk factor works through the analysis of comparing the incidence of cancer among for example the Black Africans in Africa, and the Black Africans in the UK during a specified period of time to assess cancer occurrence among them with considering all the known cancer risk factors. The past studies have discussed the topic of race and ethnicity as a cancer risk factor, but mainly as studying the diversity of one population in the country i.e., many studies have compared the

incidence of cancer among the various groups of migrants all being in a host country with the native inhabitants of the country. Therefore, and based on the research carried out in this work it is explained that the right methodology for comparing the cancer occurrence among the various ethnic groups in addition to the Whites in the UK, which is essential for better understanding the nature of the disease for controlling and applying effective prevention strategies to help improving the healthcare and saving lives. This work finally suggested in-depth prevention strategies to help prevent people from getting cancer and therefore a successful accomplishment of the research objectives has been achieved.

CHAPTER 10

RECOMMENDATIONS

10.1 Recommendations

From the conclusions drawn in this study, ultrasound and PET with MRI were identified as the most effective techniques, which can help clinicians in the overall assessment of breast cancer and in respect to screening, diagnosis, and treatment monitoring of the disease. These findings can be implemented to conduct future experimental studies based on the randomised controlled trials. These trials can substantiate the effectiveness of ultrasound and PET with MRI fusion technique by conducting practical experiments with breast cancer patients. It is therefore suggested to conduct the future trials by considering the effectiveness of the imaging techniques in the overall assessment, i.e., stage-based assessment. It is also recommended to carry out such investigations by using two different groups such as breast cancer patient group and control group. Comparative assessment of the patient group with the control group would effectively identify the strengths, weaknesses as well as limitations in using these techniques for the breast cancer assessment. Similarly, the new genetic concept of cancer presented in this work can help researchers and governments better understanding for controlling the illness. Testing for Y-Chromosome DNA haplogroups is highly recommended through which accurate data and information regarding the actual composition of the populations and the societies can be obtained for the incidence of cancer and other serious health issues. The application of the genetic points mentioned in this research such as minimising record of missing data of race and ethnicity, the Y-Chromosome DNA haplogroups list of ethnicity based on genetic testing system will strongly and quickly make the difference in the healthcare and research.

10.2 Implications

The findings of the current study have significant implications on the theoretical as well as practical aspects related to this work. The in-depth analysis of the past studies and the systematic review have provided the grounds for the assessment of different medical imaging modalities available to be used for breast cancer assessment in detail. The findings of the review have also allowed differentiating

among different traditional as well as modern techniques to highlight the improvements evolving in the imaging field. The systematic review is an important addition to the available scientific literature. The points mentioned regarding image acquisition protocols, technical aspects, as well as safety related aspects would be helpful for researchers to realise the areas needed for improvements regarding the different medical imaging techniques. Likewise, the new genetic concept of cancer presented in this study has identified migration as one major risk factor to be considered by people including researchers for better understanding cancer and prevent people from getting the disease and saving lives worldwide.

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APPENDICES

Appendix A: Aims and objectives

Aims:

- To identify the role of different types of medical imaging techniques used for the overall assessment of breast cancer.
- To investigate how breast cancer and other types of cancer caused by non-inherited gene mutations appear to run in families when family members share a specific environment or lifestyle.
- To find out what causes cancer cells to develop in relation to environmental factors and gene mutations, and the human population origins and migrations.

Objectives:

1. Systematic review is conducted to identify, evaluate and summarise the findings of all the relevant qualitative (non-numerical) and quantitative (numerical) studies available in the existing (clinical) literature to identify the comparative effectiveness of the different medical imaging techniques used for the overall assessment of breast cancer.
2. The methodology examines the various aspects of medical image formation, technical performance as well as health and safety considerations associated with the medical imaging modalities.
3. The following medical imaging techniques are discussed in this research; X-ray, computed tomography (CT), mammography, ultrasound imaging (USI), magnetic resonance imaging (MRI), radionuclide imaging (RI), positron emission tomography (PET), PET scan combined with CT scan, PET scan combined with MRI, single-photon emission computed tomography (SPECT), and SPECT scan combined with CT scan.

4. Clinical observation sessions are attended at several hospitals in the UK and abroad to observe the medical imaging procedures of various medical imaging techniques used for the overall assessment of breast cancer and other types of cancer, and to obtain medical images of different cancer cases investigated in this research for the newly proposed genetic concept of cancer.

5. Genetic samples are obtained from a number of participants in this study in addition to their detailed medical history to support the new genetic concept of cancer presented in this work. Moreover, human population origins and migrations are studied in detail along with clinical and historical evidence obtained from various sources including the participants and their families as well as hospital records.

Appendix B: Publications and presentations

The following is a list of peer-reviewed publications and conference presentations completed during my PhD studies at the University of Bradford under the supervision of Dr Mansour Youseffi, comprising data and information included within my thesis:

1. M. E. H. Rasheed, M. Youseffi, M. M. A. Jamil and N. A. A. Rahman, "Medical Imaging and Analysis of Dense Breast Tissue: A Case Study," IEEE Xplore, 2021 IEEE 17th International Colloquium on Signal Processing & Its Applications (CSPA) 2021, pp. 1–5, DOI:10.1109/CSPA52141.2021.9377288.

2. M. E. H. Rasheed, M. Youseffi, M. M. A. Jamil, T. N. T. Ibrahim and L. Parisi, "Medical Imaging and Analysis of Dedifferentiated Chondrosarcoma Using CT, MRI and Ultrasound," Journal of Physics: Conference Series, Volume 2071, International Conference on Biomedical Engineering (ICoBE 2021), 14, 15 September 2021, Universiti Malaysia Perlis (UNIMAP), Malaysia (Virtual), DOI:10.1088/1742-6596/2071/1/012053.

3. M. E. H. Rasheed, M. M. A. Jamil, N. A. A. Rahman and M. Youseffi, "Medical Imaging of Malignant External Otitis in the Presence of Squamous Cell Carcinoma," American Institute of Physics (AIP) Conference Proceedings, Volume 2401, The 2nd International Conference on Technology, Engineering and Sciences (ICTES) 2021, 3–4 April 2021, Langkawi, Malaysia, DOI:10.1063/5.0074094.

4. M. E. H. Rasheed, M. Youseffi, M. M. A. Jamil and L. Parisi, "Imaging and Analysis of Paediatric Optic Pathway Glioma and Craniopharyngioma: A Case Study," 2021 International Conference on Electrical and Electronic Engineering 2021 (Icon3E 2021).

5. M. E. H. Rasheed, M. Youseffi, L. Parisi, M. M. A. Jamil, S. A. Javid and F. Javid, "Pleuropulmonary Blastoma in A 3-Year-Old Boy: A Case Study," 2021 International Conference on Electrical and Electronic Engineering 2021 (Icon3E 2021).

6. M. E. H. Rasheed, M. Youseffi, M. M. A. Jamil, N. A. A. Rahman and R. Abd-Alhameed, "Analysis of Why Black, Asian and Minority Ethnic (BAME) Groups in the UK are Harder Hit By COVID-19, and How to Minimise the Risks," American Institute of Physics (AIP) Conference Proceedings, Volume 2401, The 2nd International Conference on Technology, Engineering and Sciences (ICTES) 2021, 3–4 April 2021, Langkawi, Malaysia, DOI:10.1063/5.0074093.

Abstract: Coronaviruses are a large group of viruses and different strains can cause different illnesses ranging from common cold to more severe diseases such as the severe acute respiratory syndrome (SARS) or the Middle East respiratory syndrome (MERS). Coronaviruses can be transmitted between people and animals, e.g., SARS-CoV was transmitted from civet cats to humans and MERS-CoV originally spread from camels to humans. There are other strains of coronaviruses amongst animals but have not infected humans so far. Coronavirus Disease 2019 (COVID-19) is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a new strain of coronaviruses that has not been previously seen in humans and has been spreading since December 2019. SARS-CoV-2 is different from other strains including SARS-CoV and MERS-CoV. SARS-CoV-2 is less fatal but more transmissible than SARS-CoV or MERS-CoV. As of November 5, 2020, the worldwide count is more than 47.9 million confirmed cases and more than 1.2 million confirmed deaths. COVID-19 symptoms are similar to flu and common cold but may become severe leading to more complications in people with chronic health conditions and in older people. According to the Office for National Statistics (ONS), 9 in 10 people dying of the disease in England and Wales, have pre-existing illness. However, having underlying health conditions is not the whole story since people from Ethnic Minorities have been hit hardest by COVID-19 compared with the White population. According to the Institute for Fiscal Studies (IFS), hospital death rate per capita to the population average amongst Ethnic Minorities, for Pakistanis is 2.9 times and Black African deaths is 3.7 times higher than those of the White Ethnic group. In this study, we have discussed how Black, Asian, and Minority Ethnic (BAME) communities are genetically different from the native inhabitants of Britain and hence why BAME groups are

affected more by the virus and being closely related to the human population origins and migrations. This work represents our view and understanding of the current situation, and it has emphasized on population genetic analysis that is vital to understand and control the novel coronavirus. Some important prevention strategies have also been recommended in this work including path to improved health and natural ways to boost body's immune system.

Keywords: Coronavirus; COVID-19; SARS-CoV-2; Black; Asian; Ethnic Minorities; Genetics; Y-DNA haplogroups; Immunity.

7. R. Abd-Alhameed, M. M. A. Jamil, T. N. T. Ibrahim, R. Qahwaji, **M. E. H. Rasheed** and M. Youseffi, "The Novel Coronavirus Causes Impairment of Blood Vessels and Respiratory System with Head-to-Toe Symptoms and Vaccine Development: An Overview," Journal of Physics: Conference Series, Volume 1793, The 1st International Recent Trends in Technology, Engineering and Computing Conference (IRTTEC) 2020, 30 September 2020, Kuala Lumpur, Malaysia, DOI:10.1088/1742-6596/1793/1/012055.

Abstract: Blood clotting was reported in April 2020 as another serious symptom due to COVID-19, but also came other reports such as young adults dying due to strokes and heart attacks. The currently known head-to-toe symptoms of COVID-19, seem to indicate vascular as well as respiratory diseases and that 40% of related death are due to cardiovascular complications. In a recently published journal paper in Lancet, the authors found that SARS-CoV-2 virus can infect the endothelial cells that line the inside of blood vessels noting that endothelial cells protect the cardiovascular system and release proteins that influence everything from blood clotting to the immune response. In the same paper, the authors showed damage to endothelial cells in the lungs, heart, kidneys, liver, and intestines in patients with Covid-19. Therefore, the emerging belief is that the novel coronavirus is a respiratory illness to begin with, but as it spreads further into blood vessels it becomes a vascular illness that is capable of killing patients via vascular system.

Keywords: Coronavirus, COVID-19, Head-to-toe symptoms, Impairment of respiratory and vascular systems; Vaccine development.

The following is a list of articles in preparation for publication completed during my PhD studies at the University of Bradford under the supervision of Dr Mansour Youseffi comprising data and information included within my PhD thesis:

1. M. E. H. Rasheed and M. Youseffi, "Case Study of a 50-Year-Old Woman with High Grade (G3) Triple-Negative Metaplastic Breast Cancer,".

2. M. E. H. Rasheed and M. Youseffi, "Complementary and alternative medicine (CAM) use for cancer patients,".

3. M. E. H. Rasheed and M. Youseffi, "Classification of the UK ethnic groups according to the human Y-Chromosome DNA haplogroups,".

4. M. E. H. Rasheed and M. Youseffi, "The right methodology for studying the incidence of cancer among the various ethnic groups in the UK,".

5. M. E. H. Rasheed and M. Youseffi, "Proposition of migration as a cancer risk factor to be added to the existing list of cancer risk factors,".

6. M. E. H. Rasheed and M. Youseffi, " Analysis of exposure to ultraviolet (UV) radiation including the UV radiation from the sun as a cancer risk factor,".

7. M. E. H. Rasheed and M. Youseffi, " The major human Y-Chromosome DNA haplogroup J and its main descendant subclades J1 and J2,".

8. M. E. H. Rasheed and M. Youseffi, " Environmental factors, gene mutations, and cancer: Proposition of a novel methodology to prove the accuracy of the geographic origins of the human Y-Chromosome haplogroups,".

9. M. E. H. Rasheed and M. Youseffi, " X-Chromosome recombination and inheritance patterns: The X-Chromosome from the father has the same share as the two X-Chromosomes from the mother combined,".

10. M. E. H. Rasheed and M. Youseffi, " Comparison and analysis of the available data according to the WHO Cancer Country Profiles for the current status of breast cancer and other types of cancer globally, in addition to the UK, and Saudi Arabia,".

11. M. E. H. Rasheed and M. Youseffi, " Artificial Intelligence (AI) and Breast Cancer Imaging: An Overview,".

12. M. E. H. Rasheed and M. Youseffi, " Normal Brain MRI,".