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THE INCIDENCE OF BREAST CANCER IN THE TURKISH REPUBLIC OF NORTH CYPRUS AND RISK ASSESSMENT USING DIFFERENT RISK ASSESSMENT MODELS

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MEDICAL BIOLOGY AND GENETICS

PhD DEGREE THESIS

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NICOSIA

The Directorate of Graduate School of Health Sciences,This study has been accepted by the Thesis Committee in Medical Genetics and Biology Program as a PhD Thesis.

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ABSTRACT

The aim of the study was to investigate the role of risk prediction models in breast cancer prevention and control in North Cyprus.To achieve this aim the thesis studies was carried out in 3 parts:

Firstly, the performances of the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), International Breast Cancer Intervention Study (IBIS) and Gail models in predicting the risk of breast cancer in the women of North Cyprus was investigated.

655 women were enrolled in the study consisting of 318 breast cancer cases and 337 hospital-based controls. Data were obtained from medical records and interviews after informed consent.

From the receiver operating curves (ROC) the models AUCs were 0.62(95%C.I=0.58-0.66) for BOADICEA, IBIS 0.59(95%C.I=0.55-0.64) and Gail 0.58(95%C.I=0.54-0.60).

The study found that the breast cancer risk prediction models maybe suitable, simple, cost-effective, and non-invasive tools for identifying high-risk women that can benefit from mammography screening.

Secondly,a simple breast cancerrisk prediction model for the women of North Cyprus was developed. Data from 655 women, consisting of 318 breast cancer cases and 337 hospital-based controls, was used to develop and internally validate the model, external validation was carried out using, 653 women consisting of 126 cases and 527 controls. Data were obtained from medical records and interviews after informed consent. A model was derived that consisted of age ≥50 years and <50 years and the presence and absence of >1 first-degree relatives (FDR) with breast cancer. From internal and external validations the model's AUCs were, 0.66 (95% CI = 0.62–0.70) and 0.69 (95% CI = 0.63–0.74) respectively. A unique model for risk prediction of breast cancer was developed to aid

in identifying high-risk women from North Cyprus that can benefit from mammogram screening.

Keywords: Breast cancer; Risk prediction models; Mammogram; Breast cancer prevention; North Cyprus.

Öz

Çalışmanın amacı, Kuzey Kıbrıs'ta meme kanserinin önlenmesi ve kontrolünde risk tahmin modellerinin rolünü araştırmaktı. Bu amaca ulaşmak için tez çalışmaları 3 kısımda gerçekleştirilmiştir: Öncelikle, Hastalık İnsidansı ve Taşıyıcı Tahmin Algoritmasının Meme ve Yumurtalık Analizi (BOADICEA), Uluslararası Meme Kanseri Müdahale Çalışması (IBIS) ve Gail modellerinin Kuzey Kıbrıslı kadınlarda meme kanseri riskini öngörmedeki performansları araştırıldı. 318 meme kanseri vakası ve 337 hastane bazlı kontrolden oluşan çalışmaya 655 kadın katıldı. Veriler tıbbi kayıtlardan ve bilgilendirilmiş onamdan sonra görüşmelerden elde edildi. Alıcı çalışma eğrilerinden (ROC), AUC modelleri BOADICEA için 0.62 (% 95 C.I = 0.58-0.66), IBIS 0.59 (% 95 C.I = 0.55-0.64) ve Gail 0.58 (% 95 C.I = 0.54-0.60) idi. Çalışma, meme kanseri risk tahmin modellerinin mamografi taramasından yararlanabilecek yüksek riskli kadınları belirlemek için uygun, basit, uygun maliyetli ve invazif olmayan araçlar olabileceğini buldu. İkinci olarak, Kuzey Kıbrıslı kadınlar için basit bir meme kanseri risk tahmin modeli geliştirilmiştir. Modeli geliştirmek ve dahili olarak doğrulamak için 318 meme kanseri vakası ve 337 hastane temelli kontrolden oluşan 655 kadından elde edilen veriler kullanılmış, 126 vaka ve 527 kontrol olmak üzere 653 kadın kullanılarak dış doğrulama yapılmıştır. Veriler tıbbi kayıtlardan ve bilgilendirilmiş onamdan sonra görüşmelerden elde edildi. 50 yaş ve <50 yaş ve meme kanserli> 1 birinci derece akrabaların (FDR) varlığı ve yokluğundan oluşan bir model türetilmiştir. Dahili ve

harici doğrulamalara göre modelin EAA değerleri sırasıyla 0,66 (% 95 CI = 0,62–0,70) ve 0,69 (% 95 CI = 0,63–0,74) olmuştur. Kuzey Kıbrıs'ta mamogram taramasından yararlanabilecek yüksek riskli kadınların belirlenmesine yardımcı olmak için benzersiz bir meme kanseri risk tahmini modeli geliştirilmiştir.

Anahtar Kelimeler: Meme kanseri; Risk tahmin modelleri; Mamogram; Meme kanserinin önlenmesi; Kuzey Kıbrıs.

DEDICATION

To My Parents

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LIST OF ABBREVIATIONS

BC: Breast cancer

ASR: Age standardized rate

BRCA: Breast cancer gene

ATM:Ataxia Telangiectasia Mutated

TP53:Tumor Protein 53

CHEK2:Check Kinase 2

PTEN:Phosphate and Tensin

CDH1:Cadherin-1

STK11:Serine/Threonine Kinase 11

PALB2:Partner and Localizer of BRCA2

ADH: Atypical ductal hyperplasia

ALH: Atypical lobular hyperplasia

LCIS: Lobular carcinoma in situ

DCIS: Ductal carcinoma in situ

DES: diethylstilbestrol

IUDs: Intrauterine devices

HRT: Hormone Replacement Therapy

MRI: Magnetic Resonance Imaging

NMRI: Nuclear Magnetic Resonance Imaging

IBIS: International Breast Cancer Intervention Study

TC: Tyrer-Cuzick

BMI: Body Mass Index

ASCO: American Society of Clinical Oncology

NICE: National Institute for Health and Care Excellence

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm

UK: United Kingdom

TRCN: Turkish Republic of North Cyprus

GLOBACAN: Global Cancer

BCRAT: Breast Cancer Risk Assessment Tool

AUC: Area Under Curve

ROC: Receiver Operating Curve

S.I: Standard Error

C.I: Confidence Interval

mHealth: Mobile Health

FDR: First Degree Relatives

OR: Odd Ratio

Wk: Week

Akt:Protein kinase B

ErbB4-truncated protein:Erythroblastic oncogene B 4-truncated

Ki-67:Antigen KI-67

GPR 120: G-Protein receptor 120

P53:Tumor protein 53

DHA: docosahexaenoic acid

MCF-7:Michigan Cancer Foundation-7

Her-2/neu:Human epidermal growth factor receptor 2

GST: Glutathione-S-transferase

CHAPTER 1

INTRODUCTION

1.1. BREAST CANCER EPIDEMIOLOGY

Breast cancer (BC) is the most common malignancy among women world wide and constitutes the highest incidence of cancer among women in the global population (Suleiman AK 2014).More than a million women worldwide are infected with BC per ye ar and more than half a million die of the disease (Tazhibi & Feizi 2014). Due to its high associated mortality, BC has become a major public health issue in developing countries across Asia, the Middle East and Africa over the last two decades (Nabi MG et al., 2016).

Also, where BC data in developing countries, such as those in the Arab w orld, are scarce, it can be expected that BC frequencies are also very high and increase rapidly in those countries (Bray F et al., 2004).

In 2018, it is estimated that 627,000 women died from breast cancer, whic h is about 15% of all women's cancer deaths (Ferlay J et al., 2018).

Hincal et al studied the prevalence of cancer in Northern Cyprus in relatio n to different European countries between 1990 and 2004 and found that breast cancer was the most prevalent form of cancer in women with a dia gnosis average age lower than in Northern and Southern Europe (Ferlay J et al., 2013 & Hincal E et al., 2008).

Pervaiz R et al also found that between 2007-2012, 665 (47.67 %) of the 1395 cancer cases enlisted in North Cyprus were women, and breast cancer was the most common form of cancer among women. (ASR 24.07) (Pervaiz R et al., 2017)

1.2. BREAST CANCER

Breast cancer occurs when breast cells develop out of control and form tumors or growths. Cancerous (malignant) or non-cancerous (benign) tumors.(Noone AM et al., 2018)

1.3. CLASSIFICATIONS OF BREAST CANCER

There are several forms of breast cancer that can arise in various parts of t he breast, such as the ducts, lobules, or tissue within them. It is possible t o classify breast cancers into two specific classes; carcinomas and sarcom as, depending on which cell origin is involved.Carcinomas are breast canc ers that derive from the breast ’s epithelial portion, consisting of the cells t hat line the lobules and the terminal ducts responsible for milk production. Sarcomas are a much rarer type of breast cancer (< 1% of primary breast c ancer) that develop from breast stromal components, including myofibrobl ast and blood vessel cells. (Sotiriou C et al., 2003 & Yu K et al., 2004)

1.4. RISK FACTORS FOR BREAST CANCER

A risk factor is described at its most basic, as something that affects the li kelihood of a person having a disease, in this case breast cancer.

Certain major breast cancer risk factors are beyond the control of individuals, like simply being a woman, for example, is the principal risk factor for breast cancer. Aging significantly raise one’s risk of breast cancer. It has been well established that if a woman has a first-degree relative (mother, sister, or daughter) diagnosed with breast cancer, the risk of developing breast cancer nearly doubles.(Collaborative Group on Hormonal Factors in Breast Cancer 2001; Hulka BS 1996; Coldizt GA 2012)

1.4.1. Genetic mutation:

Generally, about 5-10 percent of breast cancer are associated with gene mutations are inherited breast cancer. Inherited mutation in the gene BRCA1 or BRCA2 is the most common cause of hereditary breast cancer .(Collaborative Group on Hormonal Factors in Breast Cancer 2001; Hulka BS 1996; Coldizt GA 2012)

While less common and less severe in their increased risk of breast cance r than the BRCA mutations, inherited mutations in many other genes can also contribute to the development of breast cancer(Collaborative Group on Hormonal Factors in Breast Cancer 2001; Hulka BS 1996; Coldizt GA 2012).Many of the mutated genes include ATM (inheriring 2 abnormal copies of this gene causing ataxiatelangiectasia disease), TP53 (inherited mutations of this gene causing Li-Fraumeni syndrome with an increased risk of breast cancer, as well as so many other cancers such as leukemia, brain tumors and sarcomas), CHEK2(a CHEK2 mutation may increase the risk of breast cancer by abo ut two fold),PTEN (hereditary mutations in this gene may cause Cowden syndrome followed by a higher risk of non-cancerous and cancerous breast tumors as well as growth of the digestive tract, thyroid, uterus and ovaries),CDH1 (hereditary diffuse gastric cancer with an increased risk of invasive lobular breast cancer), SKT11 (mutations in this gene that result in Peutz-Jeghers syndrome with a higher risk of several forms of cancer, including

breast cancer), and PALB2 (PALB2 gene makes a protein that interacts w ith the BRCA2 gene protein, resulting in mutations in this gene causing a higher risk of breast cancer). (Collaborative Group on Hormonal Factors in Breast Cancer 2001; Hulka BS 1996; Coldizt GA 2012)

1.4.2. Family history of breast cancer:

Although fewer than 15 % of women with breast cancer have this disease in a family member, women who have close blood relatives with breast cancer are at higher risk. For example, having a first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk, whereas having two first-degree relatives with the disease increases the woman's about three times. Ironically, women with a father or brother who have breast cancer have an increased risk of breast cancer, too. (Collaborative Group on Hormonal Factors in Breast Cancer 2001; Hulka BS 1996; Coldizt GA 2012)

1.4.3. Race and ethnicity:

In general, Caucasian women are marginally more likely than African-America women to develop breast cancer, while breast cancer is more prevalent in African-American women under 45 years of age. Infact, African-American women of all ages are more likely to die from breast cancer. Certain breeds like Asian, Hispanic and Native American women have a lower chance of breast cancer development and death (Kaminska M et al., 2015 Sun YS., 2017; Howell A et al., 2014)

1.4.4. Benign breast conditions:

Women with dense breast on mammogram have a breast cancer risk that is around 1.5-2 times that of women with normal breast density even though several factors play a role in assessing breast density, such as age, menopause status, use of other medications (such as menopausal hormone therapy) and pregnancy. Some non-proliferative lesions can have a marginal effect on the risk of breast cancer. Such non-proliferative lesions include fibrosis and/or simple cysts, moderate hyperplasia,

adenosis, phyllodes, single papilloma, duct ectasia, periductal fibrosis, squamous and aprocine metaplasia, epithelial-related calcifications, other tumors (lipoma, hamartoma, hemanigioma, neurofibroma, adenomyoepithelioma), or mastitis. (Wang J et al., 2004 & Hartmann LC et al., 2005)

1.4.5. Proliferative breast lesions:

Some proliferative lesions without atypia appear to slightly increase a woman's risk of breast cancer (Kaminska M et al., 2015; Sun YS., 2017; Howell A et al., 2014). Example of such proliferative lesions include hyperplasia of the duct, fibroadenoma, adenosis of sclerosis papillomatosis or radial scar, However, some proliferative lesions with atypia in breast tissue ducts or lobules will increase the of breast cancer by 4-5 times, including atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). (Dupont WD& Page DL 1985 & Dupont et al., 1993)

1.4.6. Lobular carcinoma in situ (LCIS) or lobular neoplasia:

LCIS cells are cancer-like, growing in the lobules of the breast's milk-producing glans but are limited within the lobule's walls. (Kaminska M et al., 2015; Sun YS., 2017; Howell A et al., 2014) LCIS is historically associated with in-situ ductal carcinoma (DCIS) as a non-invasive breast cancer, although recent filed developments find that LCIS is benign. However, LCIS difers from DCIS in that if it is nottreated it usually progresses to become invasive cancer. Women with LCIS often have a substantially greater chance of developing cancer in either breast.

1.4.7. Chest radiation therapy:

Women that have been treated for another cancer with radiation therapy to the chest when they were younger have an increased risk of developing breast cancer(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014). If the individual had radiation as a teen or young adult, when the breasts were still developing, the impact of this factor on increasing risk is highest.

1.4.8. Exposure to diethylstilbestrol (DES):

Since the 1940s to the early 1970s, some pregnant women were given an estrogen-like medication DES since the rate of miscarriage was assumed to be lower.(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014) These women have a slightly higher risk of breast cancer and women whose mothers took DES during pregnancy may have a slightly higher risk of breast cancer as well.

1.4.9. Birth control and contraceptives:

Many methods of birth control use hormones which can increase the risk of breast cancer.(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014)Women who use oral contraceptives have a marginally higher risk of breast cancer than women who have never used them, but the risk tends to return to normal over time after stopping the treatment.Depo-Provera has been shown to have an increase in the risk of breast cancer as an injectable form of progesterone but there appears to be no increased risk in women five years after they stopped receiving the shots. Usually also hormones are used for birth control implants, intrauterine devices (IUDs), skin patches, and vaginal rings, which in theory may increase the

risk of breast cancer. Consequently, when contemplating the use of hormonal birth control, women will speak with their health care providers about balancing this effect with any other risk factors for breast cancer.

1.4.10. Hormone replacement therapy (HRT) after menopause:

The hormone estrogen (often paired with progesterone) was used to alleviate menopause symptoms and to avoid osteoporosis.(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014)Combined hormone therapy is required in most cases since using estrogen alone can increase the risk of uterine cancer. However, estrogen can be used by itself for women who have had a hysterectomy. Postmenopausal combined hormone therapy increases the risk of breast cancer, the chance of dying from breast cancer, and the likelihood of finding the cancer only at a more advanced stage. The elevated risk from combined HRT is reversible, however, and the effect extends only to current and new patients, as the risk of breast cancer of a individual tends to revert to that of the general population within five years of stopping HRT. Short-term estrogen use even during menopause doesn't appear to significantly raise the risk of breast cancer.

1.4.11. Excessive alcohol consumption:

Drinking alcohol is specifically related to an increased risk of breast cancer, and this factor 's increased risk increases with the alcohol intake.(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014)

For instance , women who have two to three drinks a day have about 20 percent higher breast cancer risk compared to women who don't drink alcohol.Women who only have one alcoholic drink a day run a very small risk increase.

1.4.12. Significant overweight or obese:

Before menopause, the ovaries of women produce much of the estrogen of the body, while the fat tissue produces just a small amount(Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014). When the ovaries stop producing estrogen after menopause, however, much of the estrogen in a woman comes from fat tissue.So developing more fat tissue after menopause can raise the levels of estrogen and raise the risk of breast cancer.In addition, being overweight appears to lead to higher levels of in sulin in the blood, and higher levels of insulin are associated with certain cancers, including breast cancer. Nonetheless, the connection between bo dy weight and the risk of breast cancer is complex and still needs to be ful ly understood.

1.4.13. Not having children or not breastfeeding:

Women who have not had children or who have their first after age 30 ha ve an overall slightly higher risk of breast cancer. By comparison, having several pregnancies and/or becoming pregnant at an early age reduces the risk of breast cancer (Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014).However, pregnancy appears to have various effects on different br east cancer forms, and pregnancy appears to raise the risk of triple-negative breast cancer. It has been suggested that breastfeeding may decr ease somewhat the risk of breast cancer, especially if it continues for 1.5-2 years.One potential reason for this effect is that breastfeeding decreases the total number of menstrual cycles for women during their lifetime.

Starting menstruation early or stopping menopause after age 55. Women would have more menstrual cycles if they start menstruating earl

y, particularly before age 12, and therefore have a longer lifetime exposur e to the hormones estrogen and progesterone, contributing to a slightly hi gher risk of breast cancer (Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014) .Similarly, if women go through menopause later, especially after age 55, they will have more menstrual cycles and also have a longer lifetime exp osure to estrogen and progesterone with a higher risk of breast cancer

1.4.14. Lack of physical activity:

Growing evidence indicates that regular physical activity can reduce the risk of breast cancer, particularly in women who have had menopause (Kaminska M et al., 2015; Sun YS., 2017;Howell A et al., 2014).It is not entirely clear how physical activity can reduce the risk of b reast cancer, but this may be due to the fact that levels of exercise affect b ody weight, inflammation, hormones and energy balance.

1.5. BREAST CANCER SCREENING

Screening is searching for signs of illness before a person has symptoms, such as breast cancer. Scientists are seeking to understand better what ind ividuals are more likely to get different forms of cancer.

For example, during their lifetime they look at the age of the individual, their family background and some exposures. The different forms of screening include:

1.5.1. Mammography screening test:

Mammograms are the most common breast cancer screening test. A mammogram is a breast image with x-rays. Mammography may find tumors too tiny to feel. It may also discover in-situ ductal carcinoma (DCIS).

It may also discover in situ ductal carcinoma (DCIS). In DCIS, abnormal cells line the breast duct, and can become invasive cancer in some women .In women with dense breast tissue, mammograms are less likely to find b reast tumors. Since both tumors and dense breast tissue appear white on a mammogram, where there is dense breast tissue, it can be more difficult t o detect a tumor.Younger women are more likely to have dense breast tissue.

1.5.2. Magnetic resonance imaging (MRI):

MRI is a technique that uses a magnet, radio waves and a computer to ge nerate a series of detailed images of areas within the body. This technique is also known as NMRI (Nuclear Magnetic Resonance Imaging).
MRI uses no x-rays, so the woman is not radiation-exposed. MRI can be used as a screening test for women who are at high breast cancer risk.

1.5.3. Breast Exam:

A clinical breast exam is a breast exam done by a physician or other healt h care professional. He or she will feel the breasts carefully and for lumps under the arms, or anything else that seems unusual. Women or men may do breast self-exams to check their breasts for lumps or other changes.
If you feel any lumps in your breasts, or note any other changes, talk to y our doctor.

1.5.4. Thermography:

Thermography is a technique in which a special heat-sensing device is used to measure the skin temperature that covers the breast. Tumors may cause changes in temperature, which may appear on the thermogram.

1.5.5. Tissue sampling:

Sampling of breast tissue uses cells from breast tissue to examine them u nder a microscope. Sampling of the breast tissue as a screening procedure has not been proven to reduce the likelihood of breast cancer dying. (Noone AM et al., 2018)

1.6. RISK PREDICTION MODELS

In order to be effective in the primary prevention of breast cancer it is nec essary to identify women at increased risk. Attempts have been made to d esign statistical models to assess the risk of developing breast cancer in a n individual.In general, prediction models integrate many risk factors for generating an estimation of the risk of breast cancer over a given time and /or the individual's lifetime. The Gail model (Gail MH et al., 1989) is the most commonly used model in breast cancer risk prediction and is now publicly available.The model provides estimates of the risk of developing breast c ancer over the next 5 years and a lifetime risk based on a number of risk f actors for breast cancer, namely age, hereditary susceptibility (BRCA1/2 carrier),personal breast disease history (invasive breast cancer or in situ c arcinoma, number of breast biopsy and atypical hyperplasia), family histo ry (number of first-
degree breast cancer relatives), reproductive factors (age at first menstrua l cycle and age at first child's birth), and ethnicity.Another commonly used model is the IBIS (International Breast Cancer Intervention Study) model, also known as the Tyrer-Cuzick (TC) prediction model (Tyrer J et al., 2004).
This model integrates information on endogenous and exogenous exposur e to oestrogen (age, BMI, menarche age, number of live births and age at f irst conception, menopause period, use of HRT), personal breast disease history (atypical hyperplasia, in situ lobular carcinoma), and more

detailed information on family history of breast cancer (Number of first- and second-degree breast cancer families
, age at the onset of breast cancer, relative bilateral breast cancer, relative ovarian cancer) than in the Gail model.

The TC model produces 10-year and lifetime risks of breast cancer for an individual woman. According to the 2013 ASCO (American Society of Clinical Oncology) guidelines for breast cancer chemoprevention, women with a 5-year risk of breast cancer of ≥ 1.66%, as estimated using the Gail model, are considered as having an increased risk (Visvanathan K et al., 2013). The 2013 NICE (National Institute for Health and Care, Excellence) guidelines use risk estimates from the TC model to classify breast cancer risk. moderate risk is defined as a 10-year risk of 3% to 8% or a lifetime risk of 17% to less than 30%, and high risk defined as a 10-year risk > 8% or a lifetime risk ≥ 30% (National institute for Health an Care Exellence Guidelines 2013 & Evans DG et al., 2013). The Gail model has been found to be good at predicting the absolute number of breast cancers in a population of women (Rockhill B et al., 2001 & Bondy ML et al., 1994)[1] but its discriminatory accuracy of individual risk is modest (Rockhill B et al., 2001) and even more limited when performed on women with atypical hyperplasia (Pankratz VS et al., 2008).A research evaluating the performance of various risk prediction m odels in the same population showed that the TC model has a marginally better capacity to predict the total number of cases of breast cancer and di scriminate against women with and without breast cancer compared to ot her models examined, including the Gail model (Amir E et al., 2003).

Notably, all models for assessing the risk of breast cancer depend on iden tified disease risk factors, although a considerable proportion of breast ca ncer has been suggested to grow in the absence of several proven risk fact ors (Madigan MP et al., 1995).The Breast and Ovarian Analysis of

Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (Antoniou AC et al., 2008 & Antoniou AC et al., 2004) is a risk prediction model for familial breast and ovarian cancer. The model is used to measure the odds of the mutation carrier BRCA1 an d BRCA2 and the risks of breast and ovarian cancer that are unique to ag e.This was developed using complex breast and ovarian cancer segregatio n analyses focused on a mixture of established families through populatio n-
based breast cancer research, and families with multiple affected individu als screened for BRCA1 and BRCA2 mutations.BOADICEA models the simultaneous effects of BRCA1 and BRCA2 mutations and suggests that residual family breast cancer clustering is explained by a polygenic varia ble (a large number of genes each with a small risk effect) with a variance decreasing linearly with age.BOADICEA has been validated in a large series of families from UK genetics clinics (Antoniou AC et al., 2008b). In the United Kingdom, it is recommended as a risk assessment tool in the National Institute for Health and Care Excellence clinical guideline CG164 (National Institute for Health and Care Excellence, 2013) and has been incorporated in the guidelines of several countries for the management of familial breast cancer (Ontario Breast Screening Program 2012; Riley BD et al., 2012;Smith RA et al 2012).

1.7. BREAST CANCER PREVENTION

A disease's preventive methods consist of three main group; The primary prevention aims at avoiding the occurrence of the disease by reducing ris k factor exposure.Secondary prevention aims to detect an emerging illnes s in the early stages while care is more successful, thereby reducing morta lity.Finally, tertiary prevention aims to minimize the long-term illness-induced adverse effects. Primary and secondary prevention strategies,

particularly in cancer prevention, play a crucial role in the prevention of any illness. In compari son, primary breast cancer prevention has been a daunting challenge beca use most of the proven breast cancer risk determinants aren't easy to effec t. Unfortunately, the most difficult to change are factors which have a sig nificant impact on the risk, including inherited vulnerability and factors re lated to hormone levels and reproductive events.

For example, pre-
menopause childbirth at a young age or surgical removal of both ovaries may reduce the risk of breast cancer, but at the same time violate the inte grity of a woman, and therefore are not seen as reasonable preventive me asures.Recommended risk management measures for high-
risk people, such as BRCA mutation carriers, include prophylactic mastec tomy, and chemoprevention. Treatment with the tamoxifen or raloxifene chemopreventive agents may significantly reduce the risk (Cuzick J et al., 2015).Such therapy, however, has many side effects, and is not generally recommended for women with an average risk.

Consequently, growing attention has recently been paid to the importance of physical activity,diets and alcohol intake, the few modifiable factors a ssociated with the risk of breast cancer, in disease prevention (Global Recommendations on Physical Activity for Health 2010; Nordic Nutrition Recommendations 2012; Haskell WL et al., 2007;Kushi LH et al., 2012).

1.8. MEDITERRENEAN DIETS AND BREAST CANCER PREVENTION

Diet was long suspected of affecting the risk of BC and numerous studies examined its potential impact.While most of these studies concluded that any impact of diet on risk may be low, some large-scale prospective

studies think otherwise(Fung TT et al., 2006;Trichopoulou A et al., 2009;Taylor EF et al., 2007; van der Hel OL et al.,2004;Egeberg R et al., 2008;Suzuki R et al.,2008;Schutze M et al., 2011) This emphasizes the importance of further investigating the role of diet in BC etiology.

It is important to note when researching the effects of diet on BC that individuals do not eat single foods but combinations of multiple foods that contain both nutrients and non-nutrients.Given the nature of human diets, the association and impact of any nutrient intake change, and the many nutrient-to-nutrient associations, assumptions about the impact of ingestion of a specific nutrient, food group, or dietary constituent on a particular health outcome may be misleading.For these reasons, it is useful to analyze nutrient intake patterns, which concurrently express several related aspects of dietary intake (Kant AK 1996 & Velie EM et al., 2005).

The Mediterranean diet has long been recognized as an example of a well-balanced diet but there is no "Mediterranean diet" gold standard.The Mediterranean Sea is bordered by at least 16 countries and diets differ between these nations, as well as between regions within the same area.Nevertheless, despite the above variability, the following general characteristics of a Mediterranean diet are: high consumption of fruits , vegetables, bread and other cereals, potatoes , beans, nuts and seeds; low to moderate consumption of dairy products, fish , eggs and poultry; and low consumption of red meats.Olive oil is commonly consumed in the Mediterranean diet and is an essential source of monounsaturated fat, and wine is consumed in small to moderate quantities.The combination and variety of foods included in this diet offers plenty of antioxidants such as flavonoids, carotenoids and antioxidant vitamins, plenty of phytochemicals including phytoestrogens, adequate fiber content, adequate folate and a favorable fatty acid profile (Couto E et al., 2011). These nutrients have been

linked to mechanisms of carcinogenesis and have been found (Visioli F et al., 2004), or are hypothesized to confer protective effects (Ziegler RG 2004) on total cancer incidence, and more specifically on BC incidence. The suggestion that adherence to a Mediterranean dietary pattern decrease s BC risk is also reinforced by the finding that countries bordering the Me diterranean Sea, which are more likely to adhere to such a diet, e.g. Greece , Spain, Italy and Cyprus, have the lowest BC incidence levels in Europe (GLOBACAN Cancer Fact Sheets).Turkish Republic of North Cyprus (TRNC) located in the Mediterranean Sea has a population of approximately 0.3 million Turkish Cypriot (Statistical Yearbook 2012).

An appropriate approach towards breast cancer prevention and control that will save lives is warranted.

Therefore, our aims were, firstly to compare the performances of the BOADICEA, IBIS, and Gail models in predicting the risk of breast cancer among the women of North Cyprus. Secondly, to develop a breast cancer risk model for the women of North Cyprus that will allow for the early identification of high-risk women and finally to investigate the potential positive impact of western Mediterranean dietary life style through investigating the significance of the varying amount of intake of fruits and vegetables, fish, olives and olive oil, fresh potatoes (cooked) and eggs on breast cancer risk among the women of North Cyprus.

CHAPTER 2

FIRST PART OF THE STUDY

COMPARATIVE STUDIES OF BREAST CANCER RISK PREDICTION MODELS AS SCREENING TOOLS FOR HIGH-RISK WOMEN IN NORTH CYPRUS

2.1. Background and aim:

Northern Cyprus, can be regarded as a middle-income society, small, enclosed, ideal for epidemiological research, has a typical western Mediterranean lifestyle with living conditions and diets that should be favorable for good health (Riboli E & Norat T 2003;Martinez-Gonzales M & Sanchez-Villegas A 2004) Breast cancer is a disease that has remained the leading disease among women in this region (Hincal E et al., 2008 & Pervaiz R et al., 2017). Early identification of high-risk women will lead to early preventive interventions (Pickle LM & Johnson KA 1989) that will save lives. Breast cancer prevention using risk prediction models can be an additional step towards achieving better and cost-effective breast cancer control. Therefore, this study compared the performances of the BOADICEA,IBIS and, Gail models in predicting the risk of breast cancer in women of North Cyprus.

2.2. Materials and Methods:

This study was carried out in the hospital, Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus. This hospital treats all breast cancer cases in North Cyprus. Ethical approvals were obtained from the Near East University scientific research evaluation ethics community and Dr. Burhan Nalbantoglu Devlet Hastanesi's ethics community before the research was carried out.A retrospective data from a case-control group was used because of the long latency period to breast cancer manifestation and the dynamic nature of the population, thus making it difficult for follow-up. All methods were performed following the relevant guidelines and regulations.

2.2.1. Sampling size was based following calculations:

$$n = \frac{N * t^2 p * q}{(N-1)d^2 + t^2 * p * q}$$ Equation 3.1

N = **121257 (Women Population Size)**

t = 1.96 (at **α=0.05**)

p= (prevalence rate) = 91/100000 = **0.00091** (Expected Frequency)

q= 1-p = **0.99909**

d= (Acceptable margin of Error) =**0,001**

The required sample size= 317.8 women.

2.2.2. Study group:

This was a retrospective study consisting of 655 women that were separated into two groups as follows: Case group = 318 women with confirmed cases of breast cancer. The patients with breast cancer were registered with the center's database and diagnosed based on pathological report according to the international classification of diseases for oncology 3rd edition (C50.0 – C50.9)(Sabatino SA et al., 2004). Hospital-based control groups = 337 women without breast cancer. Women with history of lobular or ductal carcinoma in-situ were excluded from the controls. The participants were between the ages of 30 to 84 years. Informed consent to participate was obtained after the aim of the study was explained by a medical professional.

2.2.3. Data collection:

Restrospective medical and demographic information of all participants was collected through interviews. The interview included: age, age at

diagnosis, age at menarche, age at first delivery, menopausal status, presence or absence of benign breast disease, history of breast cancer in first-degree relatives or other relatives, BRCA 1 and 2 mutation, body mass index, history of hormone replacement therapy including estrogen/progestin and breast density.

2.2.4. Breast cancer risk assessment:

The information collected through interviews were used in the models to predict the risk of breast cancer. The information on BRCA 1 and 2 mutation status could not be provided by the participants, so it was excluded.The IBIS model is a computer-based program that provided a woman's overall risk of breast cancer by incorporating genetic determinants such as the BRCA 1 and 2 genes (Tyrer J et al., 2004), Details about breast/ovarian cancer among family members, personal risk factors such as age, BMI, age at menarche, parity, age at first child, menopausal status, breast density, age at menopause, and benign breast disease (Tyrer J et al., 2004). The IBIS or Tyrer-Cuzick breast cancer risk evaluation tool version 8.0b was used, available at (http://www.ems-trials.org/riskevaluator/). The performance of the IBIS model was measured by estimating the breast cancer risk for each individual (Bevers TB et al., 2009). The 10year risk was divided by 2, to obtain the 5year risk. Though breast cancer risk increases with age dividing the 10year risk gave an approximate value for the 5year risk. The BOADICEA model calculated 5year risk of breast cancer in the women based on their age, family history and BRCA 1 and 2 carrier probabilities. The BOADICEA risk calculation was carried out using BWAv3 (http://ccge.medschl.cam.ac.uk/boadicea/). The National cancer Institute's online version of the breast cancer risk assessment tool (BCRAT) also known as the Gail model available at

(http://www.cancer.gov/bcrisktool/) was also used and has questions about the 5 year breast cancer risk based on age, age at menarche, age at first life birth, first degree relatives with breast cancer, previous breast biopsies with or without atypical hyperplasia, BRCA mutation and race (De La Cruz P & Brittingham A 2003). White race/ethnicity (Caucasians) variables was used for all the women in this study in estimating their risks (De La Cruz P & Brittingham A 2003). For the Gail model five-year risk assessment, a rate of less than 1.67% was defined as low risk while a rate of 1.67% or more was defined as high risk (Bevers TB et L., 2009, De La Cruz P & Brittingham A 2003). The Gail cut off value 1.67% was used for all they models while categorizing high and low risk women.

2.2.5. Statistical analysis:

The AUC plots, was utilized to measure the model's discriminative capacities. This determines whether the models will yield a higher risk for breast cancer cases and lower risk for hospital-based controls. The predicted scores were used to distinguish between high and low risk. Predicted high-risk Breast cancer cases are true positives, while predicted low-risk breast cancer cases are false positives. The test variables used were the predicted scores, and both study groups (breast cancer cases and hospital-based controls) were the outcome variable. A cut off value was used with a higher score more likely to predict the risk of breast cancer.

The predicted results were matched with reality outcome for the analysis. It is useful to quantify the performance and clinical value of predictive models using the positive predictive value (The proportion of breast cancer cases in which the model predicts the disease to occur who actually have the disease) and the negative predictive value (The proportion of breast cancer cases whom the model predicts will not have the disease and who actually do not have the disease).

All statistical analysis was done using SPSS version 24.0 analytical software.

2.3. Results:

2.3.1. Risk prediction models analysis:

The discriminatory capacity of the models as obtained from the receiver operating characteristics curves (ROC), area under the curve (AUC) as shown in (table 2.2.) are as follows: BOADICEA model AUC=0.81(95%C.I=0.77-0.84), IBIS model AUC=0.80(95%C.I=0.77-0.84) and Gail model AUC=0.76(95%C.I=0.73-0.80).

At a cut-off point of about 1.67, the sensitivities of the model's in predicting a high-risk woman among the breast cancer cases were as follows: BOADICEA=26.41%, IBIS=19.4%, and Gail=17.3%. (Table 2.1.) The specificities of the models was at 98.8%, 97.3% and 98.5% for the IBIS, BOADICEA and Gail models respectively, the sensitivities and specificities at 1.1 and 1.4 cut-offs are shown on table 2.1.

Table 2.1. The models sensitivities and specificities at different cut-off points

Cut-off ~1.1 Models	Sensitivity	Specificity
IBIS	(43.7%)	(90.8%)
BOADICEA	(58.5%)	(86.4%)
Gail	(43.4%)	(91.4%)
Cut-off~1.4		
IBIS	(26.7%)	(97.9%)
BOADICEA	(36.5%)	(92.0%)

Gail	(26.1%)	(94.4%)
Cut-off~1.67		
IBIS	(19.4%)	(97.3%)
BOADICEA	(26.41%)	(98.8%)
Gail	(17.3%)	(98.5%)

Table 2.2. Table for area under the curve for the risk prediction models

				95% C.I	
Models	Area	S.E	Sig.	Lower	Upper
BOADICEA Model	0.81	0.17	<0.001	0.77	0.84
IBIS Model	0.80	0.17	<0.001	0.77	0.84
Gail Model	0.76	0.19	<0.001	0.73	0.80

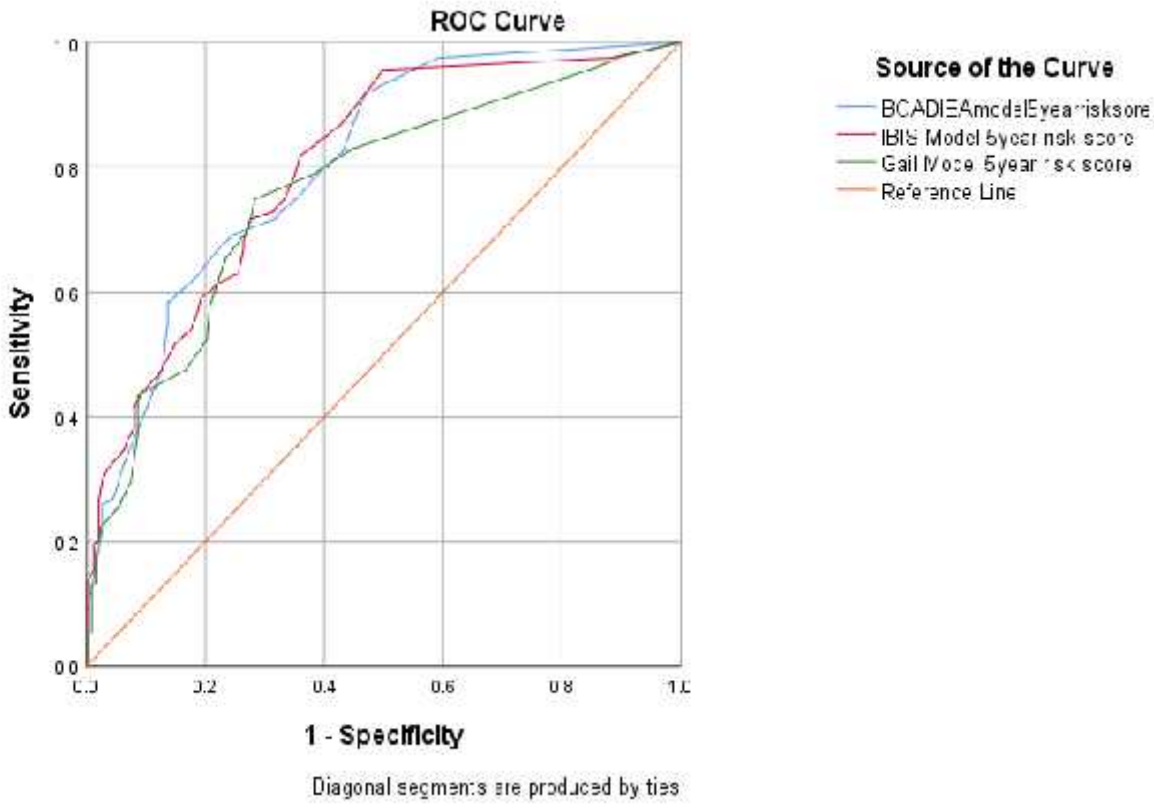

Figure 2.1. The receiver operating characteristics curve of the BOADICEA, Gail and IBIS models. This shows the discriminatory accuracy of the models. A value of 1 indicates perfect discrimination while 0.5 is by chance going to discriminate which woman will or will not have breast cancer.

2.4. Discussions:

It was found that all they models performed good in predicting the risk of breast cancer in women. Retrospective risk factors data were used to predict the risk of breast cancer by the models. The results demonstrated that the Gail, IBIS and BOADICEA models maybe suitable for predicting breast cancer. Though The BOADICEA and IBIS model gave a slightly better prediction value, all the models showed a reasonable predictive accuracy. It is important for a risk prediction model to have a good predictive accuracy (Prascandola M 2000). The models used genetic

factors such as family history to enhance their risk prediction of breast cancer. Inherited factors elucidate just about a quarter of breast cancer risk (Lichtenstein P et al., 2000). Meta and pooled studies have demonstrated that breast cancer risk is around twice higher in women with one first-degree relative with breast cancer, than women with no first-degree relative. The risk increases with a larger number of affected first-degree relatives or relatives affected under 50 years (Barnard M et al., 2015 & Pharoah PD et al 1997). BRCA 1 and 2 mutations explain the molecular pathogenesis behind 15-20% of cases with first-degree family history (Turnbull C et al., 2008, Lichtenstein P et al., 2000).

Breast density, age, menopausal status, hormone replacement and age at menarche were also risk factors. Breast density seems heritable (Martin LJ & Boyd NF 2008). But the mechanism underlying the association between breast density and breast cancer is not yet understood. Though age and menopausal status impacts breast density, younger and premenopausal women in general have denser breast (Kolb T.M et al., 2002). Women with early age of menarche have a slight increase in breast cancer risk (Willet W et al., 2004). A woman with an early age at menarche will have an increase in the time of exposure to estrogens, thus increasing breast cancer risk (Bernstein L 2002 &Kelsey JL et al., 1993). Hormone replacement therapy use is common among postmenopausal women and is linked to increased breast cancer risk (Breast cancer and hormone replacement therapy 1997).

These models can serve as suitable simple non-invasive alternative screening for the identification of high-risk women, thus streamlining the focus of the limited mammogram resources to the right group in Low income and Middle-income Countries. Using these models will also reduce unnecessary mammography need and radiation exposure on potentially low-risk women. The use of the risk prediction models has

additional advantages as it is not dependent on physical examination, easy to utilize and implement, being cost-effective and seems to enhance outcome and survival.

The poor funding of health systems in Low income and Middle income Countries causes problems in the implementation of mammography screening programs, thereby leaving many of the women out and only few from the urban centers with insurance policies are privileged to participate.

Risk prediction models can serve as additional screening tools that will yield effective results by identifying women at high-risk that will need immediate mammography, thus reducing the burden on the already constrained facilities and hence saving lives.

The progress in mobile internet services in Low income and Middle income Countries has made online materials easily accessible to everyone, Educating and empowering women on how to use the risk prediction tools online will drastically reduce the number of high-risk women that can not have access to early detection facilities. This will then protect more women at the individual and population level.

This initiative maybe similar to the mHealth initiative launched by the world health organization in 2012, whereby mobile phones were used to improve the prevention, detection and management of diseases in Low income Countries. (WHO.The International Telephone Union (ITU). 2012)Risk prediction tools at the moment can serve as cost saving tools but the benefits can only maximize when all identified high-risk women are able to receive further confirmation screening and treatment. So identified high-risk women will still need to visit health care centers for counseling and prophylactic treatment.

Because developing countries budget less fund for health care (The

World Bank. Health expenditure, total (% of GDP) 2016) There is an urgent need for the financing of health care systems to make early detection and treatment available.Our recommendations are firstly, there is a need for governments to recognize what the significance of breast cancer control using risk prediction models is to their developmental agenda and to allocate adequate resources to increase awareness and access to further medical services such as mammogram for if you save the woman you save the nation.Secondly, The education of the public and health care practitioners on methods such as risk prediction models for breast cancer control has to be a priority.Thirdly, there should be a deliberate desire to integrate and manage risk prediction, prevention, early detection and treatment of breast cancer on existing health care platforms.Lastly, while the models intend to ascertain the risk for an individual, the risk factors utilized depend on population risk from epidemiological investigations. Therefore, more studies have to be carried out among various populations of women in other to identify new lifestyle/environmental factors, biomarkers, genetic markers and incidence rates that are peculiar to that group, which can be incorporated into prospective risk models because the possibility of identifying those at high-risk would be enhanced by using a comprehensive risk model that integrates all known risk factors (Tyrer J et al., 2004).The weakness of our study is the fact that it was based on retrospectively collected data. However, the collecting process was done independently, so unlikely to have altered the results and caused bias. The AUC estimates are bound to be biased, since our study was carried out on a case-control group, but this was minimized (Reiser B 2000).

BRCA 1 and 2 information were not used because it is not a common test in the study setting and could not be provided by the participants, so a

comprehensive family history of breast cancer, which explains the BRCA 1 and 2 mutation associations with about 20% breast cancer cases, was used alongside other risk factors (Turnbull C et al., 2008, Lichtenstein P et al., 2000). Information on environmental risk factors was also not collected, because they were not considered risk predictors in the models and this may have created a gap in the awareness of interethnic risk factors in the studied population.Despite these biases and limitations the urgent need for these risk prediction models in providing relevant breast cancer control in developing societies outweighs the shortfalls.

2.5. Conclusion:

The results suggest that breast cancer risk prediction models can be suitable, simple, cost-effective, and non-invasive tools for the identification of high risk women .It may serve as a gatekeeper for mammography and a radiation saving tool for low-risk women by reducing unnecessary mammography and thereby decreasing health costs. Risk prediction models can also be used in screening women left out of mammography due to limited facilities. Hence, these models need to be explored in developing regions where access to early detection, cancer care, and mammography is limited. Though all the model's performances were similar, at a closer look the BOADICEA and IBIS models were slightly better.

CHAPTER 3

SECOND PART OF THE STUDY

RISK PREDICTION MODEL DEVELOPMENT FOR LATE ON-SET BREAST CANCER SCREENING: A MODEL STUDY FOR NORTH CYPRUS

3.1. Background and aim:

Risk prediction models can be used to identify high-risk women that will be eligible for mammogram screening. Thus, reducing the overload on the limited facilities available and narrowing the focus on the appropriate group,it can also reduce administering unnecessary radiation to women, who are not eligible, while at the same time reducing the economic burden on the government. Currently, several comprehensive breast cancer risk assessment tools exist that incorporate various risk factors for the calculation of breast cancer risk (Parkin et al., 2005). The models are known for better performances in predicting high-risk women in the regions, which they were developed (Schonfeld SJ et al., 2010). Therefore the development of a breast cancer risk model for the women of North Cyprus will allow for the early identification of high-risk women that will lead to early preventive interventions (Pickle LM & Johnson KA 1989) and will save lives.

3.2. Materials and Methods:

This study was carried out in the hospital, Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus. This hospital treats all breast cancer cases in North Cyprus. Ethical approvals were obtained from Near East

University, scientific research evaluation ethics committee, and Burhan Nalbantoglu Devlet Hastanesi's ethics committee, before the research was carried out (YDU/2018/55-523). All methods were performed following the relevant guidelines and regulations.

3.2.1. Study Population:

The retrospective dataset of 655 women, collected from April 2018 to December 2018, was used to derive the model. A total of 318 women had newly confirmed breast cancer, and 337 women were without breast cancer. Women with a history of lobular or ductal carcinoma in-situ were excluded. Only participants between the ages of 30 to 84 years were included in the whole study groups. Informed consent to participate was obtained after the aims of the study were explained by a medical professional.

3.2.2. Data Collection:

Retrospective medical and demographic information of all participants were collected through interviews. The interview included: age, age at menarche, age at first delivery, menopausal status, presence or absence of benign breast disease, history of breast cancer in first-degree relatives or other relatives, history of hormone replacement therapy including estrogen/progestin and breast density.

3.2.3. Sampling size was based on the following calculations:

$$n = \frac{N \times t^2 p \times q}{(N-1)d^2 + t^2 \times p \times q}$$ Equation 3.1

N = 121,257 (Women Population Size);

t= t value = 1.96, (at α = 0.05);

p= (prevalence rate) = 91/100000 = 0.00091 (Expected Frequency);

q= 1 − p = 0.99909; d = (Acceptable margin of Error) = 0.001;

The required sample size = 317.8 women.

3.2.4. Statistical Analysis:

The frequency of the risk factors of the study group was analyzed using descriptive statistics. An initial multivariable logistic regression was carried out. The significant variables were considered for further multivariable logistic regression. A forward multivariable logistic regression was used to access the final model. In the multivariable regression analysis, the categories that conferred protection against breast cancer were used as the reference. All statistical analysis was performed with IBM Spss (IBM, Armonk, NY, USA).

3.2.5. Internal Validation:

The whole dataset of 655 women, consisting of 318 breast cancer cases and 337 without breast cancer from the derived phase, was used to internally validate the model using bootstrap with 200 repetitions (Harrell FE et al., 1996 & Schumacher M et al.,1997). For each bootstrap, the derived model was fitted and the risk of breast cancer was estimated. The correlation between the observed and predicted values of breast cancer was estimated in the bootstrap data (called Dboot) and derived data (called Doriginal) using the Somer'D coefficient (Harrell FE et al., 1996 & Schumacher M et al.,1997).The optimism bias was assessed by subtracting Doriginal from Dboot.

3.2.6. External Validation:

Separate information of 653 women, consisting of 126 cancer cases and 527 women without breast cancer, collected between November 2018 to January 2020, were used to externally validate the model. Total scores for individuals were calculated based on the derived scoring scheme, and the c-statistic was then estimated.

3.3. Results

A total of 655 women were used to derive the model. Among them, 51.1% were above 50 years; 48.5% (318) of the women had breast cancer, while the rest reported with no breast cancer. A > 1 FDR with breast cancer was reported in 9.9% of the study population (Table 3.1).

Table 3.1. The frequencies and percentages of variables in the datasets used for the model development.

Characteristics	Frequencies (%)
Reproductive history	
Age at menarche	
≥14 years	155 (23.7%)
14–13years	421(64.3%)
>12–<13 years	0 (0%)
<12 years	79 (12.1%)
Age at first birth	
≥30 years	58 (8.9%)
25–29 years	142 (21.7%)
20–24 years	238 (36.3%)
<20 years	167 (25.5%)
Nulliparous	50 (7.8%)

Menopausal status	
Premenopausal	314 (47.9%)
Perimenopausal	13 (2.0%)
Postmenopausal	328 (50.1%)
Breastfeeding	
≥24months	285(43.5%)
<24–>18 months	0 (0%)
18–12months	236(36.0%)
<12–>6 months	0 (0%)
<6 months	83 (12.7%)
Never	51 (7.8%)
Breast density	
Extremely dense	58 (8.9%)
Heterogeneously dense	334 (51.0%)
Almost entirely fatty	263 (40.2%)
Demographic data	
>1 First degree relatives	
Yes	65 (9.9%)
No	590 (90.1%)
Second degree relatives	
Yes	41 (6.3%)
No	614 (93.7%)
Hormone Replacement Therapy	
Yes	17 (2.6%)
No	638 (97.4%)
Breast biopsy	
Yes	85 (13.0%)
No	570 (87.0%)

Age	
>50	320 (48.9%)
≤50	335 (51.1%)
Disease status	
Breast cancer cases	318 (48.5%)
Without breast cancer	337 (51.5%)

A total of 10 variables were analyzed to access the risk model, After an initial logistic regression of all the variables and two successive forward multivariable logistic regression, the risk factors that were observed to be insignificant were eliminated at each step, then we arrived at two significant risk predictors that comprised the final model, that is >1 FDR with breast cancer OR = 3.0 (95% CI 1.6–5.4) and age above 50 years OR = 3.0 (95% CI 2.2–4.1). The c-statistic of the final model on internal validation was 0.66 (95% CI 0.62–0.70). The estimated coefficients of the two variables served as the basis for the scoring with a range of 0–2. The risk scores were stratified into three groups; low-risk (0) women <50 years and with no >1 FDR with breast cancer, moderate-risk (1) women with >1 FDR with breast cancer or ≥50 years and high-risk (2)that is, women≥50 years and with >1 FDR with breast cancer. From the internal validation the average Doriginal and Dboot were (0.328) and (0.350) respectively. The bias or optimism was (0.022).

Separate information from 653 women, was used for external validation, consisting of 126 women with breast cancer and 527 women without breast cancer. From Figure 1, the c-statistics was 0.69 (95% CI 0.63–0.74), and the sensitivity and specificity are as shown in Table 3.2.

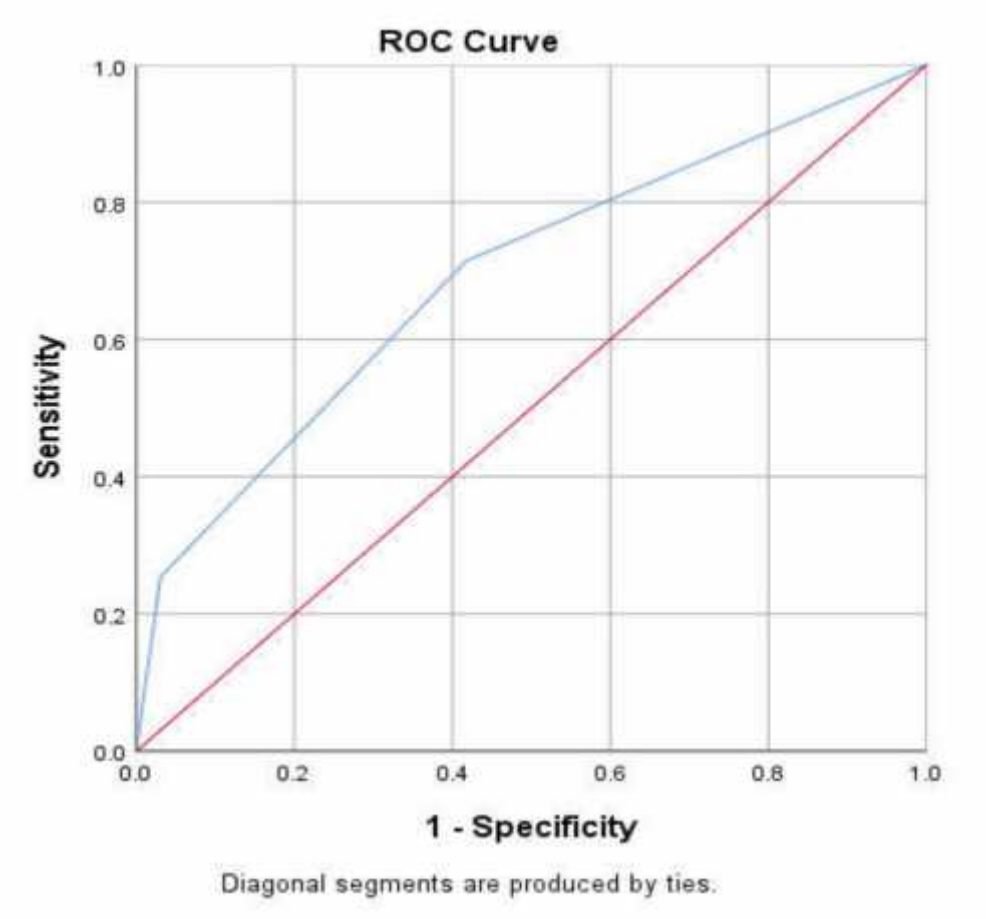

Figure 3.1. The receiver operating characteristics (ROC) curve of the simple model.This shows the discriminatory accuracy of the model. A value of 1 indicates perfect discrimination while 0.5 is by chance going to discriminate which woman will or will not have breast cancer. The red diagonal line represents the reference point. The blue line is the ROC curve of the simple model.

Table 3.2. Sensitivity and specificity of the simple model on external validation.

Cut-Off Value	Sensitivity	Specificity
0.5–1.0	71.4%	41.7%

3.4. Discussions:

In comparison, to a recent validation study carried out on a large cohort, the model showed similar c-statistics, sensitivity, and specificity to the Gail, IBIS and BOADICEA models (Terry MB et al., 2019). The other models were developed for populations with base-line etiological risk factors that differed from our setting (Schonfeld SJ et al., 2010). So, the model was developed to include only the base-line risk factors that are peculiar to the women of North Cyprus at the moment. Yet, the model can aid in categorizing high-risk women. The model utilized age ≥50 years and <50 years and presence or absence of >1 FDR with breast cancer in determining the risk of breast cancer. Inherited factors elucidate just about a quarter of breast cancer risk. Meta and pooled studies have demonstrated that breast cancer risk is around twice higher in women with one FDR with breast cancer than women with no FDR with breast cancer. The risk increases with a large number of affected FDR or other relatives affected under 50 years (Barnard M et al., 2015 & Pharoah PD et al., 1997) BRCA 1 and 2 mutations explain the molecular pathogenesis behind 15–20% of cases with FDR with breast cancer (Turnbull C et al., 2008)and about 80–85% are as a result of genetic mutations that occur due to the aging process and lifestyle-related risk factors(Kaminska M et al., 2015) Aging plays a role in the pathogenesis of breast cancer because of genetic instability, telomere attrition, epigenetic alteration, stem cell exhaustion associated with aging. From 50 years to 70 years and above, the risk of breast cancer increases (Siegel R et al., 2014). The assessment of risk is vital for the management of breast cancer. High-risk women will not automatically have breast cancer, but they are strongly advised to visit cancer clinics. They should have a mammogram at least yearly, for this has been shown to increase detection rates and reduce mortality (Le-Petross HT et al., 2011).

It is recommended that the women of North Cyprus categorized as high-risk for breast cancer can benefit from regular monitoring using mammograms, early detection, and preventive interventions such as healthy lifestyle and medication. Those women with moderate risk of breast cancer, should undergo screening of breast cancer risk using mammograms biennially. For women above 50 years with no >1 FDR with breast cancer, while those women below 50 years with >1 FDR with breast cancer can consider the use of medications, such as tamoxifen or raloxifene to reduce the risk of developing breast cancer. Risk and benefits have to be assessed by a medical professional.

Low-risk women are required to indulge in primary care since their risk is not different from the general population, but this status is liable to change in the presence of modifiable risk factors. Thus, these women are encouraged to maintain a healthy lifestyle and breast care. Increased awareness of existing and identified risk factors will aid in evaluating their current status and make the appropriate decision for mammogram screening if warranted. These recommendations are summarized in Table 3.3.

Table 3.3. Summarized recommended guidelines for the management of breast cancer risk screened by the simple model in the women of North Cyprus.

Risk Status	Suggestions/Advice	Outcome
High-risk (>1 FDR and ≥50 years)	Regular monitoring, early detection and preventive interventions	Reduced mortality
Moderate-risk (>1 FDR or	Further screening to access risk	Prevention of occurrence

≥50 years)		
Low-risk (No FDR, <50 years)	Primary care	Awareness and prevention

This model can serve as a simple, noninvasive, alternative screening for the identification of high-risk women, thus streamlining the focus of the limited mammogram resources to the right group in low- and middle-income countries such as North Cyprus. Using this model will also reduce unnecessary mammograms needed and radiation exposure to potentially low-risk women. The use of the risk prediction model has additional advantages, as it is not dependent on physical examination, easy to utilize and implement, being cost-effective and will enhance outcome and survival for women categorized as high-risk.

The poor funding of health systems in low- and middle-income countries causes problems in the implementation of mammogram screening programs, thereby leaving many of the women out and only a few from the urban centers with insurance policies are privileged to participate.

This model can serve as additional screening tools that will aid in identifying women at high-risk that will need an immediate mammogram, thus reducing the burden on the already constrained facilities and hence saving lives.

The progress in mobile internet services in low- and middle-income countries has made online materials easily accessible to everyone. Educating and empowering women on how to use the risk prediction tools online will drastically reduce the number of high-risk women that cannot have access to early detection facilities. These will protect more women at the individual and population levels.

This initiative is maybe similar to the mobile health (mhealth) initiative launched by the world health organization in 2012, whereby mobile phones were used to improve the prevention, detection, and management of diseases in low-income countries (A Guide for Countries Joining the m-Health Program. 2020). The risk assessment model can be incorporated into the mhealth features, thereby empowering women. Low-risk women through mhealth, can benefit from primary care, where healthcare teams deliver healthcare remotely, through audio, video and text. Risk prediction tools at the moment can serve as cost-saving tools. However, the benefits can only be maximized when all identified high-risk women can receive further confirmation screening and treatment. Therefore, identified high-risk women will still need to visit healthcare centers for counseling and prophylactic treatment. While the models intend to ascertain the risk for an individual, the risk factors utilized to depend on population risk from epidemiological investigations. Therefore, more studies have to be carried out among various populations of women in other to identify new lifestyle/environmental factors, biomarkers, genetic markers and incidence rates that are peculiar to that group, which can be incorporated into prospective risk models because the possibility of identifying those at high-risk would be enhanced by using a comprehensive risk model that integrates all known risk factors. Because our enrollment of breast cancer patients for this investigation is not specifically aimed to gather the early on-set breast cancer patients, we assume that our model is more suitable for the late on-set breast cancer risk prediction. That is why we added the phrase “Late On-Set Breast Cancer Screening” into the manuscript’s title. We think that the early on-set breast cancer risk prediction model should be developed in the future by using a specific cohort made up by enrollment of early on-set breast cancer patients.

The weakness of our study is the fact that it was based on retrospectively collected data. However, the collecting process was done independently, so unlikely to have altered the results and caused bias. The AUC estimates are bound to be biased since our validation was carried out on a case-control group, but this was minimized (Reiser B 2000). The internal and external validation was done using data from the same hospital but collected at different times. Information on environmental risk factors was not collected, and this may have created a gap in the risk factors of the studied population. Despite these biases and limitations, the urgent need for a risk prediction model in providing relevant breast cancer control in developing societies such as North Cyprus outweighs the shortfalls.

3.5. Conclusions:

The results demonstrated that this newly developed breast cancer risk prediction model is a simple, cost-effective, and noninvasive tool for the identification of high-risk women in North Cyprus that can be eligible for a mammogram. It may serve as a gatekeeper for a mammogram and a radiation saving tool for low-risk women, by reducing unnecessary mammograms and thereby decreasing health costs. This model is suitable for the prediction of late on-set breast cancer risk.

CHAPTER 4

THIRD PART OF THE STUDY

ROLE OF FOOD CHOICE FOR BREAST CANCER PREVENTION IN NORTH CYPRUS

4.1. Background and aim:

Breast cancer is the most predominant malignancy among the women of North Cyprus (Pervaiz R et al., 2017) as well as in similar developing societies. (Ferlay J et al., 2015) Among all primary preventions for breast cancer in developing societies, the consumption of the right foods is the most cost-effective cancer preventive intervention (2002.National Cancer Control Programmes,Policies and Managerial Guidelines,2nd ed.Geneva:WHO). Inter-societal differences in response to dietary consumption and breast cancer risk maybe linked to genetics. (Theodoratou E et al., 2017) There are polymorphisms in the interactions of diets intake and gene, that may influence epigenetics and further modify the expression of genes which influences the risk of breast cancer. (Lenihans-Geels G et al., 2016) North Cyprus has a typical western Mediterranean way of life with living conditions and diets that ought to be ideal for healthy wellbeing (Riboli E & Norat T 2003). Culture may drive the consumption of certain types of foods in high amount base on local availability. (Shayoun NR & Sankavaram K 2016). Limited evidence exists that support the probable causal role of western Mediterranean diets. Finding the specific foods that have significant impact on breast cancer risk will allow for a targeted consumption to achieve maximum benefits.

The purpose of this study was to investigate the potential positive impact of western Mediterranean dietary life style through investigating the significance of the varying amount of intake of fruits and vegetables, fish, olives and olive oil, fresh potatoes (cooked) and eggs on breast cancer risk among the women of North Cyprus.

4.2. Methods:

4.2.1. Subjects:

This was a hospital-based case-control study that was carried out in Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus. The investigation was carried out in accordance with the declaration of Helsinki, 2013. Ethical approvals were obtained from Near East University, North Cyprus ethical community and the ethical community of Dr. Burhan Nalbantoglu Devlet Hastanesi, Lefkosa, North Cyprus.

From convenient sampling the women enrolled were as follows:

Case group = 305 women with confirmed cases of breast cancer.

Hospital-based control groups = 302 women without breast cancer attending the cancer hospital for other reasons.

4.2.2. Data collection:

Breast cancer cases were approached while waiting for their oncologist appointment or while receiving chemotherapy. Patients with breast cancer were selected as diagnosed pathologically based on international classification of diseases for oncology 3rd edition (C50.0 – C50.9)(Nishio K et al., 2007) and registered with the cancer center's database.

The hospital-based controls were women attending the hospital for other reasons and have no history of breast cancer. The goals of the study was explained clearly to them and due consent to participate was verbally obtained or by filling a consent form. The controls were asked questions

about their dietary intake in the past 5-10 years, while the cases were also asked same questions about their dietary intake 5-10 years before diagnosis.

Data were collected with the use of a specially designed questionnaire through a standardized interview. The questionnaire included information on age, menopausal status, age at menarche and breast density. In addition, a diet interview was conducted on each subject using a food frequency questionnaire designed to capture the consumption of 5 food items selected from previously validated questionnaires, (Quantitative score (14-item) of adherence to the Mediterranean diet)

and commonly consumed by the people of North Cyprus. The frequency of intake of the 5 food items were categorized as follows: Eggs intake: 3-6 per week, 1-3 per week and none; Fruits and vegetables intake: 5 or more servings per day, 3-4 servings per day, 2 servings per day and none; Olives and olive oil intake: 5 or more servings per day, 3-4 servings per day, 2 servings per day and none; Fish intake: 2 servings per week, 1 serving per week and never; Fresh potatoes: 4 or more servings per week, 2-3 servings per week and 1 serving or none per week. Only the completely answered questionnaires were analyzed (table 4.1.).

Table 4.1. The standard serving of the studied foods

Foods	Amounts
1 serving of vegetables	1 cup of raw leafy vegetables, 1/2 a cup of raw or cooked vegetables
1 serving of potatoes	1 cup of diced, mashed or medium size boiled potato
1 serving of fruits	1 cup of chopped fruits, 125ml(1/2cup) of fruit juice (no added sugar) and ½

	cup dried fruits
1 serving of fish	1 can of fish, 1 cup of sliced fish or 1 fish
1 serving of egg	1 egg
1 serving of olive oil 1 serving of olives	1 tablespoon per meal 5 olives per meal

Table 4.1. Shows the standard used for the servings of each studied Mediterranean food (Nicola Shubrook 2019). A serving is equal to the quantity per meal and this can be cooked, fresh or dried.

4.2.3. Statistical analysis:

They women age, menopausal status, breast density, age at menarche and dietary intake between cases and controls were first analyzed by cross-tabulation and chi-square test. The significance was $P<0.05$.To analyze the link between the frequency of dietary intake and breast cancer risk, A multivariable logistic regression model was used and only diets consumption frequency was analyzed. No cofounding variable were used in the analysis. The fit of the model was assessed on the basis of Pearson chi-square or Hosmer-Lemershow goodness of fit. The statistical analysis was carried out using IBM SPSS.

4.3. Results:

Table 4.2. The distribution of characteristics in the study population			
Variables	Breast cancer patients	Hospital-based controls	Sig.

Age:			
0-29 years	6	109	
30-39 years	41	67	
40-49 years	54	52	
50-59 years	93	48	
60-69 years	111	26	<0.05
Breast density:			
Extremely dense	25	34	
Heterogenously dense	179	129	
Almost-entirely fatty	101	139	<0.05
Menopausal status:			
Premenopausal	117	221	
Postmenopausal	188	81	<0.05
Age at menarche =<12years 13years >=14years	 73 170 62	 6 214 82	 <0.05

A total of 305 breast cancer cases and 302 hospital-based controls were studied. The age range of the participants studied was between 18-69 years, with a mean age of 45 years. The highest number of 221 women in menarche group were premenopausal women with 13 years age at menarche, while following is 163 postmenopausal women in the same

category. The lowest, which is 29 premenopausal women had their menarche at age =<12 years. 50 postmenopausal women had their menarche at age =<12 years. The women with menarche at age =>14 were 88 pre and 56 postmenopausal women.The highest number from 201 women,with heterogeneously dense breast were premenopausal, followed by 155 post menopausal women with almost entirely fatty breast and the lowest was 7 postmenopausal women with extremely dense breast. 52 premenopausal women had extremely dense breast.

Table 4.3.Table of the dietary consumption of the study population

Diets	Breast cancer patients	Hospital-based controls	Sig.
1. Eggs:			
3-6 per week	154	225	
1-3 per week	50	49	
None	101	28	<0.05
2. Fruits and Vegetables:			
5 or more servings per day	106	161	
3-4 servings per day	48	58	
2 servings per day	45	65	
None	106	18	<0.05
3. Olives and olive oil:			
5 or more servings per day	41	49	
3-4 servings per day	52	86	
2 servings per day	115	150	
None	97	17	<0.05
4. Fish:			
2 servings per week	83	160	

1 serving per week	119	132	
Never	103	10	<0.05
5. Fresh potatoes (cooked):			
4 or more servings per week	59	134	
2-3 servings per week	98	117	
1 or none per week	148	51	<0.05

From table 4.3.,more women in the hospital-based control group consumed fruits and vegetables 5 or more servings per day (n=161) with less women in the breast cancer group consuming the same amount (n=106).Olives and olive oil was highly consumed in the hospital-based controls group with 49 women consuming 5 or more servings per day and 41 women in the breast cancer cases group. The number of women not consuming olives and olive oil increased in the breast cancer cases group while the reverse was the case in the hospital-based control group.

83 breast cancer cases consumed 2 or more servings per week of fish while 160 hospital-based controls consumed the same amount. 119 breast cancer cases and 132 hospital-based controls consume fish once in a week.The breast cancer cases that consumed 4 or more servings per week of fresh potatoes were 59 with 134 women observed in the hospital-based control group.98 and 117 women consumed 2-3 servings per week of fresh potatoes (cooked) in the breast cancer cases and hospital-based control groups respectively.3-6 eggs and 1-3 eggs were consumed per week by 154 and 50 breast cancer cases respectively, while 225 and 49 women with the same consumption rate were observed in the hospital-based control group.A multivariable logistic regression model was used to analyze the food intake frequency, the least frequency of intake was used as the reference (table 4.4.). The omnibus test's of models coefficients was significant ($p<0.05$). Cox and Snell R2 =0.442 and

Nagelkerke R2=0.590.The Hosmer and Lemeshow test was also significant ($p<0.05$). From the regression analysis the intake of fruits and vegetables 5 or more servings/week and 2 servings/week had an OR=0.09 and 0.12 respectively. The OR=0.10 and 0.11 was observed for the intake of 3-6 eggs/week and 1-3 eggs/week respectively. Olives and olive oil intake 5 or more servings/week was 0.06, while the OR of 1 serving of fish/week was 0.06. Intake of 2 servings/week of fish OR=0.04. Fresh potatoes 4 or more serving/week OR=0.15. The percentage probabilities (P) of breast cancer linked to each dietary category was calculated as P=Exp(B)/1+Exp(B)*100 and represented in the table 4.4.

Table 4.4. The logistic regression analysis of food intake frequency of the study group.

Diets	B	Sig.	OR	95% C.I LowerUpper (P%)		
1.Fruits and vegetables Never (Ref)		0.00	1.00			
5 or more servings/day	-2.4	0.00	0.09	0.04	0.18	7%
3-4 servings/day	-2.3	0.00	0.10	0.04	0.20	9%
2 times/day	-2.0	0.00	0.12	0.06	0.27	10%
2. Eggs Never (Ref)		0.00	1.00			
3-6 /wk	-2.2	0.00	0.10	0.05	0.20	9%
1-3/wk	-2.1	0.00	0.11	0.05	0.25	10%
3.Olives and olive oil Never (Ref)		0.00	1.00			
5 or more servings/day	-2.7	0.00	0.06	0.03	0.16	5%

3-4 servings/day	-2.3	0.00	0.10	0.04	0.21	8%
2 servings/day	-1.9	0.00	0.16	0.08	0.32	13%
4. Fish Never (Ref)		0.00	1.00			
2 servings /wk	-3.1	0.00	0.04	0.02	0.10	3%
1 serving/wk	-2.7	0.00	0.06	0.03	0.15	5%
5.Fresh potatoes (cooked) Never (Ref)		0.00	1.00			
4 or more servings/wk	-1.9	0.00	0.15	0.08	0.28	13%
2-3 servings/wk	-1.7	0.00	0.18	0.10	0.33	15%

4.4. Discussions:

Nutrition has long been suggested to impact breast cancer etiology in about 35% of disease cases (Jaffee EM et al., 2017), the sufficient consumption of foods containing the essential nutrients is crucial to the modification of breast cancer risk in women.The studied foods commonly consumed on the Mediterranean island of North Cyprus, which include, fresh potatoes, Olives and olive oil, fruits and vegetables, eggs, and fish reduced the probability of breast cancer in all the women, proving that they are among the healthiest diets (Willet WC et al.,1995). Interestingly, the intake of fish 2 or 1 times per week followed by 5 or more times of olives and olive oil provided the highest protection in reducing the probability of breast cancer disease in the women. A case-control study situated in Italy with 2,569 breast malignant growth cases and 2,588 controls found an inverse relationship with fish intake, especially among post-menopausal women (Braga C et al., 1997) linked to the consumption

of dietary marine n-3 polyunsaturated unsaturated fatty acids (Zheng Ju-Sheng et al., 2013).

While an epidemiological and experimental proof recommended that olive oil may decrease the risk of specific tumors, specifically breast cancer (Psaltopoulou T et al., 2011), this may be due to the high monounsaturated fat content and concentration of poly-phenolic compounds in virgin and extra-virgin olive oil (Lopez-Miranda J et al., 2010). These are the main wellspring of lipids within the customary Mediterranean diet (Quantitative score (14-item) of adherence to the Mediterranean diet). According to studies Mediterranean dietary lipids have been shown to impact breast cancer. (Escrich E et al., 2006) These Lipids play a significant role in the regulation of biological activity and are important components of the cell membrane (Hulbert AJ et al., 2005). But when the concentration of polyunsaturated lipids in membranes is too high it may lead to an upsurge in fluidity and peroxidation. (Konstantinidou V et al., 2010) Thus moderate consumption of these lipids is effective in decreasing oxidation damage in the membranes (Kritchevsky D 1999). The protective effect of the intake of Mediterranean dietary lipids on breast cancer may be through the signaling pathways such as ErbB4-truncated protein, which plays a part in mammary development and breast cancer and Akt parthway linked to apoptosis. (Jiang W et al., 2012) Mediterranean dietary lipids may decrease proliferation via the down surge of epidermal growth factor-2 signaling pathway as Ki-67 has been shown to decrease following the administration of lipids in malignant and benign breast neoplasm. (Yee LD et al., 2013 & Harahap WA et al., 2018). Dietary Lipids influence the decrease of factor-kB nuclear translocation and signaling on peroxisome proliferation-activated gamma receptor and through the interaction with the G-protein receptor GPR 120, which reduces apoptosis inhibitors and

cytokines adhesion molecules. (Calder PC 2013). Dietary lipids from Mediterranean foods are shown to partially and beneficially affect the expression of atherosclerosis-related genes,(Solanas M et al., 2010) Tumor suppressor gene p53 expression increased with the intake of fish sourced docosahexaenoic acid (DHA) (Escrich E et al., 2011). Phenolic extracts from Brava extra virgin olive oil minimized cell viability and induced cell death in MCF-7 breast cancer cells (Reboredo-Rodriguez P et al., 2018). BRCA1 and 2 genes also increased with exposure of breast cells lines to omega-3 polyunsaturated fatty acid (EPA and DHA) from fish (Bernard-Gallon DJ et al., 2002). An accompanied decrease in Her-2/neu an oncogene has been seen in BT-474 and SKBr-3 breast cancer cells treated with oleic acid supplements. (Menendez J et al., 2005) Dominguez et al observed a 30% lower risk of breast cancer linked to glutathione-S-transferase T1 null genotype in post-menopausal Chinese women living in Singapore after the intake of marine dietary lipids from fish. (Gago-Dominguez M et al., 2004) The benefits were more in post-menopausal women with GST polymorphisms that led to low or no GSTT1, GSTP1 and GSTM1 activity. (Gago-Dominguez M et al., 2004)

To be able to recommend the right nutrition for a given population, it is important to find the dietary intake that incorporates all the nutrients required (Roman-Vinas B et al., 2009) and when consumed in the right amounts will provide optimum benefits.The ability of a diet to provide prevention and reduction to diseases that are linked to it determines its nutritional sufficiency (Dhonukshe-Rutten RA et al., 2013) and genotype may be determining factor on how these nutrients are made available for body use and function. The frequency of polymorphism differ with ethnicity this interplay needs to be studied to find out how breast cancer can be modified by food intake in relation to genotype (Lenihan-Geels G et al., 2016) in this population. Most societies especially the developing

societies can explore the advantages of Mediterranean diets through research that look for diets that are affordable, effective and locally available source of sufficient micronutrients that can reduce the risk of breast cancer. The long-term control of breast cancer can be achieved, when the association between culture and nutritional selections are considered when making policies because most societies consider food as an essential part of their cultures, religious and social experiences.

Policies and programs that advocate home farms and gardens can lead to the increase availability, affordability and consumption of healthy foods such as potatoes, vegetables, fruits, eggs, fish, and olives in developing societies.Also encouraging with incentives people to set up neighbor-hood supermarkets and eateries that sell these foods will improve affordability and availability.Agricultural subsidies in developing societies for producers of these foods will encourage others to start producing thus reducing cost and increasing availability.

Cultural festivals that promote and protect healthy foods are Important in sustaining healthy eating. Civil society organizations such as farming and fishing cooperatives, religious groups, charitable organizations, women groups, should play a part in public policies creation and implementation.

Transnational food trade with proper regulations will enable the availability of variety of healthy foods coming from across the borders. Governments of developing societies that want to ensure that nutritional objectives are adhered to in other to improve the well being of their citizens need to carry out school and public education campaigns on diets and engage the food and agriculture sectors (2002.National Cancer Control Programmes,Policies and Managerial Guidelines,2nd ed.Geneva:WHO). The awareness on the pivotal role of these diets in breast cancer prevention will go a long way in increasing implementation of policies and programs that target the right

population.Our study was carried out in a typical Mediterranean setting and reproducible. The cognitive impairment arising from illness and treatment may influence the answers provided by some breast cancer patients but to overcome this, patients were ensured to be in stable state by qualified medical practitioners before the interviews was conducted. The case-control study method used has its limitations in the sense that the information collected is subject to recall bias. To minimize this a few food items were used in the food frequency questionnaire and the consumption categories were such that the participants could easily recall. However such bias may not affect the results because the true effect may not be far from what was observed. The completeness of answers to the food items was used as a conformity test. (Moisan J et al., 1990).Despite the limitations considering that the dietary habits of the people of North Cyprus is similar to the traditional Mediterranean diets, an investigation of its effect on breast cancer risk is needed at the very moment because of the increase onset of the disease.

4.5. Conclusion:

The Mediterranean diet has been shown to confer lots of health benefits and the intake of olives and olive oil 5 or more times daily, and fish 2 times weekly more significantly reduced the risk of breast cancer risk in the women of North Cyprus.

CHAPTER 5

CONCLUSION AND FUTURE PERSPECTIVE

In conclusion this thesis firstly, suggests that breast cancer risk prediction models can be suitable, simple, cost-effective, and non-invasive tools for the identification of high-risk women. They may also serve as a gate-keeper for mammography and a radiation saving tool for low risk women. Secondly, the development of a new risk model will allow for the prediction of late on-set breast cancer in the women of North Cyprus. Finally, Mediterranean diet has been shown to confer lots of health benefits and the intake of olives and olive oil 5 or more times daily, and fish 2 times weekly more significantly reduced the risk of breast cancer risk in the women of North Cyprus. Further studies on a larger study group,thatincorporates more risk factors including environmental risk factors will be needed to improve the model. The benefits of the studied foods can only be maximized when the appropriate policies that encourage the intake of healthy diet are established. The protection against breast cancer in comparison with other foods may be genotype related and calls for a need to study on a large scale the interplay between dietary intake in association with the genotype of this population.

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ARTICLES FROM THESIS

Published article

1.Title: Risk prediction model development for late on-set breast cancer screening in low-and middle-income societies: A model study for North Cyprus

Ceasar Dubor Danladi & Nedime Serakinci.(2020) Risk prediction model development for late on-set breast cancer screening in low –and middle-income societies: A model study for North Cyprus.Healthcare, 8, 213.

Submitted articles

1.Title: Breast cancer risk prediction models as screening tools for high-risk women in low-and middle-income societies: A pilot case-control study in North Cyprus (Under review)

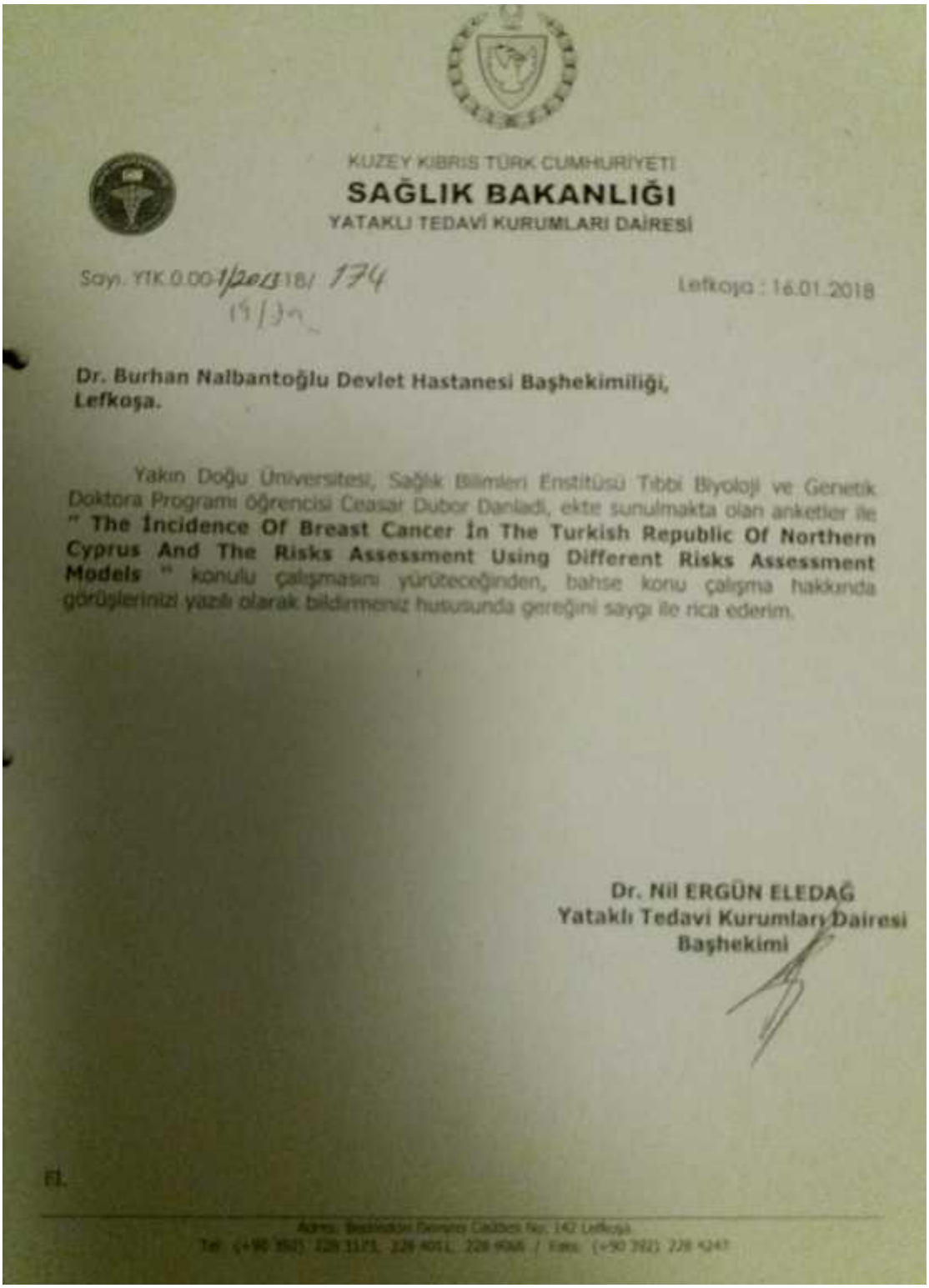
By Ceasar Dubor Danladi & Nedime Serakinci

2. Title: Role of food choice for breast cancer prevention in developing societies: A case-control study in North Cyprus (Under review)

By Ceasar Dubor Danladi & Nedime Serakinci

APPENDIX A:

AUTHORISATION LETTERS



KUZEY KIBRIS TÜRK CUMHURİYETİ
SAĞLIK BAKANLIĞI
YATAKLI TEDAVİ KURUMLARI DAİRESİ

Sayı: YTK.0.00-1/2013/18/ 174
15/3

Lefkoşa : 16.01.2018

Dr. Burhan Nalbantoğlu Devlet Hastanesi Başhekimiliği,
Lefkoşa.

Yakın Doğu Üniversitesi, Sağlık Bilimleri Enstitüsü Tıbbi Biyoloji ve Genetik Doktora Programı öğrencisi Ceasar Dubor Danladi, ekte sunulmakta olan anketler ile **" The İncidence Of Breast Cancer İn The Turkish Republic Of Northern Cyprus And The Risks Assessment Using Different Risks Assessment Models "** konulu çalışmasını yürüteceğinden, bahse konu çalışma hakkında görüşlerinizi yazılı olarak bildirmeniz hususunda gereğini saygı ile rica ederim.

Dr. Nil ERGÜN ELEDAĞ
Yataklı Tedavi Kurumları Dairesi
Başhekimi

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K.K.T.C SAĞLIK BAKANLIĞI
DR.BURHAN NALBANTOĞLU
DEVLET HASTANESİ

Sayı:YTK.1.01

Tarih: 24 Nisan 2018

Sn. Ceasar Dubor Danladı,

Etik Kurulumuzun 19 Nisan 2018 tarihinde yapmış olduğu toplantıda, " Meme kanserinde risk değerlendirmede RD modelinin oluşturulması amacı ile farklı RD metod ve yaklaşımlarının kullanılması " konulu araştırmanız tarafımızdan değerlendirilmiş olup Etik Kurulumuz tarafından uygun görülmüştür.

Bilgilerinize saygılarımızla sunulur, başarılar dileriz.

Etik Kurul YK adına
Doç Dr Düriye Deren Oygar

Doç. Dr. Düriye Deren OYGAR
İç Hastalıkları ve Nefroloji Uzmanı
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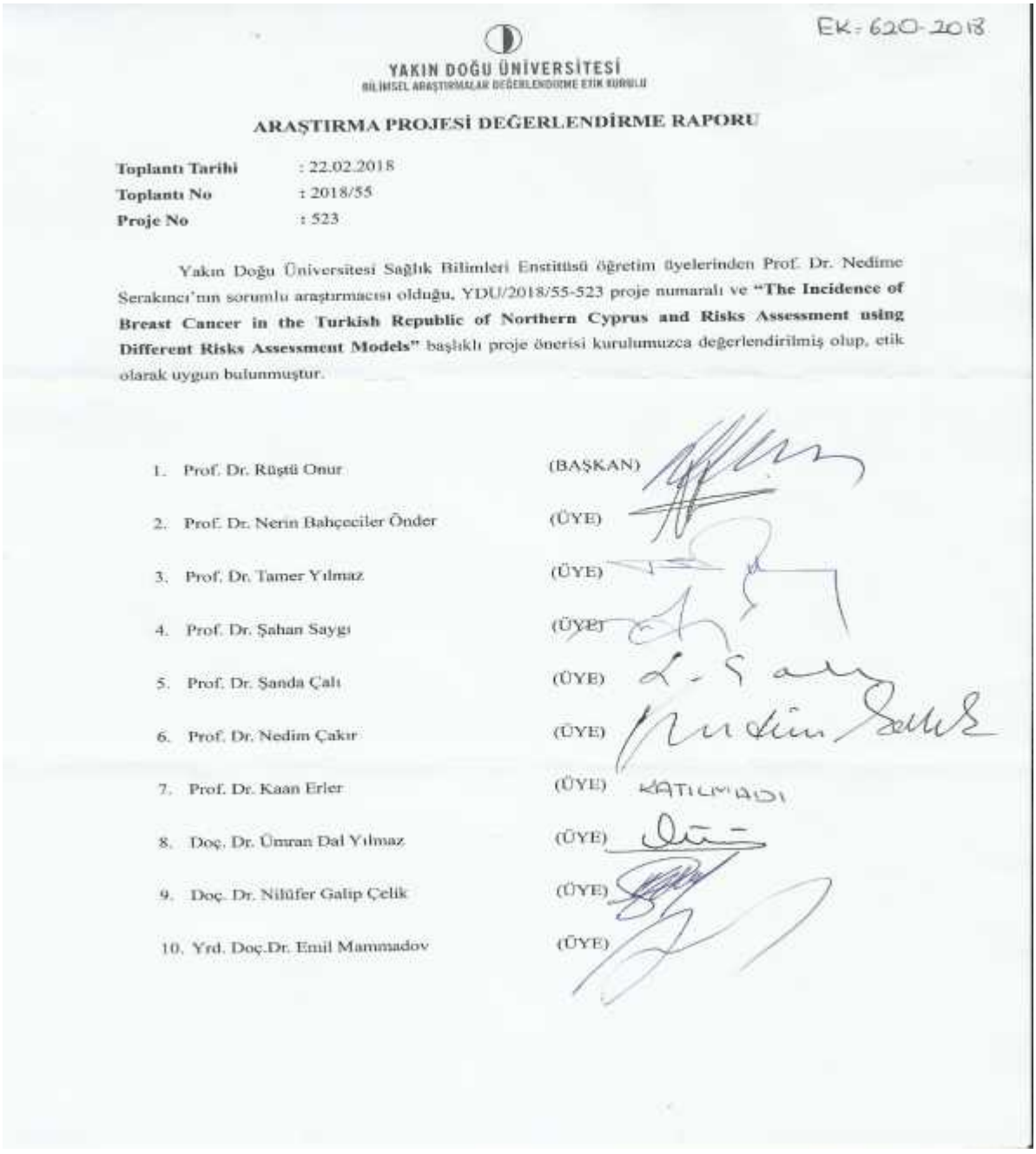
APPENDIX B:

ETHICS COMMITTEE APPROVAL



EK: 620-2018

YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR DEĞERLENDİRME ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 22.02.2018
Toplantı No : 2018/55
Proje No : 523

Yakın Doğu Üniversitesi Sağlık Bilimleri Enstitüsü öğretim üyelerinden Prof. Dr. Nedime Serakıncı'nın sorumlu araştırmacısı olduğu, YDU/2018/55-523 proje numaralı ve **"The Incidence of Breast Cancer in the Turkish Republic of Northern Cyprus and Risks Assessment using Different Risks Assessment Models"** başlıklı proje önerisi kurulumuzca değerlendirilmiş olup, etik olarak uygun bulunmuştur.

1. Prof. Dr. Rüştü Onur (BAŞKAN)
2. Prof. Dr. Nerin Bahçeciler Önder (ÜYE)
3. Prof. Dr. Tamer Yılmaz (ÜYE)
4. Prof. Dr. Şahan Saygı (ÜYE)
5. Prof. Dr. Şanda Çalı (ÜYE)
6. Prof. Dr. Nedim Çakır (ÜYE)
7. Prof. Dr. Kaan Erler (ÜYE) KATILMADI
8. Doç. Dr. Ümran Dal Yılmaz (ÜYE)
9. Doç. Dr. Nilüfer Galip Çelik (ÜYE)
10. Yrd. Doç.Dr. Emil Mammadov (ÜYE)

APPENDIX C:

INFORMED CONSENT

Consent for Participation in answering a Research questionnaire

I volunteer to participate in a research project conducted by Ceasar Dubor Danladi a student of medical Genetics department, Institute of health science, Near East University, Northern Cyprus. I understand that the project is designed to gather information for breast cancer risk assessment.

1. My participation in this project is voluntary. I understand that I will not be paid for my participation. I may withdraw and discontinue participation at any time without penalty.

2. I understand that most of the questions will be interesting and thought-provoking. If, however, I feel uncomfortable in any way with the questions, I have the right to decline to answer any question.

3. Participation involves answering a questionnaire.

4. I understand that the researcher will not identify me by name in any reports using information obtained from this questionnaire, and that my confidentiality as a participant in this study will remain secure. Subsequent uses of records and data will be subject to standard data use policies which protect the anonymity of individuals and institutions.

5. I understand that this research study has been reviewed and approved.

6. I have read and understand the explanation provided to me. I have had all my questions answered to my satisfaction, and I voluntarily agree to participate in this study.

_____ My Signature

For further information, please contact:

[Ceasar Dubor Danladi] [Tel:+905338617896, Email: danladiceasar@ymail.com]

_____ Date

_____ Signature of the Investigator

APPENDIX D:

CURRICULUM VITAE

NAME: DANLADI CEASAR DUBOR

OBJECTIVE: An enthusiastic molecular biologist and human geneticist. Motivated towards working and contributing to the development of a reputable organization through hard work,teamwork and effective communication.

TEL. NUMBERS: +905338508359, +2349096602148

EMAIL ADDRESS: danladiceasar@ymail.com

EDUCATIONAL QUALIFIACTIONS:

PhD. Medical Biology and Genetics 2020

Near East University,North Cyprus

Distinction

MSc. Molecular Biology 2014

V.N Karazin Kharkiv University,Ukraine

Distinction

BSc. Molecular Biology 2013

V.N Karazin Kharkiv University,Ukraine

Second class upper

BSc. Biochemistry 2008

Ahmadu Bello University,Nigeria

Second class lower

MEMBERSHIP OF ACADEMIC AND PROFESSIONAL BODIES/ASSOCIATIONS:

Near East University Genetics Society

International Society for the Study of Time

ACADEMIC RESEARCH:

A.I.Bozkov,N.I.Kurguzova,T.V.Krivoruchko,E.N.Lebed,A.O.Mikhailets, **C.D.Danladi**,A.A.Bozhkov,M.S.Girich,2014.A cyclic feeding regime: A new model in experimental gerontology. Advances in gerontology,2014,vol.27,no.2pp.328-335.

C. D. Danladi, N.Serakinci, A.Bozhkov,2017.The influence of cyclic feeding regime on the RNA/DNA ratio of hepatocyte nuclei of young and old rats, Scientific Research Journal (SCIRJ), Volume V, Issue XI, November 2017 72 ISSN 2201-2796.

C. D. Danladi, N. Serakinci.Breast cancer risk prediction models as screening tools for high-risk women in low and middle-income societies: a pilot case-control study in North Cyprus. Under Review.

C. D. Danladi, N.Serakinci, A.Bozhkov.Periodic calorie intake stimulates chromatin condensation in the hepatocytes nuclei of old rats. Under Review.

C. D. Danladi, M. Girrich, A. Bozhkov Intermittent fasting with limited calorie intake improves some anti-atherogenic serum proteins in old rats. Under Review.

C. D. Danladi& Nedime Serakinci.(2020) Risk prediction model development for late on-set breast cancer screening in low –and middle-income societies: A model study for North Cyprus.Healthcare, 8, 213.

C.D. Danladi&Nedime Serakinci. Role of food choice for breast cancer prevention in developing societies: A case-control study in North Cyprus. Under Review.

CONFERENCES AND WORKSHOPS:

Next Generation Sequencing 2017 Symposium and Workshop on “Data Interpretation”,”Illumina Training”,NGS in Diagnostics”.Near East University, North Cyprus.

“Life Long Learning in Healthcare” training 2017.Faculty of Pharmacy Near East University. North Cyprus.

Proteomics and Aging workshop 2013.V.N Karazin Kharkiv University,Ukraine.

Renewable energy resources for rural development 2009.Nigeria.

COMMUNITY SERVICE:

Social and Charity Community Development Service, Maiduguri, Bornu State 2008-2009.

AWARD:

Kaduna State Overseas Scholarship Scheme 2014/2015.

SPOKEN LANGUAGES:

Hausa, English, Russian and Turkish Languages.

WORK EXPERIENCE:

Student Employment

January 2018 to December 2018

Ciddi Mutfak-Lefkosa,North Cyprus.

Sales Representative

January 2015 to October 2016

Green World Health Nutrition and Supplements

Trainee

January 2010 to July 2011

Exquisite art gallery-Gwagwalada, Abuja, Nigeria.

National Youth Service Corp

Medical record and laboratory scientist

September 2008 to August 2009

Divine hospital and maternity-Maiduguri, Bornu, Nigeria.

Student Industrial Attachment

Medical record and Laboratory scientist

January 2005 to July 2005

University of Abuja teaching hospital-Gwagwalada, Abuja, Nigeria.

HOBBIES AND INTEREST

Sports, learning new things, meeting people, creative interactions.

REFERENCES

Prof.Dr. Nedime Serakinci
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