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NEAR EAST UNIVERSITY

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INCIDENCE AND TREND OF CANCER IN NORTH CYPRUS, AND BREAST CANCER RISK ASSESSMENT IN TURKISH CYPRIOT WOMEN

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ABSTRACT

The aim of this study is to investigate the incidence and trend of all cancers and to assess the risk factors particular for breast cancer (BC) in the Turkish Republic of Northern Cyprus (TRNC). To this aim, the thesis is divided into two sections.

In the first part of this study, the incidence, trends, and common types of cancer in TRNC were analysed based on data obtained from the office of the North Cyprus Cancer Registry, Ministry of Health, for 2007–2012. Data were arranged on the basis of age group, sex, and cancer types. Age-standardized incidence rates (ASRs) were estimated with the world standard population. EVIEWS (version 9) and Excel software were used for statistical analysis. The results indicated that of 1395 registered cancer cases, 52.33% (730) were reported in men and 47.67% (665) in women. The crude incidence rate was 96.41 in men and 101.74 in women. The average annual ASR was 88.88 in men and 87.76 in women with the cumulative rate of 21.47% and 14.69% in men and women, respectively. The most common cancers in men were skin (ASR 15.62), prostate (ASR 11.23), bladder (ASR 11.71), lung (ASR 8.01), and colorectal cancer (ASR 7.61), while in women were breast (ASR 24.07), thyroid (ASR 14.93), skin (ASR 10.75), colorectal (ASR 6.05), and lymphoma (ASR 4.79). Linear regression analysis confirmed rising trends for both men's (10.79, $p \leq 0.03$) and women's (14.67, $p \leq 0.04$) cancers. It is concluded that cancer incidence in the Turkish Republic of Northern Cyprus shows an increasing trend and breast cancer in women exhibits the highest incidence rates and cumulative risk

In the second part of this study, the strength of the association between the recognised BC risks and BC were investigated. Additionally, other potential risks of breast cancer were also investigated that are specific to the North Cyprus population.

This case-control study comprises 408 BC cases and 412 age-matched control recruited from Near East Hospital and Dr Burhan Nalbantoglu State Hospital in North Cyprus. Information regarding clinical and epidemiological characteristics were collected using a structured questionnaire through the standardised interview. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated by

logistic regression before and after adjusting for any potential confounding effects caused by other factors. SPSS version 20 software were used for statistical analysis.

The mean age at diagnosis of the cases was 57.7 ± 6.5 years, while the mean age of the control group was 57.5 ± 6.4 years. In addition to various recognized BC risk factors (i.e., family history, early menarche, late menopause, late pregnancy, history of past biopsy and FBD (Fibrocystic Breast Disease), strong associations with BC risk were reported from women with the following conditions: used fertility drugs for more than 6 cycles (OR = 3.305, 95% CI 1.850-5.906, $p < 0.001$); depression (OR = 2.10, 95% CI 1.33-3.30, $p < 0.001$); exposure to radiation (OR= 1.74, 95% CI 1.02-2.98, $p = 0.041$); excess consumption of oil/fats (OR = 2.703, 95% CI 1.62-4.48, $p < 0.001$) and sugar (OR =3.42, 95% CI 1.39-8.40, $p = 0.007$). However, strikingly parental consanguinity (OR = 0.16, 96% CI 0.09-0.30, $p < 0.001$) and daily water intake of 1-2 litre (OR = 0.36, 95% CI 0.19-0.66, $p < 0.001$) were protective against BC risk.

Our results demonstrate and confirm the presence of classical risk factors as well as several additional risks specific to this population. Thus, the findings will be of great benefit in establishing adequate evidence-based awareness and preventative measures for BC in North Cyprus population.

Keywords. breast cancer, risk factors, Northern Cyprus, odds ratios, cancer incidence

ÖZ

Bu araştırmanın amacı tüm kanser tiplerinin eğilimini ve insidansını araştırmak ve özellikle Kuzey Kıbrıs Türk Cumhuriyetindeki meme kanserindeki (GK) risk faktörlerini hesaplamaktır. Bu amaçla tez 2 bölüme ayrılmıştır.

Bu çalışmanın ilk bölümünde, kanser insidansını , eğilimini ve Kuzey Kıbrıstaki en yaygın tiplerini araştırdık.Toplanan verilerin kaynağı 2017-2012 arası (2010 yılı dışarda bırakılarak) Kuzey Kıbrıs Kanser Kayıtçılığı ,Sağlık Bakanlığı' dır. Temel data yaş, cinsiyet ve kanser tipleri baz alınarak gruplandırılmıştır. Kaba insidans hizi, yaş standandardize edilmiş insidans oranı (ASR), kumulatif oran ve kumulatif risk hesaplanmıştır. Eviews 9 versiyonu ve Excel yazılımı kullanılmıştır.

Çalışma esnasında toplam kayıtlı vaka 1395 tir, 730 (52%) erkek ve 665 (48%) kadındır. Kuzey Kıbrıs için hesaplanmıiş kaba insidans hizi (crude rate) erkek için 96.41 , kadın için ise 101.74 tür. Erkekte ASR 88.88 iken kadında 87.76 dır. Kuzey Kıbrıstaki kumulatif kanser oranı erkek için 21.47% , kadın için ise 14.69% ' tir. Üstelik, hem erkek (10.79, $p \leq 0.03$) hem de kadın için (14.67, $p \leq 0.04$) bu çalışma periodu boyunca kanser eğiliminde artış kayıt edilmiştir. Erkekte yaygın kanser tipleri sırasıyla ASR değerleriyle der, prostat, idrar kesesi, kolorektal ve akciğer kanseridir, 15.65, 11.23, 11.71, 8.01, 7.61. Kadında ise yaygın olarak meme, tiroid, deri, kolorektal ve lenfoma kanserleridir ki sırasıyla ASR değerleri, 24.07, 14.93, 10.75, 6.05, 4.79 dur.

Sonuç olarak Kuzey Kıbrıs Türk Cumhuriyetinde kanser insidansının artış gösterme eğilimindedir ve bunların içinde en çok meme kanseri kadınlarda en yüksek insidans oranında ve kumulatif risktedir.

Bu çalışmanın ikinci bölümünde, tanımlanmış GK riskleri ve GK nin arasındaki güçlü ilişki araştırılmıştır. İlave olarak, Kuzey Kıbrıs nüfusuna özel diğer potansiyel meme kanseri riskleri de araştırılmıştır.

Bu vaka kontrol çalışması Yakın Doğu Hastanesi ve Kuzey Kıbrıs Türk Cumhuriyeti Dr. Burhan Nalbanoğlu Devlet Hastanesinden alınan 408 GK (Meme Kanseri) vakasını ve 412 yaş uyumlu kontrol vakalarını kapsamaktadır.

Medikal ve epidemiyolojik niteliklerle ilgili bilgiler, standart mülakatlardan yapılandırılmış anketler kullanılarak toplanmıştır.Yaş ayarlı göreceli risk oranları (OR) ve 95% uyumlu aralık (CI), diğer faktörlerin sebep olduğu, önce ve sonraki potansiyel çelişen etkileri ayarlayarak lojistik regresyonla hesaplanmıştır.

Vakaların tanısındaki ortalama yaş 57.7±6.5 yaşlardır, ki kontrol grubunun ortalama yaşı 57.5 ± 6.4 yaşlardır. Çeşitli tanımlanmış GK risk faktörlerine ek olarak (aile geçmişi, erken adet, geç menapoz, geç hamilelik, geçmiş biyoysi tarihi ve fibrokistik meme hastalıkları) GK riski olarak güçlü ilişki olarak kadınlar için aşağıdaki durumlar için kayıtlandırılmıştır : 6 dönemden fazla gebe kalmak için kullanılan ilaçlar (OR = 3.305, 95% CI 1.850-5.906, p < 0.001); depresyon (OR = 2.10, 95% CI 1.33-3.30, p < 0.001); radyasyona maruz kalma (OR= 1.74, 95% CI 1.02-2.98, p = 0.041); yağın fazla tüketilmesi (OR = 2.703, 95% CI 1.62-4.48, p < 0.001) ve şeker (OR =3.42, 95% CI 1.39-8.40, p = 0.007). Ayrıca, çok önemli olarak ailesel kan bağı (OR = 0.16, 96% CI 0.09-0.30, p < 0.001) ve günlük 1-2 litre su alımı (OR = 0.36, 95% CI 0.19-0.66, p < 0.001) meme kanseri riskine karşı önleyicidir.

Sonuçlarımız, birkaç ilave bu populasyona göre olan riskleri göstermekte olduğu gibi, klasik risk faktörlerinin varlığını da göstermekte ve onaylamaktadır.Bulguların delil temelli yeterli farkındalık yaratmada ve Kuzey Kıbrısta meme kanseri için önleyici tedbirler açısındanda büyük faydası olacaktır.

Anahtar kelimeler: Meme kanseri, risk faktörleri, Kuzey Kıbrıs, odds Oranı, kanser insidansı

DEDICATION

To My Parrents

ACKNOWLEDGMENT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ASR   Age-standardized rate

BC   Breast cancer

BMI   Body mass index

BRCA1   Breast cancer1

BRCA2   Breast cancer2

CI   Confidence interval

CR   Crude rate

DDE   Dichloro-diphenyl-dichloroethylene

DDT   Dichlorodiphenyltrichloroethane

DNA   Deoxyribonucleic acid

EVIEWS   Econometric views

FBD   Fibrocystic breast disease

FFDP   Full fats dairy products

FTP   Full-term pregnancy

HRT   Hormonal replacement therapy

OD   Odds ratio

PCB   Polychlorinated Biphenyls

PMD   Premenstrual depression

SPSS   Statistical package for social science

TRNC   Turkish Republic of Northern Cyprus

CHAPTER 1

INTRODUCTION

1.1. Cancer

Cancer is the collection of related diseases with uncontrolled cell division and spreading to the surrounding tissues (National Cancer Institute). Cancer is a genetic disease caused by one or more mutation in certain genes that control normal cell function i.e. cell growth and division. These mutations may be inherited from parents (germline mutation) or somatic, and (acquired as a result of exposure to certain chemicals or radiations that damage the DNA (Lodish et al., 2000).

A cancer cell has a variety of genetic changes than normal cells, thus there are person wise differences in the genetic mutation of cancer, and each person has a different combination of mutation in their cancer than other. Some of these mutations arise as a result of cancer not due to only the cause. With the growth of cancer tumour, additional mutations arise and even different cells in the same tumour have different types of mutations (National Cancer Institute). Recently, it is known that genomic instability is the characteristics of various cancers. In hereditary cancers, a mutation in DNA repair genes results in genomic instability in DNA that result in cancer development (Yao et al., 2017).

1.2. Hereditary cancer syndrome

Genetic mutation inherited from parents to an individual that make it susceptible to early onset cancer is called the hereditary cancer syndrome (Clause et al., 1996). Often, these alterations in genes result in cancers that affect numerous tissues and mostly exhibited autosomal dominant inheritance. Various gene variants are associated with more than 50 types of hereditary cancer syndromes. One of the most common hereditary cancer syndromes is breast and ovarian cancer syndrome. Approximately 7% of the breast malignancy and 10% of ovarian malignancy are due to hereditary alteration in some tumour suppressor genes, frequently BRCA1 and BRCA2 (Clause et al., 1996).

Most of the malignancy developing genes fall into two categories, oncogenes and tumour suppressor genes (Weinberg, 1996), both are functionally different. When **Oncogenes** are mutated often induces a growth advantage to a cell (gain of function). Conversely, when a malignancy arises due to the loss of function of a gene, is considered **tumour suppressor gene**. As there are two copies of each chromosome, and thus each gene, a loss of function mutation in a single copy of the gene is usually not deleterious to the cell. As each tumour suppressor gene has a backup copy, therefore, if the other copy is also mutated, the inactivation of both copies of genes attains loss of function and advance to malignant transformation. (Claus et al., 2001). **DNA repair genes** are the third category of genes responsible for carcinogenesis when mutates. In the normal state, they are involved in fixing the damaged DNA within the cell. When these genes mutate, additional mutations develop in other genes. Together these mutations transform the cell to a cancerous state.

1.3. Cancer incidence

Cancer is the main health problem and a common cause of death worldwide, (Allemani et al., 2015). It is the second most common cause of mortality in Europe (WHO 2014). Up to 40% of the cancer deaths occur in Europe and each year 3.2 million new cancer cases (almost 54% if these cases are in men and 46% in women) register that are about one-quarter of all global cancer burden (WHO 2014). Although, variations exist in the prevalence of cancer in different parts of Europe, in the Northern and Western Europe the prevalence is highest while in the Mediterranean countries it is lower. In some Central and Eastern European countries, the lung cancer is the common cancer type while in other almost all parts of Europe, prostate cancer is the common cause of cancer mortality (Adamson et al., 2007; OECD 2008).

International prevalence and death from 27 major malignancies were reported by Ferlay et al (2012), according to their report, 14.1 million new cases and 8.2 million deaths were reported in 2012. The most prevalent cancers worldwide were lungs, breast and colorectal. While lung cancer, liver cancer, and stomach cancers were the common cause of cancer mortality (Ferlay et al., 2012), Similarly, 3.45 million new cases of 24 major cancer types in 40 European countries has been reported in the year

2012. Female breast, lung, colorectal, and prostate were the most common cancer sites (Ferlay et al., 2012).

Previously, Hinçal et al., (2008) carried out an investigation regarding the prevalence of cancer in relation to the incidence in other parts of Europe, for the years 1990–2004. This analytical study was based on the data collected from the cancer registry. Their results suggested the skin, lung, colorectal, bladder, brain, liver, prostate, and stomach as the most frequent sites for primary cancer in men. While in women, breast, gynaecological, colorectal, skin, lung, stomach, liver, bladder and brain cancer were common types (Hinçal et al., 2008).

Farazi (2014) analysed the cancer trend and risk factors in Cyprus, and showed an increasing trend of cancer between 1998 and 2008, with prostate cancer the most common subtypes in men. In women, breast cancer was reported to be more frequent. According to the findings of that study, thyroid cancer showed increasing trend in women while colorectal cancer was increasing both in men and women in the study period. The study showed overall lowered cancer incidence in Cyprus than other European countries analogous to Cyprus in their geography and lifestyle (Farazi 2014).

DeSantis et al (2015) analysed the data from GLOBOCAN 2012 to examine the global trend in female breast cancer rates for 39 countries. The analysis indicated that the breast cancer incidence rate has increased from 1993 in 9 countries in North West Europe, while their mortality rate has decreased. In France, Israel, Italy, Norway, and Spain the incidence and mortality rates have decreased, while in Colombia, Ecuador, and Japan both the incidence and mortality rates have increased (DeSantis et al., 2015).

1.4. Cancer risk factors

The exact aetiology of cancer is still not clear, however, research has identified certain factors that are associated with a person chance of developing cancer. The most studied potential risk factor for cancer are ageing, alcohol use, endogenous and exogenous exposure to hormones, lack of physical activity, obesity, radiation, sunlight, tobacco smoke, chronic inflammation, and several dietary factors (Mena et al., 2009).

1.5. Breast cancer risk factors

Breast cancer (BC) is the most frequent malignancy in the women with approximately 1.7 million cases and more than 0.52 million deaths reported in 2012 (Torre et al., 2015). Each year 1 in 9 women is at risk of developing the disease (Braunwald 2005). Numerous epidemiological studies over the last three decades have revealed a number of risk factors associated with BC (Kelsey and Horn 1992).

The well-established environmental factors for BC include exogenous and endogenous exposure to hormones, reproductive factors (i.e. age at menarche, parity, age at first full-term pregnancy (FFP), breastfeeding and age at menopause) and lifestyle factors such as smoking (Reynolds 2013), exercise (McNeely et al., 2006), alcohol use (Park 2014) etc. As the reproductive factors cannot be control or change as community health procedures, therefore, these factors called the non-modifiable risk factors (Kelsey 1992). However hormonal and lifestyle risk factors are considered as modifiable risks including prolonged use of menopausal hormone therapy (Santen 2014), excessive use of alcohol (Park 2014), physical inactivity (Wu 2013), and high body mass index (BMI) (Morimoto et al., 2010).

An estimated 30% of germline genotypes are attributed to be associated with the heritability of BC (Mucci et al., 2016). Additionally, women with an affected first-degree relative have two times higher risk of acquiring the malignancy (Pharoah et al., 1997). Certain known hereditary aspects are responsible for greater lifetime risk of BC including rare variants with moderate to high penetrance in BRCA1&2, ATM, PALB2, and CHEK2, as well as approximately 100 common genes variants with low penetrance. These high and low penetrance variants are together attributed to 37% increased risk (Michailidou et al., 2015)

Currently, it is believed that environmental risk factors for BC are of far more significance than the mutation in the high penetrance BC susceptibility genes (BRCA1 and BRCA2) (Demetriou 2012). If a related environmental factor is present, then women carrying certain genetic variants are more prone to developing the malignancy (Strumylaitė et al., 2010). A similar gene-environment interaction has also been recognised for bladder cancer, where smoker with carcinogen metabolising genes

(NAT2 and GSTM1) variants have a higher risk of developing the disorder compared with non-smokers carrying these variants (Chu et al., 2013). Also, alcohol users with gene variants in the alcohol-metabolising pathway (ADH1B and ALDH2) shown to have an increased risk of oesophageal squamous cell carcinoma as compared to non-users (Wu et al., 2012).

In addition to genetic and environmental factors, BC exhibits a wide range of ethnic and geographical variations [Michailidou et al., 2015]. A two-fold difference in BC incidence appears within Europe, being maximum in the North with an estimated 84.6 cases per 100,000 adult women, lowest in Eastern Europe with 42.6 cases per 100,000 women, and with intermediate rates in the South Europe (Parkin et al., 2005).

The relationship between potential breast cancer risk factors and breast cancer has been investigated intensively in various country's population in the last decade (Phipps et al., 2008). Several researchers investigated the relationship between reproductive and lifestyle factors and breast cancer risk (Ferlay et al., 2010).

A case–control study involving 1109 BC cases and 1177 control women participating in breast cancer National screening programme was carried out in Greek Cypriot women in 2010. The study suggested the family history of breast cancer as the strongest predictor of BC risk with 64% increased breast cancer risk. Late age at menarche (after the age of 15 years) and breastfeeding were associated with decreased breast cancer risk. The study also suggested hormonal replacement therapy as a protective factor against breast cancer (Hadjisavvas et al., 2010).

Some of the worldwide recognised risk factors for breast cancer are given below in detail.

1.5.1. Family history/ genetic risk.

One of the most well-recognised risk factors is family history. According to the Institute of cancer research's guideline, a woman with a first-degree relative (mother or sister) with breast cancer has a 2 to 3 folds' higher risk of breast cancer and almost 7% of its prevalence is due to inherited mutations (Cancer Research UK).

Breast cancer is a complex multifactorial disease, develops as a result of the strong association between genetic and environmental factors. Germline mutation in the two breast cancer susceptibility genes BRCA1 and BRCA 2 are thought to account for 5% to 10% of all breast cancer cases. However, a mutation in some other high and low penetrant genes also play a significant role in breast cancer susceptibility (Martin et al., 2000).

1.5.2. Endogenous and exogenous hormones

Research has shown that increased exposure to oestrogen hormones is directly associated with high risk of breast cancer, however, reduced exposure is considered as protective factor (Hulk BC 1996) Therefore, those factors that increase a women exposure to oestrogen, increases the risk factor of developing breast cancer, such as menarche at early age, late menopause and nulliparity (Brinton et al., 2014). Correspondingly, the decreased number of ovulation cycles are considered to be protective factors that can be achieved by moderate exercise and longer lactation period (Bernstein et al., 1994).

Oral contraceptives and hormonal replacement therapy are the primary exogenous hormones commonly used by women. However, the results of various studies show inconsistency about the effects of exogenous hormones on breast cancer risk (Chen 2008). The absence of total consistency among this literature possibly due to the fact that these exposures are not static.

1.5.3. Mammographic density

The non-radiolucent portion of the image on a mammogram is the mammographic density and represents the fibrous and glandular tissues in the breast. Research has indicated that postmenopausal women with a great proportion of mammographic density are at higher risk for developing breast malignancy than women with low mammographic density (Eng et al., 2014). The mechanism involved in this relation is not known, however, insulin-like growth factor 1 is considered to play a role (Pettersson et al., 2014). Also, it is suggested that hormones may play a role in this breast tissues percentage variations (Scheomaker et al., 2014)

Several biological mechanisms were suggested to explain the association between the different phenotypes of mammographic density and breast cancer risk (Pettersson et al., 2014). The dense area of the image in part is positively related to the number of epithelial cells at risk of malignant transformation (Gabrielson et al., 2016). This dense area also represents the fibroblast, stromal cells and fats cells (Huo et al., 2015) and connective tissues (Klock et al., 2016) in the breast, all of them possibly affect the risk of breast cancer (Boyd et al., 2010)

1.5.4. Lifestyle factors

Epidemiological studies in various ethnic groups suggested that higher and even moderate level of alcohol consumption is associated with increased risk of breast cancer (Park, S et al., 2014). Similarly, the cumulative epidemiological evidence demonstrated that breast cancer risk lowers with regular exercise as well as regular exercise also decreases the risk of disease recurrence (Wu et al.,2013). The mechanism behind this association is not fully understood but a minimum of 150 minutes' exercise per week is recommended for breast cancer patients for better prognosis (Dethlefsen et al., 2017).

1.5.5. Environmental agents

In recent years, environmental factors, commonly named endocrine disruptors have gained a great deal of civil and scientific focus. Endocrine-disrupting chemicals are abundant in the environment and their oestrogenic properties are affecting the incidence of endocrine-related diseases including breast cancer (Schug 2011). Organochlorine such as DDT, DDE and PCBs are mostly studied with the relation of breast cancer risk and suggested a positive relation with breast cancer risk (Arrebola et al., 2015).

Turkish Republic of North Cyprus (TRNC) located in the Mediterranean Sea has a population of approximately 0.3 million Turkish Cypriot (Statistical Yearbook 2012). The information regarding recent changes in cancer epidemiology as well as its common types in North Cyprus is not available. As the most appropriate approach towards control and prevention of a disease is to get information on its trend and

incidence. Therefore, we firstly aimed to investigate the incidence, trend and the most prevalent cancer types in the Turkish Republic of Northern Cyprus.

Secondly, as the main cause of morbidity and mortality in women worldwide, we also aim to investigate the main risk factors for breast cancer in women in Turkish Republic of Northern Cyprus.

CHAPTER 2.
First part of the study:

INCIDENCE OF CANCER IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

2.1.   Background and aim of the study

Cancer is the main cause of morbidity and mortality worldwide (Allemani et al., 2015). Up to 70% increase is expected in the worldwide cancer burden in the next two decades (Stewart & wild 2014). The types of cancer that were once more prevalent in the developed world are now diagnosing in underdeveloped countries even with a higher incidence rate (Jemal et al., 2010). Currently, disturbing trends in the prevalence of cancer is reporting from most countries (Thun et al., 2010).

The present status of cancer epidemiology in North Cyprus is unknown, therefore, this study aims to investigate, the incidence, trend and the most prevalent cancers in the Turkish Republic of Northern Cyprus.

2.2.   Data collections

Data were collected from North Cyprus Cancer Registry (NCCR), TRNC Ministry of Health, for the five year's period 2007-2012. The data for the year 2010 was not present at the registry, therefore this year (2010) is not included in the study. Also, there was no compiled data of cancer patients at the registry after the year 2012. The primary data is grouped according to age at diagnosis, sex and organ affected by the primary tumours. Only primary tumour cases were included in the study. Furthermore, only the residence of North Cyprus with a stay of at least half a year before diagnosis are the part of this investigation,

2.3.   Grouping of data

Separate analysis for most common cancer types in men and women were performed.

2.4.   Parameters studied

2.4.1. Crude rate

The cancer incidence is predicted by the crude incidence rate for the current existing population. A crude rate is obtained by dividing the number of total cases of specific cancer by a total number of individuals in a population, multiply by 100,000.

$$CR = R/N \times 100,000$$

R = total number of cases

N = total number of person-years   (Armitage 2008)

2.4.2. Age-standardized incidence rate per 10^5 with world standard population (ASR-W)

As cancer is an age-related disease, therefore it has a high prevalence in those countries that has a high percentage of the aged population compared to those with a young aged population (American Cancer Society 20011). Hence a false outcome is appearing if countries are compared on the basis of the crude rate of cancer incidence. Therefore, the direct standardisation method is used for ASR calculation with world standard population (Adams 2009; Doll 1966; Boyle 1991). Population statistics data for North Cyprus were acquired from statistical yearbooks for the study periods (2007-2012) from the State Planning Organization Statistics and Research Department.

Binomial approximation and 95% confidence interval (CI) were used for the calculation of variance and standard error of the age-standardized rate.

The following formula used,

$$ASR = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i}$$

$$Var\ (ASR) = \frac{\sum_{i=1}^{A}\ (a_i\ w_i^2(100\ 000 - a_i)/n_i)}{(\sum_{i=1}^{A}\ w_i)^2}$$

$$S.e (ASR) = Var (ASR)$$

$$C.I = ASR \pm Za/2 \times (S.e. (ASR)) \text{ (Armitage 2008)}.$$

Σ = Summation, which means the sum of every term in the equation after the summation sign.

a_i= Age specific rate per 100 000 in each age group.

w_i= World standard population in each age group.

n_i= Person years (Every term in the set).

$Z_{a/2}$= 1.69

2.4.3. Cumulative rate and cumulative risk

The cumulative rate is "e (the sum over each year of age of the age-specific incidence rate taken from birth to age 74, 0–74 rate)" and the cumulative risk is "the risk of developing a specific type of cancer at a certain age in the absence of any other cause of death". The cumulative rate and cumulative risk were calculated with the below-given formulas:

$$\text{Cum. Rate (0-74)} = \Sigma \text{ (age specific rate} \times \text{length of age class)}$$

$$\text{Cum. risk} = 100 \times (1\text{-exp (-cum. rate/100))} \text{ (Breslow 1987)}.$$

The 95% confidence intervals were calculated with the following formula:

$$C.I = \text{Cum. Rate ASR} \pm Za / 2 \times (S.e. (\text{Cum. Rate})) \text{ (Armitage 2008)}.$$

2.5. Statistical analysis

Linear regression analysis was used to analyse the trend of cancer in this 5 year's period. All statistical analyses were performed in the EVIEWS and Excel software. $p \leq 0.05$ was considered significant.

2.6.   Study findings

The total registered cases in this study period were 1395, comprised of 730 (52%) men and 665 (48%) women. For both, men and women increasing trend of cancer for this study period were reported. The ASR in men raised from 71.09 in 2007 to 110.12 in 2012. In the same way, ASR for women cancer in 2007 was 66.04 that increased to 120.93 in 2012 (Table 2.1).

skin, prostate, bladder, colorectal and lung cancer were the prevalent types of cancer in men with the ASRs, 15.65, 11.23, 11.71, 8.01, 7.61 respectively. In women, breast, thyroid, skin, colorectal, and lymphoma cancers with the ASRs, 24.07, 14.93, 10.75, 6.05, 4.79 respectively were the most prevalent types of cancer (Figure 2.1).

Table 2.1. Year wise number of cases and age-standardized incidence rate per 100,000 by sex for 2007-2012 (excluding 2010).

Year	Count (Men)	Men ASR/10^5	Count (Women)	Women ASR/10^5
2007	106	71.09	93	66.04
2008	91	59.28	81	57.35
2009	136	83.70	87	59.26
2011	207	116.52	201	125.26
2012	190	110.12	203	120.93
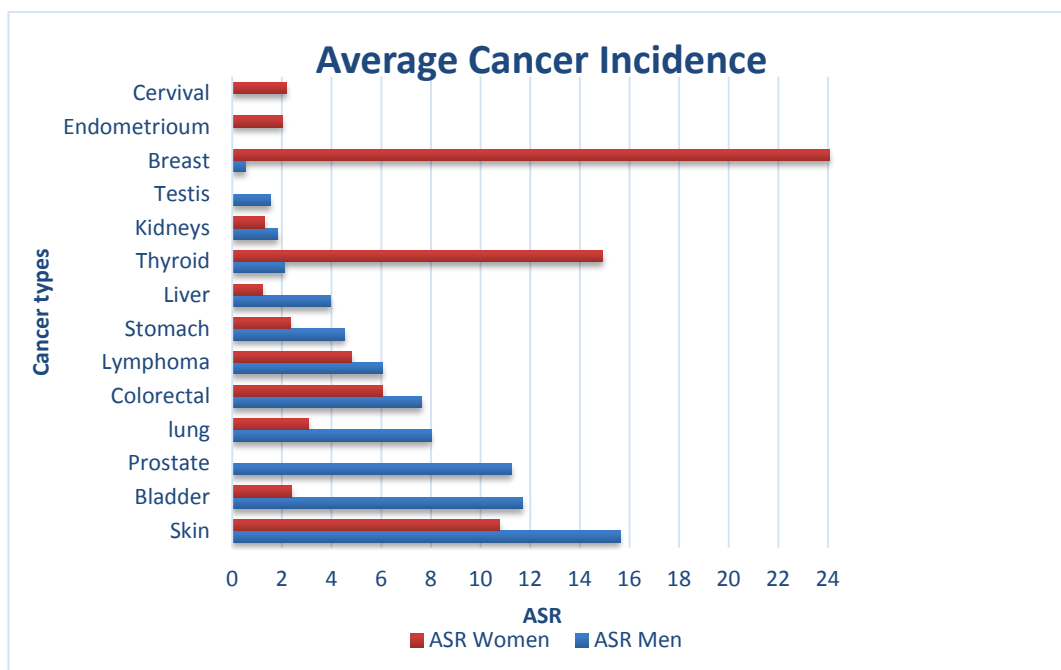
Figure 2.1. Age-standardized incidence rate per 100,000 for different cancer types by sex in the period 2007-2012 (excluding 2010)

A significant incremental linear slope of 10.79 was obtained for men cancer ASR ($p \leq 0.03$) as well as for women (14.67, $p \leq 0.04$) (Figures 2.2 and 2.3).

The crude incidence rate for men was 96.41 and for women was 101.76 per 100,000. The average ASR for this five year's period was 88.88 ± 6.56 in men and 87.71 ± 6.73 in women. While the cumulative rate was 21.47% in men and 14.69% in women. The cumulative risk calculated for this population was 19.32% in men and 13.66% in women (Table 2.2).

In men, the highest incidence rate was reported for skin cancer (ASR 15.62, C. Rate 3.81%, C. Risk 3.74%) with melanoma and non-melanoma collectively (Table 2.2).

The prostate cancer with ASR 11.23 and bladder cancer with ASR 11.71 were the second and third most common cancer in men respectively. The cumulative rate

for prostate cancer was 2.87% and the cumulative risk was 2.82%. The fourth and fifth common cancers in men were lung cancer (8.01) and colorectal cancer (7.61).

In women, the most common type of cancer was breast with ASR 24.07. The thyroid cancer with ASR 14.93 and the skin cancer with ASR 10.75 were the second and third common types in women respectively. Other common types in women were colorectal cancer, lymphoma cancer, lungs cancer, bladder cancer, gynaecological, stomach, kidney, and liver cancer. (Table 2.2).

The breast cancer also reported the highest cumulative rate (4%) and cumulative risk (3.92%). (Table 2.2).

Figure 2.2. the trend of cancer incidence among men in TRNC 2007-2012 (excluding the year 2010)
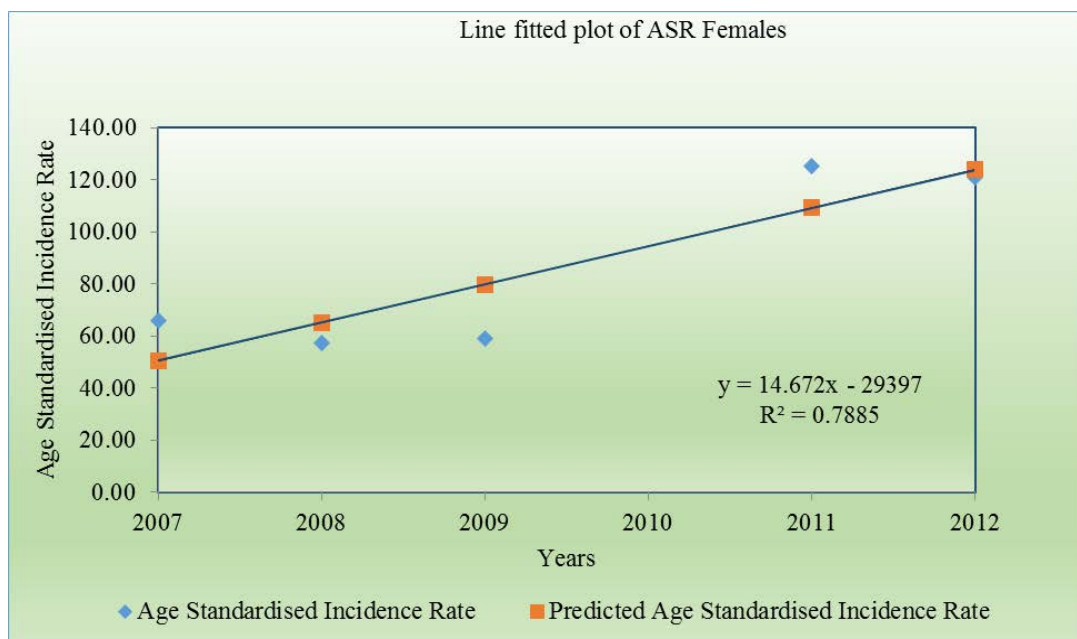
Figure 2.3. Trend of cancer incidence among women in TRNC 2007-2012 (excluding the year 2010)

Table 2.2. Crude rate, the Age-standardized rate with world standard population (ASR_W) per 100,000 with 95%confidence intervals (C.I), Cumulative rate (C. Rate), and cumulative risk (C. Risk) of twelve cancer types by sex, the average for 5 years (2007-2012 ex. 2010), TRNC.

Cancer type	Crude rate	ASR-W/10^5 with 95% C.I	%Cumulative Rate (0-74) with 95% C.I	%Cumulative Risk, (0-74)
Males				
Skin	16.38	15.62 ± 2.78	3.81 ± 0.12	3.74
Bladder	12.15	11.71 ± 2.42	2.78 ± 0.10	2.74
Prostate	12.41	11.23 ± 2.30	2.87 ± 0.11	2.82
Lung	8.45	8.01 ± 1.98	2.86 ± 0.11	2.82
Colorectal	8.32	7.61 ± 1.90	1.39 ± 0.06	1.38
Lymphoma	6.34	6.05 ± 0.44	1.51 ± 0.08	1.49
Stomach	4.75	4.52 ± 1.49	1.49 ± 0.08	1.48
Liver	4.23	3.95 ± 1.39	0.86 ± 0.05	0.86
Thyroid	2.25	2.11 ± 1.01	0.52 ± 0.04	0.52
Kidneys	1.85	1.82 ± 0.96	0.64 ± 0.05	0.63

Testis	1.58	1.53 ± 0.87	0.60 ± 0.05	0.60
Breast	0.53	0.53 ± 0.53	0.07 ± 0.01	0.07
All cancers males	96.41	88.88 ± 6.56	21.47 ± 0.28	19.32
Females				
Breast	28.30	24.07 ± 3.49	4.00 ± 0.09	3.92
Thyroid	16.98	14.93 ± 1.00	2.00 ± 0.06	1.98
Skin	12.24	10.75 ± 2.38	1.49 ± 0.05	1.47
Colorectal	7.19	6.05 ± 1.75	1.28 ± 0.06	1.27
Lymphoma	5.20	4.79 ± 1.63	0.48 ± 0.02	0.48
Lung	3.52	3.07 ± 1.26	0.45 ± 0.03	0.45
Bladder	2.91	2.38 ± 1.09	0.67 ± 0.04	0.66
Stomach	2.45	2.34 ± 1.10	0.55 ± 0.04	0.55
Cervical	2.60	2.20 ± 0.38	0.53 ± 0.04	0.53
Endometrium	2.75	2.01 ± 1.00	0.52 ± 0.04	0.52
Kidneys	1.53	1.30 ± 0.81	0.25 ± 0.02	0.25
Liver	1.38	1.23 ± 0.81	0.15 ± 0.01	0.15
All cancers females	101.74	87.71 ± 6.73	14.69 ± 0.17	13.66

2.7. Discussion

This part of the thesis investigated the trend and incidence of cancer in North Cyprus, for the period of 2007-2012 (excluding 2010). The world cancer burden is on rising; hence, 14.1 million new cancer cases were registered in 2012, while in 2008 the number of newly registered cases was 12.7 million (Ferlay et al., 2008).

The current lifetime risk of developing cancer in the United State are 50% in men and 30% in women, while in 1950 this risk was as lower as 25% in both sexes (men and women) (Clapp et al., 2006). Other developed countries like United Kingdom, Belgium, Germany, Italy, Mexico, Netherland, Poland, and Norway also indicated the similar rise in their cancer incidence (OECD 2004). The lifestyle (obesity, physical inactivity, and smoking etc.) change and environmental factors are believed to responsible for the current rise of cancer (Belpomme et al., 2007; Keyghobadi et al., 2015). According to Irigaray et al., (2007), there are many

carcinogens present in the environment including radiations, insecticide and pesticide, viruses, bacteria, pathogens, food preservatives, hormones and growth factors, pharmaceutical drugs, pollutants, and chemicals in cosmetics etc. that are responsible for the current rise in global cancer incidence (Irigaray et al., 2007).

The world total ASR for all types of cancer in men is 202.0 and in women is165.2 (Ferlay et al., 2015). However, the incidence in TRNC is as lower as one-half compared to the rest of the world (men ASR 88.88, women ASR 87.71), but its trend is increasing that is evident on the upward slopes of the regression lines for both sexes (men and women) for the study period. In the case of cumulative risk, the world has a risk value of 20.95% for men, and 16.38% for women, while in North Cyprus this value is 19.32% in men and 13.66% in women. The standardized rate of various cancer types such as stomach cancer, colorectal, cancer, prostate cancer, lung cancer, and kidney cancer, in North Cyprus, suggest a lower incidence than that of the world. However, higher incidence rate is reported in North Cyprus in the case of bladder cancer and thyroid cancer than that of the world (Ferlay et al., 2015) (Table 2.2).

As a most frequent type of cancer in women globally, breast cancer burden is one-fourth of all types of cancer with the standardized rate of 38.9 (Ferlay et al., 2015). In almost all European countries, breast cancer indicated an increasing trend (Farazi 2014), however in some Asian countries, although the trend is on rising, the incidence is lower (Afsharfard et al., 2013). In North Cyprus women, the breast cancer ASR (24.07) with a cumulative risk of 3.92% also suggests this cancer as the most frequent of all types. Breast cancer is rare in men (C. Risk 0.07%) (Table 2.2). Studies have suggested various risk factors for breast cancer including, early menarche, late menopause, being obese, the lack of physical activity, and hormonal replacement therapy etc. (Farazi 2014; Salim et al., 2009). The prolonged use of oral contraceptive is also thought to be a risk for breast cancer (Karim et al., 2015). Consistently, similar risk factors for breast cancer were reported in men. In addition to the hormonal (androgen) imbalance in men, the benign breast disease, other organs diseases such as liver and testes, family history, Klinefelter syndrome, exposure to X-rays and

ultraviolet rays and obesity etc. are the main risks for breast cancer. (Davies & Welch 2006).

The thyroid cancer is the second most common cancer with a cumulative risk of 2.0% in the TRNC women. A higher incidence of thyroid cancer in Cypriot women was also reported by Farazi (2014). The study indicated a two times increase in the thyroid cancer incidence in a ten years' period (1998-2008) (Farazi 2014). Furthermore, a similar increase in the thyroid cancer was reported from other European countries as well (Ron et al., 2006). The recognised aetiology for the thyroid cancer include childhood exposure to ionisation radiations, and the past history of nodules in the thyroid gland (Warren et al., 2001). Further investigations are required to demonstrate whether this high incidence of thyroid cancer in North Cyprus is reflected by the presence of certain risk factors on this island such as exposure to radiations, recurrent use of fine needle aspiration for tumour detection or there is some sort of carcinogen in the environment (Siegel et al., 2015).

In North Cyprus, skin cancer in men and women both showed a higher incidence and C. risk. In some other countries, such as Australia, New Guinea and Ireland, skin cancer diagnosed with higher frequency among men (WHO 2011). There is a link between skin cancer risk and ultraviolet radiations (UVR) (American Cancer Society 2013). In the TRNC, the ultraviolet radiations are high due to the continuous sunshine throughout the year in the island. The circadian level of ultraviolet rays in the North Cyprus are higher than other Mediterranean countries (Lucas et al., 2010). The other prevalent cancer types in North Cyprus are prostate cancer, bladder cancer, colorectal cancer, lung cancer, liver cancer, kidney cancer, and lymphoma cancer both Hodgkin lymphoma and non-Hodgkin lymphomas together.

The smoking-related cancers i.e. bladder cancer and lung cancer indicated very different incidence in this study. A high incidence rate is reported from bladder cancer than that of lung cancer. This can be explained as, due to the genetic and epigenetic influence on the risk of bladder carcinogenesis, the bladder cancer is linked to environmental factors that account for high incidence in non-smokers. As

environmental and genetic interaction together modifies bladder cancer risk, therefore, the incidence is different in different populations (Kiriluk et al., 2012).

Tobacco smoke is also related to some other types of cancer such as oral cavity, pharynx, oesophagus, stomach, gynaecological and blood cancer etc. (USD Health and Human Services 2014). Up to 20% of all cancer deaths are thought to be associated with tobacco smoking (Stewart & Wild 2014). In North Cyprus population, the actual smoking status in men and women is unknown. However, the western lifestyle and the genetic predisposition together modulate the risk of these cancers (Hamdi et al., 2005)

The third most common cancer in men in TRNC is prostate cancer. This is the second common cancer in men in the world and most prevalent in the underdeveloped countries (Ferlay et al., 2008). Insufficient evidence is available about the aetiology of prostate cancer, however like other prevalent cancer types, the role of genetic and environmental factors is important in the development and progression of prostate cancer. The family history, older age, and race (African) are the recognised risk factors (Shavers et al., 2009). The lifestyle (smoking, alcohol, exercise etc.) and dietary factors also play role in prostate carcinogenesis (Mandair et al., 2014).

This study suggests a lower incidence of gynaecological cancers (endometrium cancer with cumulative risk 0.52%, and cervical cancer with cumulative risk 0.53%) in North Cyprus women (Pervaiz et al., 2017). The main risk factors for gynaecological cancer are not known, however, some studies suggest the relation of cervical cancer and the infection of human papillomavirus (Muñoz et al., 2003). Similarly, large number of ovarian cycles, miscarriages, and live births are linked with increased risk of endometrial cancer (El-Khwsky et al., 2006)

2.8. Conclusion

In conclusion, this study revealed an increasing incidence and trend of cancer in the Turkish Republic of Northern Cyprus. Among men, skin cancer was the most prevalent type during the study period while among women that was breast cancer. Further studies on the risk factors associated with the most frequent types of cancer in this population are required. Furthermore, population-based screening programs

should be implemented for the early detection of breast, thyroid, and prostate cancer. In addition, public awareness about the risk factors is recommended.

CHAPTER 3
Second part of the study*:*

RISK FACTORS ASSESSMENT FOR BREAST CANCER IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

3.1. Background and aims

BC is the most common malignancy among Turkish Cypriot women (11). The Mediterranean lifestyle of the North Cyprus population is rapidly changing towards a western style that affecting the health status of the region (Panagiotakos et al., 2007). At present, the main risks for BC in Turkish Cypriot women are not known, hence the study of risk factors attributed to BC in the Turkish Cypriot population is crucial. Therefore, this case-control study aims to investigate:

1. The strength of association of worldwide recognised breast cancer risks (hormonal, reproductive and lifestyle) and breast cancer in North Cyprus population.
2. To evaluate additional potential breast cancer risk factors (i.e. workplace and home environment, depression and infertility drugs used etc.) in this part of the island.
3. To assess the possible role of association of the quantity of daily fat, sugar and water consumption and breast cancer risk.
4. To assess the role of dietary factors in postmenopausal breast cancer risk.

3.2. Recruitment of study participants and data collection

In this case-control study, participants were recruited from the medical oncology, radiation oncology, and general surgery departments of Near East Hospital and Dr Burhan Nalbantoglu State Hospital in TRNC. A structured questionnaire was designed and face-to-face interviews were conducted to obtain information regarding the sociodemographic and potential risk factors. All study participants were given a written informed consent form in English or Turkish. Prior written permission was

obtained from the North Cyprus Ministry of Health, as well as from the head of the Near East Hospital in Nicosia.

The study group included 408 women aged ≥ 45 years with histopathological confirmed primary BC who had visited the Near East University hospital and Dr Burhan Nalbantoglu Government hospital between July 2016 and December 2016. Cases with less than 45 years of age were not included in the study due to the different aetiology of early-onset BC. Almost 90% of the patients were recruited from the Oncology department of the state hospital in Nicosia, while the remainder were enrolled from Near East University Hospital, North Cyprus. Only Turkish Cypriot women were interviewed and included in the study. Patients who were from the Southern part (Greek Cypriot) of the island and were seeking treatment in North Cyprus were not included in the study.

The control group consisted of 412 age-matched Turkish Cypriot women without any known malignancy who had visited the hospital for a routine health examination. An introductory letter about the aims and goals of the study was given to each of the cases and control women; those who were willing to participate in the study were interviewed by a trained interviewer.

The questionnaire comprised questions regarding age, education level, income status, marital status, age at menarche and menopause, parity, age at FFT, duration of breastfeeding, family history of BC, history of benign breast disease and past biopsy, premenstrual syndrome, hormonal replacement therapy (HRT), use of fertility drugs, oral contraceptive use, consanguinity, exposure to diagnostic radiation, exposure to pesticides in residential and work environment, occupational and shift work risks, lifestyle (smoking, alcohol use, exercise, etc.) and various commonly used dietary factors (Appendix A).

To assess the strength of association between the consumption of various commonly used dietary factors including fat, sugar, water, dairy products, olive oil, alcohol, coffee and black tea and postmenopausal breast cancer risk, separate analysis were carried out.

3.3. Data Analysis

For both cases and control, frequencies of categorical variables were calculated separately. The frequencies were cross-tabulated and variations in the respondent's characteristics between cases and control were analysed by Chi-square test. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for estimating the strength of association between each hypothesised risk factor and BC before and after adjusting for the confounding effects of other variables. For controlling age differences between cases and control, all model estimations were adjusted for age. A p-value of linear trend was noted in the case of ordered categorical variables, such as breastfeeding duration, etc. In the first step, univariate logistic regression models were used to ascertain whether there was any association between each hypothesised risk factor and BC risk. In order to reduce the number of variables in the multivariable model (only for combined analysis of pre-and postmenopausal BC risk) variables with $p > 0.25$ were disregarded and those with $p \leq 0.25$ were included in the multivariable logistic regression model. In the next step, all variables with $p > 0.05$ were disregarded and those with $p \leq 0.05$ were included in the final multivariable model. In all cases, the fit of the model was assessed on the basis of the Pearson chi-square or Hosmer-Lame-show goodness-of-fit statistics, which produced a non-significant result. SPSS version 20 was used for statistical analysis.

3.4. Definitions

The cases were asked to provide their age at diagnosis, while the control group were asked to provide their age at enrolment in the study. A gestational period of 24 weeks was considered pregnancy. The use of Oral contraceptive and HRT was considered for a minimum one month. Premenstrual depression (PMD) was considered an up to 4-days depression period before each menstruation for at least 1 year. Pesticide exposure for at least one-time, chemicals (dry cleaning chemicals, alkyl phenol, mercury, lead, cadmium, etc.) exposure for at least 6 months and Smoking was considered at least one cigarette a day for a minimum of 6 months. Any form of regular exercise for three hours a week for the previous six months was considered.

For the dietary factors, "dietary intake questionnaire for the quantitative estimation of adherence to Mediterranean Diet" was used with some modification for this population (Martinez-Gonzalez et al., 2004), and habitual intakes over the previous year (date of interview for controls, date of diagnosis for cases) were considered. Sugar consumption was considered as anything containing added sugar (i.e., jam, frozen and non-frozen desserts, candies, and soft drinks, etc.), with a serving size of one teaspoon (5-7 grams) and one glass of soft drink (250 -300 grams). For full-fat dairy products (FFDP), a serving size of 100 grams was considered. However, the respondents were asked for the frequency and not the quantity of olive oil consumed (Martinez-Gonzalez et al., 2004).

3.5. Study findings

A total of 820 women (408 BC in the study group and 412 in the age–matched control group) took part in the study, with a 99% participation rate. Cases that were diagnosed age less than 45 years and those who demonstrated an unwillingness to participate in the study were excluded. The mean age at diagnosis of the study group cases was 57.7–6.5 years, while the mean age of the control group was 57.5–6.4 years.

3.6. Breast cancer risk prediction in the univariable model

3.6.1. Sociodemographic factors

Location, marital status, BMI and family history demonstrated some strong association with BC risk in the univariate model adjusted for age. More cases (45.6%) were from rural locations than control (35.9%). Therefore, rural location was associated with an increased risk of BC (OR = 1.47, 95% CI 1.11–1.95, p = 0.007). Similarly, single women were more in cases (19%) than in control (10.4%). Being married was associated with a 51% reduced risk of BC in cases than control (OR = 0.49, 95% CI 0.32–0.73, p < 0.001). The number of obese women was also higher in cases (53.4%) than control (36.7%), with more than a twofold increase in BC risk associated with being obese (OR = 2.37, 95% CI 1.50– 3.73, p < 0.001). More cases reported family history (55.9%) of BC (first and second-degree relatives combined) than that of control (31.6%) (OR = 2.713, 95% CI 2.03–3.61, p < 0.001). However,

income status and education level did not show significant relation with BC risk (p = 0.144 & p = 0.828 respectively) (Table 3.1).

3.6.2. Reproductive factors

A significant number of women from the cases group (80%) reported menarche at the age of ≤12 years. A decreased BC risk of 82% was associated with menarche age >12 (OR = 0.18, 95% CI 0.13–0.25, p < 0.001). Non–menopausal woman reported an approximate 2.8 times decreased BC risk than women who had reached menopause at the age of 50 years or less (OR = 2.89, 95% CI 1.22–6.83, p = 0.015), and as much as 5.4–fold decreased BC risk compared with women who had reached menopausal age over 50 (OR = 5.48, 95% CI 2.31–13.02, p < 0.001).

More control women (78.9%) were reported to be parous than cases (57.6%). A 64% decreased BC risk was associated with a parous woman (OR = 0.36, 95% CI 0.26–0.49, p < 0.001). Similarly, more cases (18.9%) than control (6.65) reported their FFP at an age of more than 30 years old. A 74% decreased BC risk was associated with women with FFP before 30 years of age (OR = 0.18, 95%CI 0.11–0.29, p < 0.001).

Women with up to two and more than two children showed a decreased risk of 47% and 73%, respectively, in the univariate model (OR = 0.53, 95% CI 0.37–0.76, OR = 0.27, 95% CI 0.19–0.38, p < 0.001). Similarly, 57% of cases and 34% of control reported that they had never breastfed their children. Moreover, breastfeeding was also associated with a decreased BC risk (i.e., a 60% decreased risk in cases of breastfeeding for less than one year (OR = 0.40, 95%CI 0.29–0.55)), while it was 65% for more than one year (OR = 0.35, 95% CI 0.25–0.52, p < 0.001). In the case of oral contraceptive use, 53% of cases and 46% of the control group reported the use of oral contraceptives for at least one month, but their relationship with BC risk factors was not statistically significant (OR = 1.134, 95% CI 0.86–1.50, p = 0.34). However, a significant relationship between HRT use and BC risk was reported with a 70% and 72% increased risk for up to 5 years and more than 5 years, respectively (OR = 1.70 95% CI 1.18–2.43, and OR = 1.72, 95% CI 1.12–2.64, p = 0.002).

More cases (31%) than control (13.6%) reported the use of drugs for infertility treatment. The use of fertility drugs for up to 6 cycles was associated with a 2.3–fold risk, while more than 6 cycles were associated with a 3–fold increased BC risk in the univariate model (OR = 2.38, 95% CI 1.40–4.05, OR = 3.11 95% CI 2.01–4.80) (p < 0.001).

3.6.3. General health-related factors

A history of Fibrocystic Breast Disease (FBD) was reported by 55% of cases and 34% of control, with a twofold increased BC risk associated with FBD in the univariate model (OR = 2.10, 95% CI 1.56–2.83, p < 0.001). Similarly, more cases (15.7%) than control (10.2%) reported history of past biopsy, which was related with a 62% increased BC risk (OR = 1.62 95% CI 1.06–2.46, p = 0.02).

The number of cases with consanguineous parents was less (19.6%) than that of the control group (36.9%). Therefore, consanguinity was associated with a 58% decrease risk of BC in this univariable model (OR = 0.42, 95% CI 0.30–0.55, p < 0.001). Furthermore, 56.6% of cases and 42.7% of control respondents reported PMD with the OR = 1.74 (95% CI 1.32–2.30, p < 0.001). Similarly, exposure to diagnostic radiations (chest X-rays) was also significantly associated with a BC risk (p<0.001) as 83% of cases and 70% of control indicated exposure to radiation on at least one occasion after puberty (OR = 1.80, 95%CI 1.23–2.62, p = 0.002).

3.6.4. Residential and workplace factors exposure

In NC, exposure of women to night shift work is uncommon, as only 44 women (18 cases and 26 control) reported that they had worked on night shifts. Night shift work and chemical exposure did not indicate a significant association with BC risk (p = 0.23 & 0.08, respectively). However, a 39% increased BC risk was associated with pesticide exposure in the univariate model (OR = 1.39, 95 % CI 1.03–1.88, p = 0.029).

3.6.5. Lifestyle and diet-related factors

Smoking was positively associated with BC risk as 57.6% of cases and 41.5% of control reported that they were smokers. Approximately 90% increased BC risk was associated with smoking (OR = 1.90, 95% CI 0.81–1.42, p < 0.001) in the univariable

model. Exercise or physical activity were negatively related with BC risk, as the control group (55.8%) were more physically active than cases (41.4%). Hence, daily exercise decreased the BC risk up to 44% (OR = 0.56, 95% CI 0.42–0.74, p < 0.001). Additionally, a strong positive relation between BC risk and the use of alcohol was reported in the univariate logistic regression model with almost a twofold increased risk of BC (OR = 1.90 95%CI 1.12–3.06, p < 0.001).

In the case of dietary products, quantities of oil, margarine and sugar consumption were indicated to have a strong significant positive relation; the quantity of daily water intake and use of FFDP had a negative relation, while the consumption of olive oil (p = 0.85), coffee (p = 0.86) and black tea (p = 0.23) did not show any significant relation with BC risk.

In subcategories, the risk increased significantly with the increase in the quantity of oil (p< 0.001) and sugar consumption (p < 0.001). However, in the case of margarine intake, more cases (46.3%) reported ≤ 60 grams of daily margarine consumption than control (38%) (OR = 1.217, 95% CI 0.87–I.69, p = 0.24), while more control (33%) than cases (25%) reported >60 grams of daily consumption (p = 0,018) for a period of at least 3 years (OR = 0.75, 95% CI 0.52–1.08, p = 0.12). Neither of these two subcategories were significant individually; however, their combined effect was significant (p = 0.018).

Daily water intake of 1 to 2 litters was found to decrease the BC risk by almost 61% (OR = 0.39, 95% CI 0.25–0.59) and consumption of > 2 litters by 60% (OR = 0.40 95% CI 0.26–0.61, p < 0.001). However, FFDP of ≥ 4 servings indicated a significant 38% (OR = 0.62, 96% CI 0.33–1.10) decreased risk in BC (p = 0.03).

Table 3.1. Sociodemographic characteristics and age-adjusted odds ratios (95% CI) for breast cancer cases and control

Variables	Cases (N= 408)	%	Control (N= 412)	%	OR[1]	95%CI	p–value[2]
Socio–demographic factors							
Location							
Urban	222	(54.4%)	264	(64.1%)	1		0.007
Rural	186	(45.6%)	148	(35.9%)	1.471	(1.114–1.954)	
Income status							
< 5000TL	158	(38.7%)	174	(42.2%)	1		0.144
5000–10,000 TL	232	(56.9%)	229	(55.6%)	1.123	(0.845–1.492)	
> 10,000TL	18	(4.4%)	9	(2.2%)	2.257	(0.984–5.180)	
Education							
Primary	104	(25.5%)	115	(27.9%)	1		0.828
Secondary	189	(46.3%)	188	(45.6%)	1.110	(0.795–1.550)	
Tertiary	66	(16.2%)	61	(14.8%)	1.205	(0.777–1.869)	
University	49	(12.0%)	48	(11.7%)	1.184	(0.731–1.919)	
Marital Status							
Single	78	(19.1%)	43	(10.4%)	1		0.001
Married	330	(80.9%)	369	(89.6%)	0.489	(0.327–0.731)	
BMI*							
<25	38	(9.30%)	63	(15.3%)	1		0.001
25–29.9	152	(37.3%)	198	(48.1%)	1.276	(0.809–2.012)	
≥ 30	218	(53.4%)	151	(36.7%)	2.375	(1.509–3.738)	
Family History							
No	180	(44.1%)	282	(68.4%)	1		0.001
Yes	228	(55.9%)	130	(31.6%)	2.713	(2.038–3.613)	
Reproductive factors							
Menarche Age							
≤ 12 years	329	(80.6%)	79	(19.4%)	1		0.001
>12 years	182	(44.2%)	230	(55.8%)	0.186	(0.136–0.255)	
Age at Menopause							
No menopause	7	(1.7%)	27	(6.6%)	1		0.001
≤ 50 years	193	(47.3%)	246	(59.7%)	2.898	(1.229–6.830)	
> 50 years	208	(51.0%)	139	(33.7%)	5.487	(2.311–13.03)	
Parity							
No	173	(42.4%)	87	(21.1%)	1		0.001
Yes	235	(57.6%)	325	(78.9%)	0.363	(0.267–0.494)	
Age at FFP (First full–term pregnancy)							
≥30 years	77	(18.9%)	27	(6.6%)	1		0.001
<30 years	158	(38.7%)	298	(72.3%)	0.184	(0.114–0.297)	
Nil	173	(42.4%)	87	(21.1%)	0.693	(0.416–1.154)	
No. of Children							
No children	173	(42.4%)	89	(21.6%)	1		0.001
Up to 2	128	(31.4%)	121	(29.4%)	0.536	(0.375–0.767)	
More than 2	107	(26.2%)	202	(49.0%)	0.271	(0.191–0.383)	

Variables	Cases (N= 408)	%	Control (N= 412)	%	OR[1]	95%CI	p–value[2]
Breast Feeding							
Never	236	(57.8%)	143	(34.7%)	1		0.001
Less than 1 year	114	(27.9%)	170	(41.3%)	0.406	(0.296–0.557)	
More than 1 year	58	(14.2%)	99	(24.0%)	0.359	(0.244–0.527)	
Oral Contraceptive use							
No	191	(46.8%)	207	(50.2%)	1		0.340
Yes	217	(53.2%)	205	(49.8%)	1.143	(0.868–1.505)	
HRT							
Never used	249	(61.0%)	302	(73.3%)	1		0.002
Up to 5 years	96	(23.5%)	67	(16.3%)	1.702	(1.188–2.439)	
> 5 years	63	(15.4%)	43	(10.4%)	1.726	(1.127–2.643)	
Fertility drug used (FD)							
Never	282	(69.1%)	356	(86.4%)	1		0.001
≤ 6 cycles	44	(10.8%)	23	(5.6s%)	2.389	(1.408–4.053)	
> 6 cycles	82	(20.1%)	33	(8.0%)	3.115	(2.017–4.809)	
General health-related factors							
History of FBD[†]							
No	160	(39.2%)	212	(51.5%)	1		0.001
Yes	226	(55.4%)	142	(34.5%)	2.108	1.569–2.832)	
Don't know	22	(5.4%)	58	(14.1%)	0.502	(0.294–0.856)	
History of past biopsy							
No	344	(84.3%)	370	(89.8%)	1		0.023
Yes	64	(15.7%)	42	(10.2%)	1.621	1.068–2.460)	
Consanguinity							
Non–cons.	328	(80.4%)	260	(63.1%)	1		0.001
Consanguineous	80	(19.6%)	152	(36.9%)	0.42	(0.302–0.569)	
PMD[‡]							
No	177	(43.4%)	236	(57.3%)	1		0.001
Yes	231	(56.6%)	176	(42.7%)	1.745	(1.322–2.304)	
History of radiation exposure							
No	67	(16.4%)	123	(29.9%)	1		0.001
1 to 2 times	143	(35.0%)	149	(36.2%)	1.801	(1.235–2.626)	
3 or more times	198	(48.5%)	140	(34.0%)	2.60	(1.795–3.752)	
Residential and workplace factors exposure							
Night shift work							
No	390	(95.6%)	386	(93.7%)	1		0.236
Yes	18	(4.4%)	26	(6.3%)	0.688	(0.371–1.277)	
Pesticide exposure							
No	269	(65.9%)	299	(72.6%)	1		0.029
Yes	139	(34.1%)	113	(27.4%)	1.395	(1.034–1.883)	
Other Chemical Exposure							
No	225	(55.1%)	250	(60.7%)	1		0.089
Yes	183	(44.9%)	162	(39.3%)	1.274	(0.964–1.683)	

Variables	Cases (N= 408)	%	Control (N= 412)	%	OR[1]	95%CI	p–value[2]
Lifestyle factors and diet-related factors							
Smoking							
No	173	(42.4%)	241	(58.5%)	1		0.001
Yes	235	(57.6%)	171	(41.5%)	1.904	(1.442–2.514)	
Physical activity							
No	239	(58.6%)	182	(44.2%)	1		0.001
Yes	169	(41.4%)	230	(55.8%)	0.564	(0.428–0.745)	
Alcoholic consumption							
Never	277	(67.9%)	332	(80.6%)	1		0.001
≤ 300 ml/day	44	(10.8%)	28	(6.8%)	1.90	(1.123–3.060)	
> 300 ml/day	87	(21.3%)	52	(12.6%)	2.04	(1.397–2.990)	
Oil consumption							
< 20ml	89	(21.8%)	135	(32.8%)	1		0.001
20–40 ml	124	(30.4%)	184	(44.7%)	1.037	(0.729–1.475)	
> 40ml	195	(47.8%)	93	(22.6%)	3.251	(2.254–4.689)	
Butter consumption							
Never	99	(24.3%)	86	(20.9%)	1		0.37
≤ 60 grams	165	(40.4%)	185	(44.9%)	0.779	(0.543–1.116)	
> 60 grams	144	(35.3%)	141	(34.2%)	0.893	(0.615–1.296)	
Margarine							
Never	117	(28.7%)	119	(29%)	1		0.018
≤ 60 grams	189	(46.3%)	156	(38%)	1.217	(0.872–1.697)	
> 60 grams	102	(25.0%)	137	(33.3%)	0.752	(0.523–1.081)	
Sugar consumption (servings/day)							
≤ 3	11	(2.70%)	52	(12.6%)	1		<0.001
4–6	140	(34.3%)	189	(45.9%)	3.645	(1.831–7.256)	
> 6	257	(63.0%)	171	(41.5%)	7.415	(3.752–14.65)	
Water intake							
<1 litre	93	(22.8%)	44	(10.7%)	1		0.001
1–2 later	148	(36.3%)	177	(43.0%)	0.39	(0.255–0.593)	
> 2 litre	167	(40.9%)	191	(46.4%)	0.40	(0.267–0.614)	
FFDP[§] use							
Never	33	(8.1%)	30	(7.3%)	1		0.035
1–3 savings	313	(76.7%)	290	(70.4%)	0.980	(0.582–1.649)	
≥ 4 servings	62	(15.2%)	92	(22.3%)	0.62	(0.339–1.107)	
Olive oil							
Never	49	(12.0%)	45	(10.9%)	1		0.856
Sometimes	183	(44.9%)	190	(46.1%)	0.879	(0.558–1.384)	
Daily	176	(43.1%)	177	(43.0%)	0.903	(0.572–1.425)	
Coffee consumption							
Never	35	(8.6%)	31	(7.5%)	1		0.868
1–2 cups	224	(54.9%)	227	(55.1%)	0.878	(0.523–1.474)	
≥3 cups	149	(36.5%)	154	(37.4%)	0.867	(0.508–1.480)	

Variables	Cases (N= 408)	%	Control (N= 412)	%	OR[1]	95%CI	p–value[2]
Black tea consumption							
Never	42	(10.3%)	28	(6.8%)	1		0.239
1–2 cups	240	(58.8%)	254	(61.7%)	0.644	(0.386–1.073)	
≥3 cups	126	(30.9%)	130	(31.6%)	0.668	(0.389–1.146)	

Notes: 1. Univariable odds ratios adjusted for age. 2. *p* values for the difference between binary variables or *p*-value for linear trend across ordinal categorical variables. ∗ Body mass index. † Fibrocystic breast disease. ‡ Pre–menstrual depression § Full fats dairy products

3.7. Breast cancer risk prediction in the multivariable model

On the basis of the univariate analysis, the following variables (all with $p > 0.25$) were dropped from the multivariable logistic regression model: level of education, oral contraceptive use, butter consumption, olive oil consumption and coffee consumption.

Although some variables, including rural/urban location, marital status, parity, number of children, breastfeeding history, HRT usage, pesticide exposure, physical activity, margarine use, FFDP use, and alcohol use were significant in the univariate model, their effects were markedly attenuated in the multivariable adjusted model, as none of them attained statistical significance in the adjusted multivariable logistic regression model (Rural location (OR = 1.37 95% CI 0.90–2.00, $p = 0.136$); being married (OR = 0.69, 95% CI 0.31–1.53, p = 367); being non–parous (OR = 3.71, 95% CI 0.13–103.04, $p = 0.43$); number of children up to 2 (OR 0.60, 95% CI 0.02–16.3) & more than 2 children (OR = 0.47, 95% CI 0.01–13.56, $p = 0.720$); breast feeding < 1 year (OR = 0.74, 95% CI 0.38–1.42) & > 1 year (OR = 0.57, 95% CI 0.27–1.20, $p = 0.338$); HRT ≤ 1 year (OR = 1.56, 95% CI 0.91–2.66) & > 1 year (OR = 1.62, 95% CI 0.85–3.08, $p = 0.135$); pesticide exposure (OR = 1.37, 95% CI 0.89–2.11, $p = 0.148$); physically active (OR = 0.74, 95% CI 0.48–1.13, $p = 0.165$); margarine consumption ≤ 60 grams (OR = 0.73, 95% CI 0.43–1.22) & > 60 grams (OR = 0.70, 95% CI 0.40–1.21, $p = 0.375$); FFDP 1–3 servings (OR = 0.80, 95% CI 0.38–1.68) & FFDP use ≥ 4 servings (OR = 0.45, 95% CI 0.19–1.06, $p = 0.07$); alcohol intake ≤ 300 ml/day (OR = 0.91, 95% CI 0.34–1.91) & > 300 ml/day (OR =1.09, 95% CI 0.62–1.91, $p = 0. 91$)). The risk profiles associated with income status ($p = 0.80$), night shift work exposure

(p = 0.98), chemical exposure (p = 0.46), and black tea intake (p = 0.09) were less affected as these remained insignificant in the adjusted multivariate model as well. (Table 3.2).

In contrast, BMI, family history, menarche age, age at menopause, age at FFP, fertility drug use, smoking, FBD, history of past biopsy, consanguinity, PMD, exposure to radiation, as well as the quantity of oil, sugar and water consumption were significant (p ≤ 0.05) predictors of BC risk for the study group in the adjusted multivariable analysis, as given in Table 3.3 (Figure 3.1).

Table 3.2. Odds ratios (95% CI) of breast cancer by respondent's characteristic's, adjusted for the effects of all other factors

Variable		(OR)[1]	95%CI	p–value[2]
Socio–demographic factors				
Location	Urban	1		0.136
	Rural	1.375	(0.905–2.091)	
Income status	< 5000TL	1		0.806
	5000–10,000 TL	0.867	(0.565–1.332)	
	> 10,000TL	0.870	(0.260–2.909)	
BMI	<25	1		0.004
	25–29.9	1.734	(0.876–3.433)	
	> 30	2.936	(1.473–5.850)	
Family history	No	1		0.000
	Yes	2.285	(1.494–3.493)	
Reproductive Factors				
Menarche Age	12 or less	1		0.000
	12 and above	0.204	(0.129–0.324)	
Age at menopause	No menopause	1		0.006
	≤ 50 years	6.726	(1.825–24.789)	
	> 50 years	7.991	(2.203–28.988)	
Marital Status	Single	1		0.367
	Married	0.694	(0.313–1.536)	
FTP	Yes	1		0.439
	No	3.717	(0.134–1.03)	
Age at FFP	≥ 30 years	1		0.000
	< 30 years	0.183	(0.113–0.296)	
	Nil	0.697	(0.418–1.160)	
No. of children	No children	1		0.720
	Up to 2	0.600	(0.022–16.314)	
	More than 2	0.490	(0.018–13.560)	

Variable		(OR)[1]	95%CI	p–value[2]
Breastfeeding duration	Never	1		0.338
	≤ 1 year	0.744	(0.388–1.426)	
	> 1 year	0.571	(0.271–1.204)	
HRT	Never used	1		0.135
	Up to 5 years	1.566	(0.919–2.669)	
	> 5 years	1.622	(0.852–3.087)	
Fertility drugs used	Never	1		0.000
	≤ 6 cycles	1.820	(0.814–4.070)	
	> 6 cycles	3.779	(2.010–7.106)	
General health-related factors				
Fibrocystic breast disease	No	1		0.000
	Yes	2.366	(1.488–3.761)	
	Don't know	0.733	(0.332–1.617)	
Past biopsy	No	1		0.001
	Yes	3.357	(1.599–7.046)	
Consanguinity	Non–consanguineous	1		0.000
	Consanguineous	0.176	(0.095–0.325)	
PMD	No	1		0.009
	Yes	1.896	(1.177–3.054)	
Radiation exposure	No radiation	1		0.006
	1 to 2 times	1.759	(0.993–3.118)	
	3 or more times	2.529	(1.432–4.465)	
Residential and workplace factors exposure				
Night shift work	No	1		0.981
	Yes	1.011	(0.409–2.501)	
Pesticides Exposure	No	1		0.148
	Yes	1.375	(0.894–2.117)	
Other Chemical exposure	No	1		0.463
	Yes	1.168	(0.772–1.767)	
Lifestyle factors and diet-related factors				
Smoking	No	1		0.020
	Yes	1.657	(1.084–2.534)	
Physical activity	No	1		0.165
	Yes	0.740	(0.484–1.132)	
Oil consumption	< 20ml			0.000
	20–40 ml	1.074	(0.637–1.812)	
	> 40ml	2.861	(1.668–4.910)	
Margarine	Never	1		0.375
	≤ 60 grams	0.730	(0.435–1.224)	
	> 60 grams	0.700	(0.404–1.214)	
Sugar consumption (Servings/day)	≤ 3	1		0.001
	4–6	3.072	(1.187–7.952)	
	> 6	5.236	(2.042–13.423)	
Water intake	<1 litre	1		0.005
	1–2 litre	0.392	(0.204–0.751)	

Variable		(OR)[1]	95%CI	p–value[2]
	> 2 litters	0.349	(0.183–0.666)	
Other FFDP	Never	1		0.079
	1–3 savings	0.804	(0.385–1.682)	
	≥ 4 servings	0.451	(0.192–1.061)	
Alcohol consumption	Never	1	1	0.917
	≤ 300 ml/day	0.914	(0.436–1.914)	
	> 300 ml/day	1.090	(0.620–1.915)	
Black Tea consumption	Never	1		0.093
	1–2 cups	0.475	(0.218–1.038)	
	≥3 cups	0.393	(0.169–0.911)	

Note: 1. Multivariable odds ratios adjusted for age, BMI, family history, menarche age, age at menopause, parity, Breastfeeding, smoking, exercise and HRT. 2. p values for the difference between binary variables or p-value for linear trend across ordinal categorical variables.

Table 3.3. Odds ratios (95% CI) of breast cancer by respondent's characteristics, adjusted for the effects of all other significant variables

Variables		OR[1]	95% CI	P–value[2]
BMI	<25	1		
	25–29.9	1.604	(0.852–3.017)	0.143
	≥ 30	2.831	(1.490–5.379)	<0.001
Family history	No	1		
	yes	2.299	(1.535–3.441)	<0.001
Menarche Age	≤ 12 years	1		
	>12 years	0.226	(0.148–0.344)	<0.001
Age at menopause	No menopause	1		
	≤ 50 years	5.491	(1.669–18.061)	0.005
	> 50 years	7.215	(2.197–23.693)	<0.001
Age at FFP	≥ 30 years	1		
	< 30 years	0.267	(0.171–0.416)	<0.001
	Nil	1.210	(0.623–2.352)	0.574
Fertility drugs used	Never	1		
	≤ 6 cycles	1.465	(0.698–3.077)	0.313
	> 6 cycles	3.305	(1.850–5.906)	<0.001
Smoking	No	1		
	Yes	1.695	(1.142–2.515)	0.009

Variables		OR[1]	95% CI	P–value[2]
History of FBD	No	1		
	Yes	2.292	(1.493–3.519)	<0.001
	Don't know	0.692	(0.320–1.496)	0.349
History of past biopsy	No	1		
	Yes	3.306	(1.643–6.655)	0.001
Consanguinity	No	1		
	Yes	0.169	(0.095–0.302)	<0.00
PMD	No	1		
	Yes	2.104	(1.339–3.305)	0.001
Radiation exposure	No	1		
	1 to 2 times	1.747	(1.024–2.981)	0.041
	3 or more	2.546	(1.504–4.309)	0.001
Oil consumption /day	< 20ml	1		
	20–40 ml	1.031	(0.631–1.685)	0.902
	> 40ml	2.703	(1.627–4.488)	<0.001
Sugar consumption Servings /day	≤ 3	1		
	4–6	3.422	(1.393–8.409)	0.007
	> 6	5.420	(2.224–13.208)	<0.001
Water intake	<1 litre	1		
	1–2 litre	0.36	(0.194–0.666)	0.001
	> 2 litres	0.36	(0.199–0.677)	0.001

Note: 1. Multivariable odds ratios adjusted for all significant variables ($p \leq 0.005$). 2. p values for the difference between binary variables or p-value for linear trend across ordinal categorical variables.
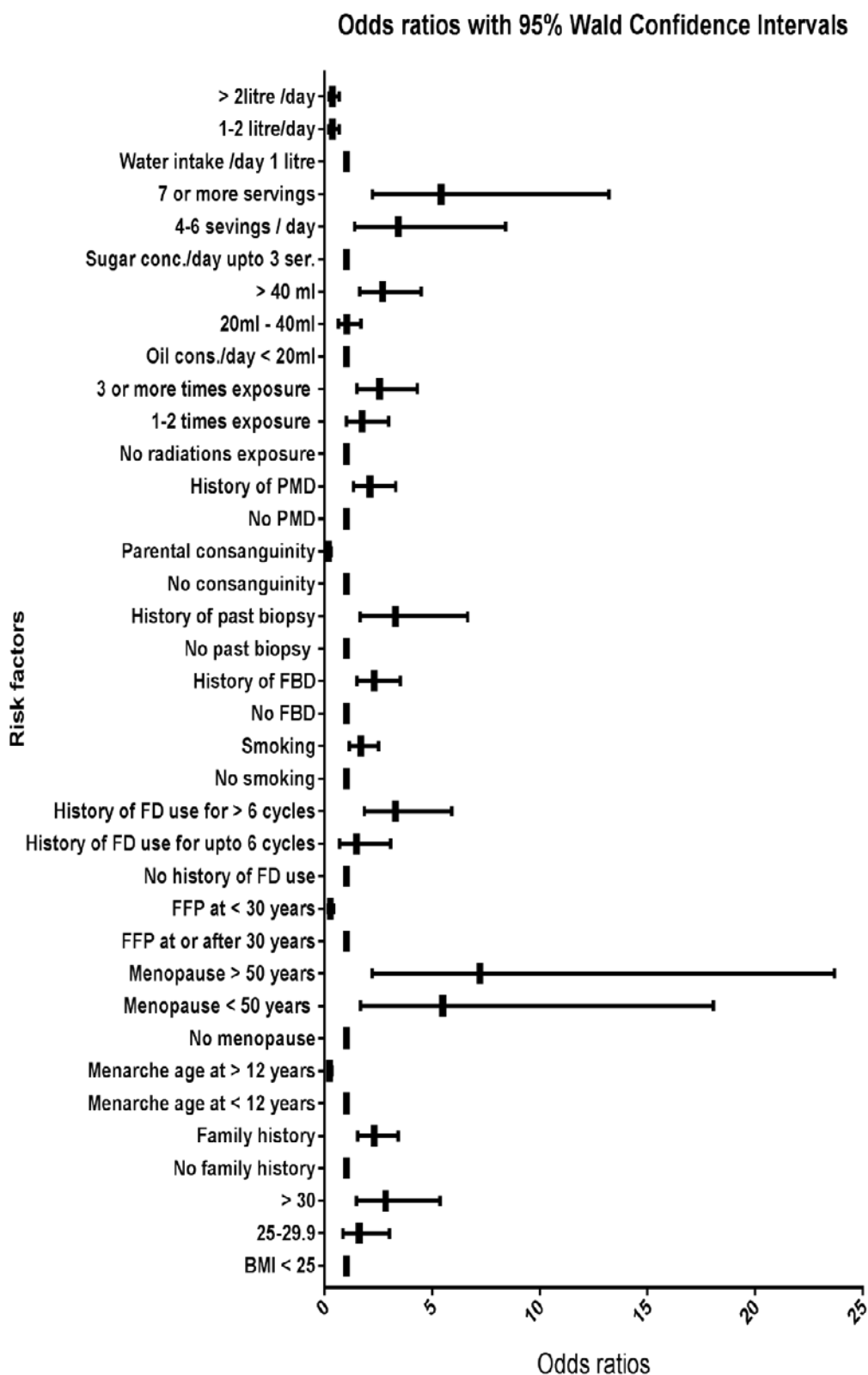
Figure 3.1. Adjusted odds ratios with 95% Wald confidence interval.

3.8.Dietary factors and postmenopausal breast cancer risk

There were total 786 (out of the total sample 820) postmenopausal women including 401 histologically confirmed post-menopausal BC cases and 385 control cases.

In the multivariable adjusted logistic regression model, more than 3–fold increased risk of BC were reported for daily oil consumption of ≥ 40ml (OR = 3.22, 95% CI 2.01-5.17, p < 0.001). While, a 4.1-fold increased risk was associated with daily 4 to 6 serving of sugar (OR = 4.19, 95% CI 1.79-9.80, p = 0.001), this risk further increased to more than 7-folds (OR = 7.5, 95% CI 3.25-17.32, p < 0.001) when daily sweets consumption was increased to > 6 servings. However, daily 1 to 2-liter water intake were found to associated with 64% decreased BC risk (OR = 0.36, 95% CI 0.20-0.63, p = 0.001) in multivariable logistic regression model. While, no significant association were observed between consumption of FFDP, olive oil, coffee intake and BC risk. Interestingly, daily 3 or more cups of tea intake were associated with 54% decreased risk of BC (OR = 0.46, 95% CI 0.22-0.98, p = 0.043). Table 3.4. (Figure 3.2)

Table 3.4. Adjusted odd ratios with 95% CI for dietary factors and postmenopausal breast cancer risk

Variables	Cases (n = 401)		Control (n=385)		Univariable		p–	Multivariable		p–
	n	%	n	%	OR[1]	(95% CI)	value[2]	OR[3]	(95% CI)	value[2]
Oil/fats consumption/day										
(≤ 20ml)	11	2.7%	52	13.5%	1					
(21–40 ml)	137	34.2%	170	44.2%	0.99	(0.69–1.42)		0.98	(0.62–1.54)	0.83
(> 40ml)	253	63.1%	163	42.3%	3.08	(2.12–4.48)	<0.001	3.22	(2.01–5.17)	<0.001
Sugar consumption, servings/day										
≤ 3	11	2.7%	52	13.5%	1					
4–6	137	34.2%	170	44.2%	3.92	(1.96–7.81)		4.19	(1.79–9.80)	0.001
> 6	253	63.1%	163	42.3%	7.60	(3.84–15.03)	<0.001	7.50	(3.25–17.32)	<0.001
Water consumption/day										
<1 litre	89	22.2%	39	10.1%	1					
1–2 litre	148	36.9%	168	43.6%	0.38	(0.24–0.58)		0.36	(0.20–0.63)	
> 2 litre	164	40.9%	178	46.2%	0.39	(0.25–0.61)	<0.001	0.37	(0.21–0.64)	0.001
FFDP* use/day										
Never	30	7.5%	25	6.5%	1					
1–3 servings	309	77.1%	275	71.4%	0.94	(0.54–1.64)		0.94	(0.47–1.89)	0.86
≥4	62	15.5%	85	22.1%	0.61	(0.32–1.14)	0.06	0.53	(0.24–1.17)	0.119

Variables	Cases (n = 401)		Control (n=385)		Univariable		p–value[2]	Multivariable		p–value[2]
	n	%	n	%	OR[1]	(95% CI)		OR[3]	(95% CI)	
Olive oil use/day										
Never	49	12.2%	44	11.4%	1					
Some time	179	44.6%	177	46.0%	0.90	(0.57–1.42)		1.13	(0.62–2.06)	0.67
Daily	173	43.1%	164	42.6%	0.78	(0.59–1.48)	0.89	1.37	(0.75–2.51)	0.30
Daily coffee intake										
Never	34	8.5%	29	7.5%	1					
1–2 cups	218	54.4%	213	55.3%	0.87	(0.51–1.49)		0.67	(0.34–1.36)	0.27
≥3 cups	149	37.2%	143	37.1%	0.90	(0.52–1.55)	0.89	0.61	(0.29–1.26)	0.18
Daily black tea intake										
Never	40	10.0%	26	6.8%	1					
1–2 cups	236	58.9%	231	60.0%	0.67	(0.40–1.14)		0.51	(0.25–1.01)	0.057
≥3 cups	125	31.2%	128	33.2%	0.65	(0.37–1.14)	0.30	0.46	(0.22–0.98)	0.043

Note: 1. Univariable odds ratios adjusted for age. 2. P values for the difference between binary variables or p-value for linear trend across ordinal categorical variables. 3. Multivariable odds ratios adjusted for age, BMI, family history, menarche age, age at menopause, parity, Breastfeeding, smoking, exercise and HRT. * Full fats dairy Products.
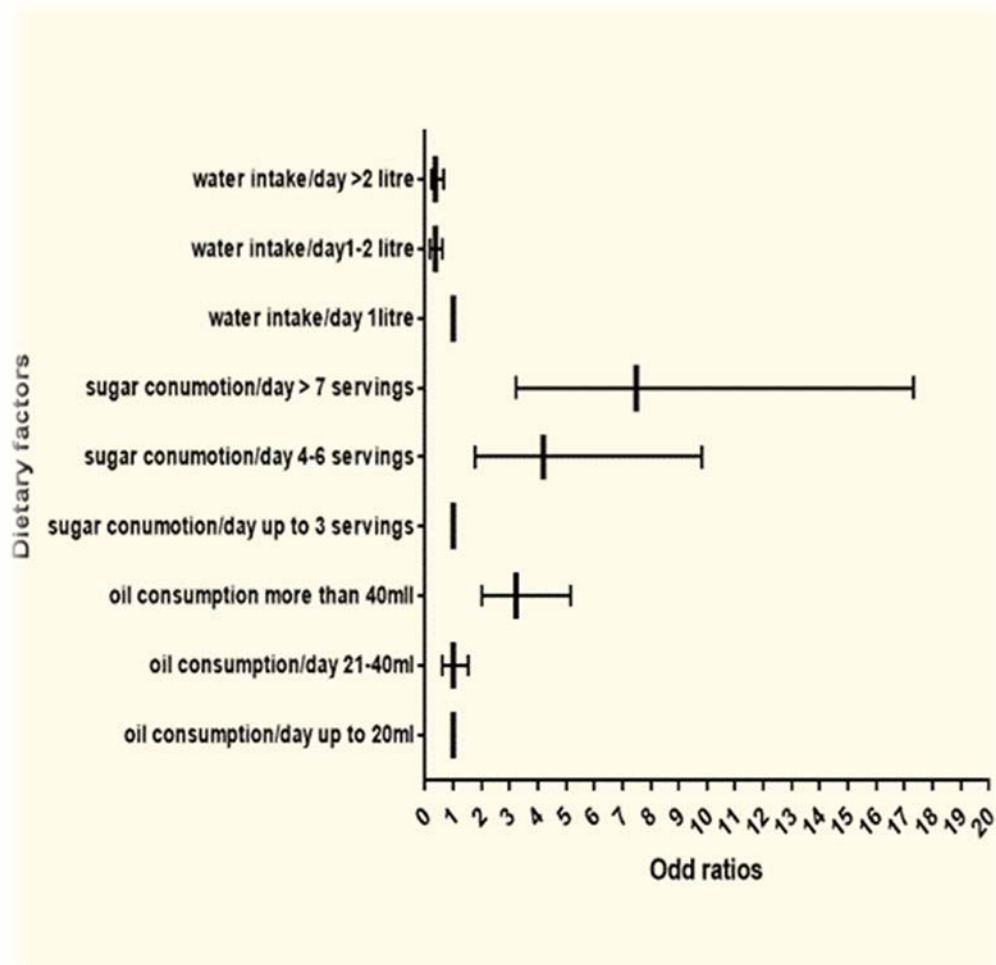
Figure 3.2. Odds ratios and 95% Wald confidence interval for post-menopausal breast cancer risk.

3.9. Discussion

Turkish Cypriot women diagnosed with BC between the years 2006-2016 were recruited randomly for this study. Among the total potential risk factors investigated (33 variables), 15 were found to be significant, including obesity (BMI $\geq$ 30), family history, menarche at the age of 12 years or younger, being menopausal and reaching menopause after the age of 50 years, age at FFP of $\geq$ 30 years, using fertility drugs for more than 6 cycles, history of FBD and past biopsy, being born from non-

consanguineous parents, depression, exposure to diagnostic radiations, daily oil consumption of more than 40 ml, daily sugar consumption of more than 3 servings, and daily water intake less than 1 litre, in the final multivariable logistic regression model (Pervaiz et al., 2017).

The differences between the rural-urban incidences of BC are thought to be due to the greater distance from health care facilities and the lower socio-economic conditions in the rural population. Nevertheless, the variations in the rural-urban lifestyle and income status are not diverse in NC. Similarly, the higher quest of education in women delays the age at marriage and age at FFP, and also reduces parity or some time affecting the marital status and subsequently affecting the BC risk. There is no direct role of marital status in BC risk modification. This is actually the strong interaction between marital status and reproduction that possibly affects the BC risk.

Almost a threefold increased BC risk was reported from obese women (BMI > 30 kg/m2) in the Turkish Cypriot population (pre- and post-menopausal combined). BMI is the degree of adiposity and has been categorised by the World Health Organization (WHO) as less than 18.5 (underweight); 18.5–24.9 (normal); 25.0–29.9 (overweight); and more than 30.0 kg/m² (obese) (WHO 2004). Various conflicting results are available from previous studies that have analysed the association of BC risk and obesity in pre-menopausal women. A number of studies have indicated that general obesity is associated with a decreased BC risk in pre-menopausal women, and an increased risk in post-menopausal women (Amadou et al., 2013) This inverse association varies in various ethnic groups and is well known in Caucasian women; however, it is inconsistent among Asian women. Several studies have suggested that a higher BMI may also be associated with an increased BC risk for pre-menopausal BC (Kawai et al., 2010). Due to the specific age group (45 and above) of our sample, most of our study participants (96%) were post-menopausal women, while only 4% were pre-menopausal.

The positive relationship between family history and BC risk OR = 2.29 (95%CI 1.53-3.44) in this population corresponds to the findings of other case-control and cohort studies in different geographical regions and in different populations.

Pooled analysis of 38 studies has reported a 2.1% (95% CI 2.0-2.2) relative risk of BC in first and second-degree relatives with BC (Pharoah et al., 1997).

The association of BC risk with reproductive factors is well established. The positive relation of the increased risk of developing BC and various reproductive factors such as early menarche, late menopause and late age at FFP in this study are in concordance with the published literature (Kelsey and Horn et al., 1993). The early age at menarche and late age at menopause expose women to increased levels of oestrogen and progesterone simultaneously (Hilton & Clarke 2015). These hormones enhance the mitotic activity of breast cells during the luteal phase of the menstrual cycle as well as the possibility of tumorigenesis (Burkman et al., 2003). Therefore, early menarche and late menopause suggested increase the period of mitotic activity and subsequently increasing the BC risk. Furthermore, early FFP stimulates early breast tissues changes that are responsible for low susceptibility to BC (Kelsey and Horn et al., 1993). However, there is a complex relation between pregnancy and BC risk. In addition to the long-term protective effect of pregnancy (Goldrat et al., 2015), the risk of breast carcinogenesis increases in the short term after pregnancy (Coates et al., 2015). According to Pike's model 21, women with a full-term pregnancy at a given age experience an increased risk of BC in the following 5-10 years compared to nulliparous women. Similarly, giving birth to the first child close to menopausal age increases a women's lifetime risk of contracting BC to a greater level than if she was nulliparous (Pike et al., 1983).

Similarly, the strong univariable association of the BC risk with the number of children and breastfeeding duration is attenuated in the multivariable adjusted model, indicating that the observed association was confounded by other reproductive factors. Furthermore, no or only weak associations of BC risk were observed with oral contraceptive use and HRT. The inverse association between HRT and BC risk did not persist in the final adjusted model. Surprisingly, a direct association with BC risk was observed with the history of fertility drugs usage (for the treatment of polycystic ovary syndrome and/or for inducing ovulation), as an insignificant BC risk of 46% was associated with fertility drugs used for 6 or fewer cycles; however, this risk increased

to OR= 3.3 (95% CI 1.85-5.90) when the drugs were used for more than 6 cycles. This is an unexpected result because literature does not suggest any relation between the history of fertility drugs usage and BC risk (Van den et al., 2016) nonetheless, a relative risk of BC ranging between 2.7 to 3.8 has been reported by past studies from women using human menopausal gonadotropin for at least 6 cycles (Burkman et al., 2003).

Smoking (current or past) was the only significant lifestyle factor and a 69% increased BC risk was associated with smoking in the multivariable logistic regression in North Cyprus females. Biological data is available that links active smoking at a young age with breast carcinogenesis. Potential risks from the history of FBD and previous biopsy were found to have a significantly increased risk for BC in the final model. FBD are characterised by proliferation in glandular tissues, generally within the breast lobules, and these are comprised of benign fibrous tissues and dispersed cysts inclosing amorphous material (Wu et al., 2013). As a common process, the majority of studies have been shown to correlate FBD disease and BC risks, with particular respect to its the microscopic aspect, thus emphasising the importance of accurate diagnosis (Orr et al., 2016). However, BC risk suggested to depend on the histology of the breast lesion, not the biopsy itself (Ellis et al., 2016), biopsy-proven non-proliferative lesion has no elevated risk while proliferative disease without atypia and atypical ductal/lobular hyperplasia are related with an increased BC risk (Hartmann et al., 2005). A recent study provided details regarding benign breast disease and BC risk and estimated that greater than 80% of these cancers are invasive, regardless of the type of benign histology categories, and also indicated that younger women (aged < 45 years) at the time of breast biopsy for benign disease have a higher risk of BC than older women (Vissscher et al., 2016)

Strikingly, parental consanguinity appeared to protect against BC in the North Cyprus population. Hence the BC risk of those women who were born of consanguineous parents was reduced by 84% compared with those born of non-consanguineous parents. In North Cyprus society, consanguinity practice is infrequent. Nevertheless, marriages between second and third-degree relatives are comparatively

more common than between first degree relatives. Therefore, consanguinity turns out to a unique and useful factor for the reduction of BC risk in Turkish Cypriot women.

An association between a depression period of a minimum of 4 days during the premenstrual phase and the risk of BC was assessed. The analysis confirmed that there was a 74% increased risk of BC in the final adjusted model. Premenstrual syndrome (PMS) includes a range of behavioural, emotional and physical symptoms experienced by a woman in the luteal phase of the menstrual cycle and are very common (80-90%) in the reproductive age population (Halbreich et al., 2006). The actual pathophysiology of PMS is unknown; however, some hormonal changes, unhealthy eating, stress and serotonergic dysfunction are known to be the cause of PMS (Takeda et al., 2006). The association between BC risk and depression is well known, as evidence from studies on experimental animals, as well as human and clinical trials, have suggested that depression may influence BC development through several mechanisms, such as interfering with the DNA repair mechanism and by triggering abnormal activity of the hypothalamic-pituitary-adrenal axis, etc. (Soygur et al., 2007) In our study, no significant increased BC risks were reported in cases of exposure to pesticide in the adjusted model. Other studies have suggested that the carcinogenic effect of pesticides is strongest when exposure occurs before puberty, when breast development starts, women at age 14 when exposed to DDT had significantly increased risks of BC (Clapp et al., 2008)

In terms of dietary factors, the daily consumption quantities of oil, sugar and water were assessed in relation to the risk of BC. The estimations confirmed that large amounts of oil and sugar consumption were significantly positively associated with BC risk, while daily water intake of approximately 1 to 2 litres was found to reduce the BC risk by up to 64%. However, the risk remains the same even after increasing water intake above 2 litres per day (OR 0.36, 95% CI 0.199 -0.677). Other studies have also supported the beneficial effect of drinking water on various cancers including bladder cancer, colorectal cancer, and BC prevention (David et al., 2004). The relationship between oil or fat intake and BC is unclear; however, there is evidence that lower fat intake reduces the concentration of bio-available serum sex hormones

(Parry et al., 2011) which are the proposed main risk factors for BC. Similarly, worldwide sugar consumption has increased threefold in the last 50 years, and WHO (World Health Organization) in collaboration with FAO (Food and Agriculture Organization of the United Nations) has issued various recommendations for the reduction of sugar consumption (WHO 2014). In addition to metabolic syndromes, excessive sugar consumption is associated with several types of cancers, including BC (Friberg et al., 2011). Sugars are found to enhance cell proliferation and migration, induce DNA damage, and increase inflammation (Liu and Heaney 2011). No significant association between BC risk and the consumption of butter, margarine, other HFDPs, coffee and tea were reported in the final adjusted model, although the effects of the margarine and HFDP consumption were significant in the age-adjusted univariable model. Different eating patterns and cancer rates in different countries suggest that dairy products may influence BC risk. However, dairy products are a diverse group of foods, with different factors that can potentially influence the risk. Some dairy products, such as whole milk and some cheese, have relatively high saturated fat content and may increase the risk. Additionally, several contaminants and growth factors, such as insulin-like growth factor I in dairy products, may have potential carcinogenic effects and could promote BC cell growth. However, the calcium and vitamin D content in dairy products have been hypothesised to reduce the BC risk. Nevertheless, the available epidemiological evidence is not sufficient to support the association between BC risk and dairy products.

3.10. Conclusion

As the first epidemiological study on BC risk at the north part of the island, a comprehensive range of factors (i.e., recognised as well as other potential BC risk factors specific to this population) was assessed. In addition to strong associations with various already recognized factors i.e. BMI, family history, menarche age, age at menopause, age at first full-term pregnancy, smoking, and history of FBD, the BC risk in North Cypriot women was found to be associated with PMD, diagnostic radiation exposure, and the quantity of oil and sugar consumption. However, consanguinity and adequate daily water intake were protective factors. Furthermore, a strong association between consumption of fats and sugar and postmenopausal BC risk were reported.

Adequate daily water intake has proved to have beneficial effects on the primary prevention of postmenopausal BC. Overall the results of the study can help with the development of a risk assessment tool for the North Cyprus population in order to identify high-risk individuals that will improve the prevention of the disease.

CHAPTER 4

OVERALL CONCLUSION AND FUTURE PERSPECTIVE

In conclusion, this thesis suggests an increasing incidence and trend of cancer in North Cyprus. The most common cancer in men was skin cancer, while in women was breast cancer. The cumulative risk of skin cancer and breast cancer were the highest of all other types in men and women respectively.

In the second part of the study on the descriptive epidemiology of breast cancer, lifestyle, reproductive and dietary variables predict breast cancer risk in Turkish Cypriots similar to those that reported in other populations. Thus establishing that lifetime oestrogen exposure, family history of breast cancer, obesity, history of benign breast disease, PMD and quantity of fats and sweets used remained the main arbiter of BC risk in Turkish Cypriot women. At the same time, the study suggests parental consanguinity and use of adequate daily water intake as protective factors.

We also concluded that there is a strong association between consumption of fats and sugar and post-menopausal breast cancer risk. Water intake has beneficial effects on the primary prevention of postmenopausal breast cancer in North Cyprus women.

As the most appropriate approach against cancer is the preventive strategies, therefore the results of this study can help with the development of a risk assessment tool for the North Cyprus population in order to identify high-risk individuals for breast cancer that will help in the prevention of the disease.

This study provides an opportunity for future investigations about the risk factors for most prevalent cancers in Turkish Cypriot women, a population about whom no information about cancer susceptibility is available. Further studies are required to elucidate the risk factors that are associated with the other most prevalent cancers in the TRNC. For cancer control and prevention implementing population-based screening programs, fostering public awareness about the risk factors, and

encouraging people for regular screening of the breasts, thyroid, and prostate are recommended.

Therefore, long follow-up studies are required about the aetiology of prevalent cancers. Moreover, biological investigations on the molecular and genetic bases of cancer such as high breast cancer risk susceptibility loci in some high and low penetrance genes and oestrogen receptor gene are required in this population.

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ARTICLES FROM THIS THESIS

Publish Articles

1. Title; Incidence of cancer in the Turkish Republic of Northern Cyprus

Pervaiz, R., Tulay, P., Faisal, F., & Serakinci, N. (2017). Incidence of cancer in the Turkish Republic of Northern Cyprus. *Turkish journal of medical sciences*, 47(2), 523-530.

1. Title; Dietary factors modify post-menopausal breast cancer risk; a case-control study from Turkish Cypriot population

Pervaiz, R., Tosun, Ö., Besim, H., & Serakinci, N. (2017). Dietary factors modify post-menopausal breast cancer risk: a case-control study from Turkish Cypriot population. *Biomedical Research and Therapy*, *4*(03), 1171-1184.

Submitted Article:

2. Title: Risk factors assessment for breast cancer in North Cyprus: A comprehensive case-control study from Turkish Cypriot women. (Under review)
by
Ruqiya PERVAIZ
Özgür TOSUN
Hasan BESIM
Nedime SERAKINCI

Appendix A: Study questionnaire

Questionnaire

Serial No ………….………   Date: …...………...

Subject; Case…....... Control………

Personal Profile Name……………… (Optional) Address…………………………….

Section A: Assessment of Worldwide established risk factors.		
QUESTIONES	ANSWERES	
1. Your age in years?		
2. Living area?	City ……………………………………..	1
	Village……………………………………	2
3. Educational level?	Primary…………………………………..	1
	Secondary……………….…..…….............	2
	Tertiary………………….……………..…	3
	University……………..…………….........	4
4. Marital status?	Single………………….…................……..	1
	Widow………………….………………....	2
	Divorced………………………….……..…	3
	Married………………….……………..…..	4
5. BMI	Height………………………………….…	?
	Weight…………………….……………......	?
6. Family History 7(a). Do you have multiple family members who have had breast, ovarian and/or prostate cancer?	Yes…………………………………….…	1
	No…………………………………….…..	2
	Don't know…………………………….….	3
7(b). Which of your first degree relatives have breast cancer?	Mother ……………………………………..	1
	Sisters……………………………….……	2
	Daughters …………………………............	3
	Nil ….....…………………………..………	4
7. BRCA1 or BRCA2 gene mutation.	Yes………………………….……...........	
	No………………………………...…….…	

Do you have a mutation in either the BRCA1 or BRCA2 gene or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer?	Don't know………………………….…...	1
		2
		3
8. Age at Menarche. What was your age at the time of your first menstrual cycle?	≤ 12 years……………………………....... 13-14 years…………………...……...……. ≥ 15 years………………….....………......	1 2 3
9. Age at menopause. 9(a). Have you gone through menopause (Have you stopped having menstrual periods)?	Yes …………………….…………..… No……………………………...…………	1 2
9(b). If yes, what was your age at the time of your last menstrual period?	≤45 years……………………...………… 46- 50 years………….…………….….. ≥51 years…………….……………………	1 2 3
10. Parity 10(a). Did you ever become pregnant?	Yes……………...……………………… No……………….…………………...	1 2
10(b). Age at first full-term pregnancy What was your age at your first full-term pregnancy?	< 30 years…………………...............……. ≥ 30 years………………………………	1 2
10(c). Number of Children		
10(d). Breastfeeding Have you ever breastfeed/for how long you breastfeed?	Never………………………………….. ≤ 6 months……………………………. 7-12 months………………………..…… > one year……………………….…….....	1 2 3 4
11. Oral contraceptive Use Have you ever use oral contraceptives for one month or more?	No……………………………………. …. Yes……………………………..………… .	0 1
12. Hormonal Replacement Therapy (HRT)	< 6 months……………………..……….. 6 months – 5 years……………….…...……	1 2 3

Have you ever used hormonal replacement therapy?	> 5 years …………………...…..………….... Never……………………………….………..	0
13. Infertility drug use Have you ever used infertility drugs? If yes how long?	Never.……………………………………….. Up to 3 months…………………………….. 6 to 12 months………………..…………..... 2- 5 years…………………………………... More than 5 years……………………….....	0 1 2 3 4
14. Smoking 14(a). Did you ever smoke 6 cigarettes per day for up to 6 months?	Never……….………………..…………….... Past……………………………..……....…... Current…………………………….........…...	0 1 2
14(b). Did you live with at persons who smoked in your presence at least for 6 months? If yes? For how many years?	Yes …………………………...………… .. No …………………………….…………….	1 2
15. Physical Activity Do you walk (or do another moderate activity cycling, running, sports, gym etc) for at least 30 minutes on most days or at least 3 hours per week?	Yes………………………….....………..…… No………………………………….……..….	1 2
16. Benign breast disease 16(a). Do you have fibrocystic breast?	Yes………………………...…………..……. No…………………………………………...	1 2
17. Have you exposed to physical trauma on the breast? If yes, what type was that...?	Yes……………………………………… No… ……………………………………....	1 0
17(b). Have you ever had a biopsy?	Yes…………………………………………... No…………………………….……………...	1 0
17(c). If yes, how was the result?	Malignant………….……….……………..…	1 2

	Benign…………………….…….…….. .
18. If yes, what type of cancer?	
The following questions (from No. 21 to 22) are for case only	
19. What is the date of diagnosis?	
20. What is your age at diagnosis?	
21. How was the problem discovered?	Accidentally…………………….……..… 1 Routine self-examination………………..… 2 Routine physical examination by health professional……………………………….. 3

Section B: Premenstrual syndrome and psychosocial condition.	
1. Did/is your menstrual cycle was/is regular?	Yes…….…………………….......… 1 No……………………………….....… 0
2. What was/is the average length of your menstrual cycle?	
3. (a). Did/Do you ever had/have premenstrual breast pain or tenderness, headache or a migraine?	Yes …………………………….......… 1 No……………………………………. 0
4. (a). Did/Do you ever had/have premenstrual depression?	Yes.…………………………. …..……… 1 No………………………………………. 0

Section C: Consanguinity (Degrees of relationship)

Q. Did your parents were relatives before marriage?   Yes   No

If yes, how were they related...?

Q1. Did you ever have the following radiation screening or therapy in the past?

Type	No	1 time	2-3 times	≥ 4	Age at first radiation
X-rays					
Computerised Tomography scan					
Radiation therapy, If yes, please indicate the part of the body where used.					

Section E: Dietary risk factors

Q1. How often do you consume the following? Tick mark (√) the square.

Food name	Frequency of consumption			
Oil consumption (table spoon/ day)	Never	Up to 1.5 (20 ml)	2-3 (30-45ml)	More than 3 (>45 ml)
Butter (table spoon/ day)	Never	4 table spoon ≤ 60 grams	> 4 tablespoon > 60 grams	--
Margarine (table spoon/ day)	Never	4 table spoon ≤ 60 grams	> 4 tablespoon > 60 grams	--
Sugar consumption (table spoon/ day)	Never	≤ 3	4-6	> 6
Water consumption (litre /day)	≤ 1	1-2	>2	--

Full-fat dairy products consumption (yoghurt, milk, cheese etc.) servings/day	Never	1	2-3 times	≥ 4
Use of Olive Oil	Never	Rare	3-5	Daily
Alcohol (ml/day)	Never	≤ 300 About 1 glass	> 300	--
Coffee consumption (cups/day)	Never	1-2	3	≥ 4
Turkish tea consumption (cups/day	Never	1-2	3	≥ 4

Section F: Risk factors from Residential Area, Industrial chemicals and Agrochemicals	
Industrial Aria. 1. (a). Did you ever live in a home within one mile (1.5km) of industries? (b). If yes, how long you live there?	Yes………………………………… 1 No……………………………….. 2
Agricultural Land Aria 2. (a). Did you ever live in a home within one mile (1.5km) of an agriculture land? b). If yes, how long you live there?	Yes………………………………… 1 No……………………………….. 2
3. During your lifetime, have you ever personally mix or applied, pesticides or herbicides on your home, lawn or garden? If yes for how long?(days per year)	No……………………………….. 1 Yes…………………………..… 2
4. Can you think of any other ways you have been exposed to chemicals during your life?	No……………………………….. 1 Yes………………………………. 2
5. What chemical how long?	

Section G: Occupational (worksite exposures) & Shift work Risks

Q1. List the job you have done for the at least 6-month period.

S.no.	Job title	For how long you did that job?	Night shift work?	Your main tasks in that occupation?	Your monthly income
1					
2					
4					
4					

Thank you very much.

Appendix B: Ethic committee approval

EU : 410 — 2016

YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR DEĞERLENDİRME ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 22.09.2016
Toplantı No : 2016/39
Proje No : 316

Yakın Doğu Üniversitesi Sağlık Bilimleri Fakültesi / Moleküler Biyoloji ve Genetik öğretim üyelerinden Prof. Dr. Nedime Serakıncı'nın sorumlu araştırmacısı olduğu, YDU/2016/39-316 proje numaralı ve **"Risk Factors Assessment for Breast Cancer in Turkish Republic of Northern Cyprus (TRNC)"** 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. Doç. Dr. Ümran Dal   (ÜYE)

7. Doç. Dr. Çetin Lütfi Baydar   (ÜYE)   KATILMADI

8. Yrd. Doç. Dr. Emil Mammadov   (ÜYE)

Appendix C: Authorization letters

KUZEY KIBRIS TÜRK CUMHURİYETİ
SAĞLIK BAKANLIĞI
YATAKLI TEDAVİ KURUMLARI DAİRESİ

Sayı. YTK.0.00-1/2013-16/ 6080   Lefkoşa : 07.11.2016

Dr. Burhan Nalbantoğlu Devlet Hastanesi Başhekimliği,
Lefkoşa.

Yakın Doğu Üniversitesi Sağlık Bilimleri Fakültesi, Tıbbi Biyoloji ve Genetik Bölümü Doktora öğrencisi Ruqiya Pervaiz'in, **''KKTC'de Meme Kanseri için Risk Faktörlerinin Değerlendirmesi''** konulu çalışmasını Kasım 2016-Haziran 2017 tarihleri arasında, hizmetler aksamayacak şekilde, Hastaneniz ilgili biriminde ekinde belirtilen anket formları aracılığı ile ankete katılmak isteyen hastalara uygulaması ve çalışmasının raporlarını yayınlamadan önce Bakanlığımızla paylaşması kaydıyla uygun görülmüştür.

Bilgilerinizi ve gereğini saygı ile rica ederim.

Dr. Nil ERGÜN ELEDAĞ
Yataklı Tedavi Kurumları Dairesi
Başhekimi

Dağıtım: Sağlık Bakanlığı,
Sn.Prof.Dr.İhsan Çalış
Sn.Ruqiya Pervaiz.

SB.

Adres: Bedreddin Demirel Caddesi No: 142 Lefkoşa.
Tel: (+90 392) 228 3173, 228 4011, 228 4068 / Faks: (+90 392) 228 4247

KUZEY KIBRIS TÜRK CUMHURİYETİ
SAĞLIK BAKANLIĞI

Sayı: SAB.0.00- 5175/10-16/3362

Lefkoşa : 04.11.2016

Yataklı Tedavi Kurumları Dairesi Müdürlüğü,
Lefkoşa.

Yakın Doğu Üniversitesi Sağlık Bilimleri Fakültesi Dekanı Prof. Dr. İhsan Çalış'tan alınan ve bir sureti ekte tarafınıza gönderilen yazıya bahse konu, Sağlık Bilimleri Fakültesi Tıbbi Biyoloji ve Genetik Bölümü doktora öğrencisi Ruqiya Pervaiz'in "KKTC'de Meme Kanseri İçin Risk Faktörlerinin Değerlendirmesi" isimli tez çalışmasının, Dairenize bağlı Hastanelerde yapması Bakanlığımızca uygun görülmüştür.

Bilgilerinize ve gereğini saygı ile rica ederim.

Kemal Deniz DANA
Müsteşar

Dağıtım: Sn. Prof. Dr. İhsan Çalış,
Sn. Ruqiya Pervaiz.

BAÖ.

Adres: Bedreddin Demirel Caddesi No: 142 Lefkoşa.
Tel: (+90 392) 228 3173, 228 4011, 228 4068 / Faks: (+90 392) 228 3893

APPENDIX D. INFORMED CONSENT FORM (FOR THE PATIENTS / PARTICIPANTS)
Information Package

Title of Study: **Risk Factors Assessment for Breast Cancer**

Objective of Study: To find out if certain exposures to life style, hormonal, menstrual abnormalities, workplace or home environment and dilatory factors increase the chance of developing breast cancer in susceptible people.

NEU Involvement: This project is being conducted as part of my PhD studies at Near East University North Cyprus.

Contact Details of Researchers:

Ms Ruqiya Pervaiz

(Doctor of Philosophy Student)

 Ph. (0090) 5338746957

Email: ruqiyapervaiz@awkum.edu.pk

Supervisor: Prof. Dr. Nedime Serakinci

Ph. (0090) 392 675 1000 Ext: 3007, 1181, 1033

Email: nedimeserakinci@gmail.com

Prof. Dr. Hasan Besim

Ph (0090) 392 444 0535 Ext 1165

Email: hbesim@yahoo.com

Postal address: Department of Molecular Genetics

Near East Avenue, Nicosia, Northern Cyprus

Post code: 99138

Description of the Study Project

You are invited to participate in a research study conducted by Ruqiya Pervaiz (Doctor of philosophy student) from the NEAR EAST UNIVERSITY in the Department of Medical Biology and Genetics.

I have learned that exposure to various potential risk factors may increase the chance of developing breast cancer in susceptible individuals. The purpose is to help the understanding of what causes Breast Cancer. You were selected as a possible participant in this study because you are a patient of breast cancer. If you decide to participate, you will be given a face to face interview with a standard set of questions. You will be asked questions about whether your family members have Breast Cancer, where you have lived throughout your life, occupations you have held throughout your life, and various questions about possible exposures you may have experienced in your life. You will only be expected to answer the questions to the best of your ability. You are also welcome to have a family member (e.g. your partner) with you in the interview to help you answer the questions. The interview will take approximately 1 hour of your time. You may also be invited to be re-interviewed at a later date to allow us to measure how reliable the interviews are.

The project will help us to understand the possible causes of Breast Cancer better. A better understanding of the disease may eventually lead to preventive measures for the disease However; I cannot guarantee that you personally will receive any benefits from this research. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. Subject identities will be kept confidential by author in any publication or dissemination of the results of this research, through the use of aggregate (grouped) data, rather than information about you as an individual. Your name or identifying information will not be released in any of the published or disseminated results of the study.

Your participation is voluntary. Your decision whether or not to participate will not affect your relationship with the Near East Hospital. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without penalty. If you have any questions about the study, please feel free to contact (contact information given above).

If you have questions regarding your rights as a research subject, please contact the NEAR EAST INSTITUTIONAL REVIEW BOARD. You will be offered a copy of this form to keep. Your signature indicates that you have read and understand the information provided above, that you willingly agree to participate, that you may withdraw your consent at any time and discontinue participation without penalty, that you will receive a copy of this form, and that you are not waiving any legal claim.

Participant	**Witness**	**Interviewer**
Name,	Name,	Name,
Surname	Surname	Surname
Address	Address	Address

Phone   Phone
Signature   Signature

NFORMED CONSENT FORM FOR ADULTS (FOR THE CONTROL GROUP)

You are invited to participate in a research study conducted by Ruqiya Pervaiz (Doctor of philosophy student) from the NEAR EAST UNIVERSITY Department of Medical Biology and Genetics.

I have learned that exposure to various potential risk factors may increase the chance of developing breast cancer in susceptible individuals. The purpose is to help the understanding of what causes Breast Cancer. You were selected as a possible participant in this study because you are an age matched control for the study. If you decide to participate, you will be given a face to face interview with a standard set of questions. You will be asked questions about whether your family members have Breast Cancer, where you have lived throughout your life, occupations you have held throughout your life, and various questions about possible exposures you may have experienced in your life. You will only be expected to answer the questions to the best of your ability. You are also welcome to have a family member (e.g. your partner) with you in the interview to help you answer the questions. The interview will take approximately 1 hour of your time. You may also be invited to be re-interviewed at a later date to allow us to measure how reliable the interviews are.

The project will help us to understand the possible causes of Breast Cancer better. A better understanding of the disease may eventually lead to preventive measures for the disease However; I cannot guarantee that you personally will receive any benefits from this research. Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. Subject identities will be kept confidential by author in any publication or dissemination of the results of this research, through the use of aggregate (grouped) data, rather than information about you as an individual. Your name or identifying information will not be released in any of the published or disseminated results of the study.

Your participation is voluntary. Your decision whether or not to participate will not affect your relationship with the Near East Hospital. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without penalty. If you have any questions about the study, please feel free to contact (contact information given above).

If you have questions regarding your rights as a research subject, please contact the NEAR EAST INSTITUTIONAL REVIEW BOARD. You will be offered a copy of this form to keep. Your signature indicates that you have read and understand the information provided above, that you willingly agree to participate, that you may withdraw your consent at any time and discontinue participation without penalty, that you will receive a copy of this form, and that you are not waiving any legal claims.

Participant	**Witness**	**Interviewer**
Name,	Name,	Name,
Surname	Surname	Surname
Address	Address	Address
Phone	Phone	
Signature	Signature	

APPENDIX E. CURRICULUM VITAE

RUQIYA PERVAIZ
Ph.D. CANDIDATE, DEPARTMENT OF MEDICAL GENETICS
NEAR EAST UNIVERSITY, NORTH CYPRUS

LECTURER IN DEPARTMENT OF ZOOLOGY, AWKUM PAKISTAN

Email. ruqiyapervaiz@awkum.edu.pk

Phone # 00905338746957

1. **RESEARCH INTEREST**
   Understanding the molecular aspect of diseases, molecular epidemiology, and genetic diversity. Special areas of interest include:
   a) Genetic Engineering
   b) Population Genetics, Aquaculture and Medical Entomology.
   c) Cancer Research and molecular aspects of genetic diseases.

2. **FACULTY APPOINTMENTS**.
   a) **LECTURER (From 18th August 2009- Till date)**
   Department of Zoology, Abdul Wali Khan University, Mardan Pakistan.

   Subject taught;

   i)   Genetics
   ii)   Embryology
   iii)   Medical Entomology
   iv)   Human Physiology
   v)   Biotechnology
   vi)   Laboratory practical in all of the above subjects

   b) **ASSISTANT DIRECTOR FISHERIES (From 3rd February 2008 to 18th august 2009).**
   Directorate of Fisheries, Government of Khyber Pakhtunkhwa Peshawar. Pakistan.

3. **EDUCATION RECORD (Throughout 1st Division)**

Degree / Certificates	Year	Board/University	Percentage/CGPA/Division
Ph.D. Medical Biology and Genetics	2013-Onwards	Near East University Nicosia, North Cyprus.	In Progress

M. Phil. Genetic Engineering and Biotechnology	2011	Institute of Biotechnology and Genetic Engineering the University of Agriculture Peshawar.	3.8/ 1st Division
Master of Science (Zoology)	2006	Department of Zoology University of Peshawar	1st Division
Bachelor of Science (Biology)	2003	University of Peshawar	1st Division
Intermediate (Pre-Medical	2011	BISE Peshawar	1st Division
Matric/ SSC (Biology)	1999	BISE Peshawar	1st Division

4. PUBLICATIONS

Articles:

1. **Pervaiz, R**., Pinar T, Faisal, F., Serakinci, N. **(2017).** Incidence of Cancer in the Turkish Republic of Northern, Cyprus. *Turkish Journal of Medical Sciences*,47, 523-530 (Web of Science (**SCI expanded Impact factor: 0.78) SCOPUS, NCBI PubMed**).

2. **Pervaiz, R**., Faisal, F., & Serakinci, N. **(2017)**. PRACTICE OF CONSANGUINITY AND ATTITUDES TOWARDS RISK IN THE PASHTUN POPULATION OF KHYBER PAKHTUNKHWA, PAKISTAN. *Journal of Biosocial Science*, 1-7. Cambridge University press. doi:10.1017/S0021932017000189. **(Web of Science (SSCI) Impact factor: 1.55, Scopus, NCBI PubMed).**

3. **Pervaiz, R**., Tosun, Ö., Besim, H., & Serakinci, N. **(2017).** Dietary factors modify post-menopausal breast cancer risk: a case-control study from Turkish Cypriot population. *Biomedical Research and Therapy*, 4(03), 1171-1184 **(Web of Science ESCI)**

4. **Pervaiz, R**. Faisal. F, **(2017).** Breast cancer outcome in Africa is associated with Socioeconomic development and health care setups. *WCRJ 2017; 4 (2): e890. Indexed in Web of Science ESCI).*

5. **Pervaiz, R**. Faisal. F**, (2017).** Cancer incidence and mortality are associated with human development index and health set-up in Africa. J Egyptian Nat

Cancer Inst (2017), http://dx.doi.org/10.1016/j.jnci.2017.05.003 (**Elsevier) Indexed in web of Science, Scopus & NCBI PubMed.**

6. **Pervaiz, R. (2015).** Genetic Mutations Associated with Breast Cancer in Pakistan. *Malaysian Journal of Medical and Biological Research,* 2(3), 308-3013.

7. **Pervaiz, R,** Ijaz Ali, Sajid Ali, Najib ur Rehman, Farzana, Riaz Muhammad, Ahmad ur Rehman Saljoqi, Musharaf Ahmad. **(2013).** Increasing resistance to combination therapy among the chronic HCV 3a infected patients in KPK. *Life Science Journal*, 10(12), 223-426**. (Scopus)**

8. Shams, S., Ayaz, S., Khan, S., Khan, S. N., Gul, I., **Parvez, R**., Attaullah, S., & Hussain, M. **(2011).** Prevalence and detection of cytomegalovirus by polymerase chain reaction (PCR) and simple ELISA in pregnant women. *African Journal of Biotechnology*, *10*(34), 6616-6619.**Web of science and Scopus**.

9. **Pervaiz, R.**, Ercantan, O., **(2017).** Non-communicable diseases mortality is associated with the socioeconomic status of the countries. (Accepted for presentation in conference **ICSCCW 2017**)

10. Pervaiz, R., Tosun, Ö., Besim, H., & Serakinci, N. (2017). Risk factors assessment for breast cancer in North Cyprus: A comprehensive case-control study from Turkish Cypriot women. Journal: (Under review).

Thesis (M.Phil.)

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2. International Conference on Computational and Social Sciences Joint venture of Abdul Wali Khan University, Mardan, Pakistan and Reccep Tayyip Erdogan University, Rize Turkey 26th August to 28th August 2014.

3. ICSCCW 2017 9th International conference on theory and application of soft computing, computing with words and perception, will be on 22nd-23rd August Hungary Budapest.

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