ASSOCIATION BETWEEN DIETARY PATTERNS AND RISK OF BREAST CANCER AMONG POLISH MIGRANT WOMEN TO THE UNITED STATES

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ABSTRACT

ASSOCIATION BETWEEN DIETARY PATTERNS AND RISK OF BREAST CANCER AMONG POLISH MIGRANT WOMEN TO THE UNITED STATES

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Diet and breast cancer has been a focus of many studies, however, most of them evaluated the association between specific nutrients or foods and breast cancer risk, and only few have assessed the effect of dietary patterns. This study examined the association between dietary patterns and the risk of breast cancer in Polish migrant women to the US.

Analyses were based on data from the US component of the Polish Women's Health Study (138 breast cancer cases and 284 frequency matched controls). Using factor analysis, six factors were retained and based on food groups that had high loadings on a given pattern, were labeled as follows: "healthy Western", "unhealthy Western", "Polish", "alcohol drinker", 'high in dairy fat/sugar" and "meat/potatoes".

Only the "Polish" dietary pattern emerged as significantly reducing breast cancer risk. The observed odds ratios (OR) and confidence intervals (CI), when comparing highest vs. lowest quartile, were: 1) OR=0.49; 95% CI: 0.25-0.98, for all women, 2) OR=0.48; 95% CI: 0.16-1.43, for pre-menopausal women, and OR=0.29; 95% CI: 0.11-0.81 for post-menopausal women. Results for the other dietary patterns were consistent with those previously observed in literature. The "healthy Western" dietary pattern showed a trend towards reduced breast cancer risk and the "alcohol drinker" dietary pattern, showed a trend towards increased breast cancer risk.

This study supports the hypothesis that traditional Polish diet, high in consumption of cabbage foods, has a potential to reduce breast cancer risk.

To My Beautiful Children

Saman & Sepehr

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Chapter 1: Introduction

1.1) International Variation In Breast Cancer Incidence And Mortality

According to GLOBOCAN, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008.[1] Lung cancer is the most common cancer worldwide, both by number of cases and deaths; 1.6 million cases (12.7% of total) and 1.4 million deaths (18.2% of total) respectfully in 2008.[2] Breast cancer is the second most common cancer overall in the world and the fifth rank of cancer deaths.[3] Furthermore, it is the most common cause of female cancer worldwide with an estimated 1.38 million new cases occurring among women in 2008 (accounting for 23% of all female cancer cases; almost one quarter of all female cancer cases) and an estimated of 458,400 female breast cancer deaths (14% of total female cancer deaths) .[1,3]

Age-Standardized breast cancer incidence (ASR, to 2008 world population) ranged from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe with highest rates occurring generally in the developed countries (greater than 80 per 100,000, except Japan) and considerably lower rates in most developing countries (less than 40 per 100,000).[3] For instance, age-standardized incidence rate (ASR's) is 26.0 in Central America, 32.5 in Western Asia, 39.1 in Caribbean, 44.3 in South American, 68.9 in Southern Europe, 76.7 Northern America, 84.0 Northern Europe and 85.5 in Australia, per 100,000 women.[4,5]

In North America and European countries, it was observed that breast cancer incidence rates were increasing through the late 1990s, yet breast cancer mortality remained stable or even decreased in US and Europe over the past 25 years.[6,7] Some of the observed reductions in mortality have been hypothesized to be due to: 1) early detection through mammography, thus breast cancer is detected at earlier stages improving survival, and 2) better treatment. [6]

In the US, female breast cancer was the most common cancer among women with 182,460 new cases (ASR's 76.0 per 100,000 women) which represented 26.4% of all female cancer cases and the second cause of deaths among women after lung cancer with 40,481 (ASR's 14.7 per 100,0000) accounting for about 15% of all female cancer deaths in 2008.[8] However, the US female breast cancer incidence rate (ASR's 76.0 per 100,000) is much higher compared to the rest of developing world (ASR's 38.9 per 100,000) and also higher compared to developed countries (ARS's 66.4 per 100,000). Although US female breast cancer mortality rate (ASR's 14.7 per 100,000) is less than that of other developed countries (ASR's 15.3, per 100,000), it is higher compared to female breast cancer mortality rate in the world (ASR's 12.4, per 100,000). [8]

It has been estimated that 230,480 women were be diagnosed with and 39,520 women died of breast cancer in 2011 in United States. [9,10] The population of the United States is not as homogeneous as in other countries around the world, thus it is important to note that not all races/ethnic groups in the United States have equal breast cancer incidence rates. Based on the Surveillance Epidemiology and End Results (SEER) database (rates standardized to 2000 US population), White women have the highest age-standardized incidence rates (127.3 per 100,000 women) followed by Black (119.9 per 100,000 women), Asian/Pacific Islander (93.2 per 100,000 women), Hispanic (92.1 per 100,000 women) and American Indian/Alaska Native (77.9 per 100,000 women) [9]. According to SEER the age-adjusted death rate for all races was overall 23.5 per 100,000 women per year in US (based on patients who died in 2004-2008 in US). However, the survival rates are better for White American women compared to Black American women. The adjusted mortality rates are as follows: Black American women have the highest age-adjusted mortality rate (32 per 100,000) followed by White American (22.8 per 100,000 women), American Indian/Alaska Native (17.2 per 100,000 women) , Hispanic (15.1 per

100,000 women) and Asian/Pacific Islander (12.2 per 100,000 women)[9]. Based on these statistics, Asian American women rank third in terms of breast cancer incidence among the various races; however, they have the lowest mortality. Also White American women have better survival relative to Black American though White American women have higher incidence rate.

Based on rates from 2006-2008, it is estimated that in US, 12.3% of women born today will be diagnosed with breast cancer at some time during their lifetime (by the age of 80). This number can also be expressed as 1 in 8 women will be diagnosed with breast cancer during their lifetime.[11]

In Poland, breast cancer was estimated as the most common cause of female cancer with 15,571 (24%) new cases in 2008 (ASR's 48.9, per 100,000).[4] Number of deaths has been estimated as 5,362 cases (13.2% of female cancer deaths) with a mortality rate of 14.7(ASR per 100,000). Data show that breast cancer in Poland, was the second cause of deaths, following lung cancer (ASR's for lung: 14.7 per 100,000 with 13.9% of all female cancer deaths) in 2008.[4] According to these estimates breast cancer incidence rate (ASR) in Polish native women is estimated to be nearly one half that in the United States. However, breast cancer incidence is increasing in Poland. The reported ASR's/100,000 women in the late 1980's were 38.7 for Warsaw City and 22.9 for Warsaw Rural areas. Lifestyle differences, such as diet or other environmental risk factors, between women living in urban vs. rural settings, or those living in United States and those living in Poland, have been suggested to contribute to the two or at times three fold differences in breast cancer incidence in between countries. When Polish women migrate to US their breast cancer risk increases (doubles) and becomes almost as high as that of US White women in their own lifetime. Therefore, studying Polish migrant women to the US offers an opportunity to evaluate effects of lifestyle changes on breast cancer risk.

Breast cancer has multiple risk factors, some of them more consistently observed, such as family history, reproductive history, obesity, lactation, while other factors such as physical activity, diet and other environmental factors need more investigation. Moreover, when identifying risk factors for breast cancer, timing when exposure occurs has been shown to play an important role in the effect size of the risk factor. When a woman is exposed to risk factors, such as irradiation, certain foods, alcohol ingestion, and smoking, at a younger age, her later risk of breast cancer in adulthood is increased relative to women who had such an exposure only during adulthood. .[12,13] This suggests that modifications of certain risk factors only in adulthood may not be as effective as if such risk modification occur much earlier in life. Therefore, it has been suggested in the literature that preventative measures may be most effective in breast cancer risk reduction if they occur between late childhood and early adulthood when the breast tissue develops.[13]

1.2) Question To Be Addressed In This Thesis

1.2.1) Aim and Hypothesis

Aim

To assess whether there is association between usual dietary patterns of food consumption during adulthood (1985-1989) and later risk of breast cancer in Polish migrant women to US. Usual adult diet was determined with the use of food frequency questionnaire (FFQ) for the time period 1985-1989.

Hypothesis

Dietary pattern high in consumption of vegetables, especially cabbage foods during adulthood (adjusted for other established and potential risk factors for breast cancer) will decrease the risk of breast cancer among Polish migrant women to the US.

1.2.2) Source of Data

The analysis are based on data from the Polish Women's Health Study (PWHS) which consists of two parallel case-control studies, one in Polish-born migrant women residing in US and the second among Polish native women residing in Poland. The same data collection instruments were used to collect information from the study participants in both countries. The analyses for this thesis are based on information obtained from 422 Polish migrant women residing in the United States: 138 incidence breast cancer cases and 284 controls.

PWHS was designed to assess whether specific life-style changes that occur after migration of Polish women to US, can explain part of the increase in breast cancer incidence and mortality of Polish-migrant women residing in US. After migration, one of the life style changes includes dietary shifts away from the traditional Polish diet to more Western diet that is predominant in the US. Therefore, these analyses were conducted to examine if there is an association between dietary patterns during adulthood, assessed by food frequency questionnaire for the time period 1985-1989 and breast cancer risk in Polish-migrant women. Since this study was carried out both in Poland and US, the time period 1985-1989 was chosen as the reference time period, in order to capture the traditional Polish diet before introduction of market economy to Poland after the fall of Communism in 1989.

Additional information was also collected on other established risk factors such as reproductive history, physical activity, family history, and occupational histories. In multivariate analyses these risk factors, which can be potential confounders, were included in all models evaluating the association between dietary patterns and breast cancer risk.

1.3) Organization of This Thesis

This thesis includes five chapters as follow: Introduction (Chapter 1), Background (Chapter 2), Methods (Chapter 3), Results (Chapter 4), and Discussion/Conclusions (Chapter 5). Chapter 4 contains all the results and tables.

Chapter 2: Background

2.1) Definition of Breast Cancer

Based on the American Cancer Society, definition of breast cancer is "a malignant tumor that starts in the cells of the breast".[14] "A malignant tumor is a group of cancer cells that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body".[14] There are five stages in the development of breast cancer: stage 0 (*in situ)* – stage 4 (distant metastasis). *In situ* breast cancer is defined as "cancer cells that remain within the basement membrane of the elements of the terminal duct lobular unit and the draining duct" while invasive breast cancer can be defined as "a dissemination of cancer cells outside the basement membrane of the ducts and lobules [of the breast] into the surrounding adjacent tissue [and distant organs]" (stages one through four).[15] For this study, breast cancer cases were defined as women who were histologically- or cytologically confirmed to have diagnosis of first primary invasive breast cancer.

2.2) Etiology of Breast Cancer

Breast cancer etiology is multi–factorial.[17] Some of the risk factors are not modifiable, such as specific gene mutations, age, race, while others can be attributed to some environmental exposures. Yet others are related to the personal behaviors, or so called lifestyle factors, such as smoking, drinking, physical activity and diet. It should be noted that some risk factors have stronger influence on risk than others and their influence on breast cancer risk may change over time due to factors such timing of exposure and other concurrent or past lifestyle factors. Epidemiological studies on migrant populations have observed that migrants acquire the rates of breast cancer incidence of host countries within 1-2 generations.[16,17] These studies have contributed to our ability to assess the role of environmental factors in determining risk of various cancers.

2.2.1) Non-Modifiable Risk Factors

Gender: The main risk factor for developing breast cancer is gender. Females are at a higher risk than males of developing breast cancer. Male breast cancer accounts for less than 1% of all reported breast cancer cases.[17]

Age: Risk of developing breast cancer increases with age. In addition, in a high risk country like US, in contrast to low risk countries, the risk continues to rise for post-menopausal women reaching a plateau only around the age of 80, while it plateaus around menopause in low risk countries like Japan or other developing countries.[17,18] According to National Cancer Institute (NCI) statistics, from 2004-2008, the median age at diagnosis of breast cancer in US was 61 years old and more than 83% of breast cancers were reported in post-menopausal women.[18] The median age of breast cancer mortality was reported as 68 years old and more than 93% of breast cancer deaths occurred in post-menopausal women.[18,19]

Genetics: About 5% to 10% of breast cancer cases are attributed to hereditary risk factors such as mutations in specific genes.[17,20] The two genes that contribute most to hereditary breast cancer risk are the tumor suppressor genes, BRCA1 and BRCA2. Fifty-two percent of the hereditary breast cancers can be attributed to BRCA 1, while 32% are attributed to BRCA2 gene mutations.[21] Among women with germline mutations in the BRCA1 and BRCA2 tumor suppressor genes, the reported estimates for lifetime risk of developing breast cancer vary from

46% to 87%, depending on the population studied.[21] This high lifetime risk for BRCA1/BRC2 mutation carriers is in sharp contrast to that of 11% in the general population.[22]

Family History: Family history of breast cancer is another strong non-modifiable risk factor.[17] The risk varies with the number of first degree relatives (mother, sister, or daughter) with breast cancer. When only one first degree relative is affected, the risk doubles, while having 2 first-degree relatives increases the risk about 3-fold.[17] However, eight of nine women with sporadic breast cancer usually do not report any positive first-degree family history of breast cancer. Altogether, less than 15% of women with breast cancer have a family member with this disease.[21] This means that most (over 85%) women who get breast cancer *do not* have a family history of this disease.

Risk of Second Primary Breast Cancer: A woman with cancer in one breast has a 3- to 5-fold increased risk of developing a new primary cancer in the other breast or in another part of the same breast.[17] This risk is independent of risk of metastasis, which is recurrence of the first primary either in the other breast or metastases to other organs.

Race/Ethnicity: In the US, White women have higher age standardized lifetime incidence of breast cancer than African-American women, but African-American women are more likely to die of this cancer.[9] However, in women under 45 years of age, breast cancer is more common in African- American women. Other ethnic groups such as Asian, Hispanic, and Native-American women have a lower lifetime risk of developing and dying from breast cancer.

2.2.2) Potentially Modifiable Risk Factors

Age at Menarche and Menopause: Women who started menstrual cycles at an early age (before age 12) and/or have menopause at a later age (after age 55) are at a higher risk of breast cancer. [17] For instance, women who have a natural menopause (defined as permanent cessation of menses for at least 6 months) after age of 55 are twice as likely to develop breast cancer as women whose menopause occurred before age 45. [17] The increase in risk may be due to a longer lifetime exposure to the hormones estrogen and progesterone.

Age at First Full Term Pregnancy: Nulliparity and late age at first live-birth both increase the lifetime risk of breast cancer.[17,23] The risk of breast cancer in women who have their first child after the age of 30 is about twice that of women who have their first child before the age of 20. The highest risk group is those who have a first child after the age of 35; these women appear to be at an even higher risk than nulliparous women. An early age at birth of a second child further reduces the risk of breast cancer.

Hormone Replacement Therapy and Oral Contraceptive Use: Hormone therapy with estrogen (often with progesterone) has been used for many years to relieve symptoms of menopause as well as to prevent osteoporosis (thinning of the bones). The US Preventive Services Task Force in their report in 2004, recommended against the routine use of HRT based on good evidence from studies conducted in representative populations, since the risks including that of breast cancer exceeded the benefits.[24] The association of breast cancer with use of oral contraceptive (OC) pills is not well established. In a 2008 brief review of breast cancer risk and use of oral contraceptive pills, it was concluded that use of oral contraceptive pills did not lead to a significant increase in breast cancer risk. [25] Other studies, however, contradict these findings.

One of the first studies to investigate OC use and breast cancer risk evaluating “current use” vs. “ever used” observed increased breast cancer risk for current users (Odds ratio (OR) 4.0, CI= 1.8-9.0).[26] However, over time the composition (levels of estrogen and progesterone) of OC pills has changed. Therefore these results published in 1980’s; need to be viewed in the context of the composition of OC pills on the market at that time.

Reproductive History and Breast Feeding: The rising incidence of breast cancer in the developing world can be to some extent attributed to the changing behavioral patterns with the adoption of reproductive patterns similar to the developed nations such as increase in nulliparity, late age at first full term pregnancy and reduced duration of lactation. It has been estimated that risk of breast cancer increases on average by 3-5% per year delay in age at first full term pregnancy. [23] The association between total parity and breast cancer risk has been inconsistent. Some studies have shown a protective effect with increasing parity, while others do not support this observation.[23,27] It has also been observed that the protective role of multiparty is stronger for breast cancers arising at a later age.[27] Lactation is another factor that has been shown to be protective against breast cancer risk. In a collaborative reanalysis of data from 47 epidemiological studies it was observed that cases of breast cancer had a shorter average duration of breast feeding (9.8 months) in comparison to controls (15.6 months). It was estimated that the relative risk of breast cancer decreased by 4.3% for every 12 months of breast feeding. It was also observed that average duration of breast feeding differed among the developed and the developing nations, with an average of 8.7 and 29.2 months for developed and developing nations respectively.[28]

Alcohol Consumption: Alcohol consumption is another modifiable breast cancer risk factor and is linked to an increased risk of developing breast cancer. Female drinkers with one drink per day, have about 10% increase of developing breast cancer compared to female non-drinkers.[29] In a meta-analysis, breast cancer relative risk was reported as RR=1.10 for 12g/day of alcohol (1 drink per day) comparing female-drinkers to non-drinkers.[30] Those who have 2 to 5 drinks daily have about 1½ times the risk of women who do not drink alcohol. Several biologically plausible mechanisms have been proposed for the association between breast cancer and alcohol consumption. Acetaldehyde, metabolite of alcohol has been shown to be carcinogenic and also, known to destruct folate and induce secondary hyperproliferation.[31] In addition, it has been proposed that the increased risk for breast cancer from alcohol consumption can also be partly explained by higher estrogen levels in heavy drinkers.[32]

Physical Activity: Physical activity during lifetime through its effect on weight reduction and hormonal levels has been shown to be protective against breast cancer.[33] In a systemic review of the literature on physical activity and breast cancer (literature review through early 2006), it was concluded that there was an inverse association between physical activity, measured during various lifetime periods, such as adolescence and adulthood, and breast cancer risk. The reduction in risk was observed to be stronger for postmenopausal women. However, it is not clear whether the magnitude of the protective effect is similar for physical activity during adolescence vs. adulthood and whether there is an additional protective effect for those who are active throughout their lifetime.[34]

Obesity: Obesity has a different effect on breast cancer risk based on menopausal status. Several studies have established that obesity is associated with increased breast cancer risk in post-menopausal women whereas such an association has not been observed in pre-menopausal women.[35,36] The differential effect of adiposity on breast cancer has not been fully explained, although it has been proposed that the protective effect of obesity for pre-menopausal women is due to the increase in anovulatory cycles that obese women experience, thus lower total exposure to estrogens. [37-39] The increase in breast cancer risk due to obesity in postmenopausal women can be due to some extent explained by the higher levels of circulating estrogens in postmenopausal women who are overweight.[40,41] Also, studies have observed that sex hormone binding globulins are lower in obese post-menopausal women contributing to a higher level of bioavailable estradiol. [40-42]

Diet: Diet may account for about 35% of all cancers.[79] Many studies examined the relationship between dietary pattern or specific nutrients and breast cancer risk and survival. Different ethnic or social groups show differences in breast cancer incidence that could be explained by different dietary patterns. In relation to dietary factors only alcohol consumption has most consistently been associated with increased risk of breast cancer. The evidence is less clear for the consumption of (animal) fat, meat, fruit and vegetables (inverse association). Dietary fat has been studied most extensively, yet results continue to be inconsistent. Specific types of fat, particularly monounsaturated fat and increased ratio of omega-3 to omega-6 fatty acids, have been associated with reduced risk of breast cancer. [49] A wide variety of other dietary factors have been studied in relation to breast cancer including total energy, dietary fiber, alcohol, micronutrients, phytochemicals, specific foods, and food constituents.

i) **Dietary Fat:** A possible role of dietary fat in breast cancer has been first hypothesized based on ecological studies. [43] However, results from analytical studies such as case-control and cohort studies have been inconsistent, with case-control studies showing a positive association (OR ranging between 1.2-1.5) whereas no such association has been observed in cohort studies. [44-48] Bingham et al (2003) expressed this in-consistency as "dietary measurement error" which may explain the absence of a significant relationship between dietary fat and breast cancer risk.[46] As a part of European Prospective Investigation of Cancer and Nutrition (EPIC), authors evaluated diet in 13070 women who were resident in Norfolk, UK, between 1993 and 1997. Nested case-control study of 168 incident breast cancer cases and four age and date of entry matched controls (case: control: 1:4) evaluated the association of dietary fat and breast cancer risk when diet was measured both by Food Frequency Questionnaire (FFQ) and 7 day food diary. When intake was measured by a 7 day food diary, analysis of data showed that saturated fat intake had significant association with breast cancer risk with a hazard ratio of 1.22 (95% CI: 1.06-1.40, p-value for linear trend<0.005; per quintile energy-adjusted fat intake). When intake was quantified using a Food Frequency Questionnaire (FFQ), no significant association was detected (hazard ratio=1.10; 95% CI: 0.94-1.29, p-value for linear trend=0.23).[46] Nevertheless, both cohort and case-control studies evaluating the association between breast cancer and specific types of fat have reported protective effects with monounsaturated fatty acids and omega-3 fatty acids with considerable consistency. [49]

ii) **Vegetables and Fruits**: The role of fruits and vegetables in breast cancer etiology has also been studied widely. In a meta-analysis of case-control studies, a statistically significant protective effect of vegetables intake on breast cancer risk was observed

(OR= 0.86; 95% CI: 0.78-0.94).[50] However, in the same paper, meta-analysis of the cohort studies did not find a significant reduction in risk.[50] In a pooled analysis of 8 cohort studies conducted by Smith-Warner *et al* (2001), authors also did not observe any significant reduction in breast risk either for total “fruit and vegetable” consumption (Relative Risk (RR)=0.93, 95% CI=0.86-1.00; p-value for trend=0.12) or total “vegetables” consumption (RR=0.96, 95% CI=0.89-1.04; p-value for trend=0.54). Only a weak non-significant association was observed for total “fruits” consumption (RR=0.93,0 95% CI=0.86-1.00; p-value for trend<0.08), while comparing highest to lowest quartile of intake in calculating all risk ratios.[51]

iii) <u>Nutrient Patterns, Dietary Fiber, Protein and Vitamins</u>: A case-control study conducted by Ronco AL *et al* (2011) in Uruguay (442 new cases, 442 hospitalized controls) showed a nutrient pattern named “antioxidants” and a dietary pattern labeled “high-meat” as being associated with breast cancer risk. The “high-meat” pattern was associated with a strong increase of breast cancer risk, while the “antioxidants” pattern reduced breast cancer risk (OR=3.5, 95% CI: 1.94-6.30; p-value for trend<0.0001 and OR=0.44, 95% CI: 0.27-0.74; p-value for trend<0.001 respectfully after adjusting for the potential confounders, comparing the highest vs. the lowest quartile).[52] Jia-Yi Dong and colleagues (2011) in meta-analysis of 10 prospective studies evaluating association between dietary fiber and breast cancer risk, found an inverse significant dose-response association between dietary fiber intake and breast cancer risk (RR=0.89, 95% CI: 0.83-0.96). Dose-response analysis showed that every 10-g/d increment in dietary fiber intake was associated with a significant 7% reduction of breast cancer risk. [53] Weisburger et al (2002) proposed that heterocyclic amines (HCA) could be major initiators in the process of breast carcinogenesis, while fats may act as promoters in the later stage. Moreover, Rohan *et al* (1998) examined the relationship between diet and breast cancer risk in population based case-control study in Australia with 451 new breast cancer cases (1:1). Authors found little variation in risk through levels of daily intake of energy, protein, and total fat, saturated fat, monounsaturated fat, polyunsaturated fat and cholesterol.[54] Also Edefouni et al, (2008) in a population based case-control study, found four major dietary patterns labeled as: "animal products", "vitamins and fibers", "unsaturated fats" and "starch-rich". Data in this study supported that the "starch-rich" diet was associated with increased risk of breast cancer (OR=1.34, 95% CI: 1.10-1.65), while both "animal products" and "unsaturated fats" were protective (OR=0.74 95% CI: 0.61-0.91 and OR=0.83, 95% CI:0. 68-1.00 respectfully). However, "vitamins and fiber" pattern didn't have any significant association with breast cancer in that study (OR=0.87, 95% CI: 0.73-1.04); all OR's were computed by comparing the highest vs. lowest quartile with adjustment for potential confounders.[55]

2.3) Literature Review of Epidemiologic Studies Assessing the Effect of Dietary Patterns on Breast Cancer Risk

Diet and breast cancer has been reported in many studies but most of them focused either on specific nutrients or foods and only few have addressed overall dietary patterns and breast cancer risk. Since eating patterns allow for examination of how many dietary exposures are working together, the study of the relationship between dietary patterns and chronic diseases such as cancer, diabetes or cardiovascular disease has recently become an important topic in nutritional epidemiology of chronic disease.

Factor analysis/principal component analysis has been used to identify dietary patterns. These statistical methods combine variables into factors which characterize the dietary patterns of the study population.

A recent meta-analysis of dietary patterns and breast cancer risk evaluated results from 10 cohort and 8 case-control studies. The “prudent/healthy” pattern was identified in all 18 studies; “Western/unhealthy” pattern in 17 studies and “alcohol drinker” pattern in 4 studies.[56] Results in this meta-analysis are as follow: when all studies were combined, the “Western/unhealthy” dietary pattern was not associated with breast cancer risk (OR=1.09; 95% CI: 0.98-1.22; p-value for trend=0.11, comparing the highest vs. the lowest category). A significant increase in breast cancer risk was observed for the “alcohol drinker” dietary pattern (OR=1.21; 95% CI: 1.04=1.41; p-value <0.01, comparing the highest vs. the lowest category), whereas the “prudent /healthy” dietary pattern was protective for breast cancer (OR=0.89; 95% CI: 0.82-0.99; p-value<0.02, comparing the highest vs. the lowest category).

Authors also examined separately findings from case-control studies and cohort studies. The results differed in each subgroup.

A. **<u>Case-Control Studies</u>**: a significant increase in breast cancer risk was observed for the “western/unhealthy” dietary pattern (OR=1.31; 95% CI: 1.05-1.63, p-value<0.02, comparing the highest vs. the lowest category) but no significant decrease in risk for the “prudent /healthy” pattern has been observed (OR=0.84; 95% CI: 0.67-1.05; p-value= 0.12, comparing the highest vs. the lowest category), even though the actual observed odds ratio (OR=0.84) has the same magnitude as that of the overall comparison. This is most likely due to the decreased sample size when evaluating only the case-control studies.

B. **<u>Cohort Studies</u>**: same result as for all combined studies were obtained; for both the "Western/unhealthy" pattern and "prudent/healthy pattern". There was no significant difference between the highest quartile and lowest quartile and breast cancer risk in the "Western/unhealthy" pattern (OR=0.99; 95% CI: 0.90-1.08; p-value=0.82),and there was a small decrease in breast cancer risk between highest quartile and the lowest quartile in the "prudent/healthy pattern" (OR=0.93; 95% CI: 0.88-0.98; p-value<0.01). Authors in this study concluded that breast cancer risk may have association with some food patterns.

Below is a further discussion of the findings from the individual studies included in meta-analysis as well as the **two** additional cohort and **two** case-control studies that have been published since 2010.

2.3.1) Cohort Studies

One of the first studies evaluating dietary patterns and breast cancer risk was conducted by Paul Terry in a Swedish cohort (1987-1990) of 61,463 women with an average follow-up of 9.6 years and 1,328 incident breast cancer cases. For assessing dietary patterns, a validated Food Frequency Questionnaire (FFQ) containing 67 food items, was applied. After food grouping, 24 food groups were retained. Using factor analysis on 24 food groups, three major dietary patterns were obtained in this study: "Western" pattern (red and processed meats, refined grains, fat, and sweets), "healthy" pattern (fruit and vegetables, fish and poultry, low fat dairy and whole grain) and "drinker" pattern(wine, beer, and spirits). After adjusting for potential confounders, no association was observed between either the "healthy" dietary pattern or the "Western" dietary pattern and breast cancer risk (Risk Ratio=0.92; 95% CI: 0.76-1.13, p-value for trend=0.52 and Risk Ratio=1.00; 95% CI: 0.79-1.26, p-value for trend=0.92, respectfully). The only significant association between dietary pattern and breast cancer was observed for the “drinker” pattern; women in the highest category of the “drinker” pattern had an increase in breast cancer risk (Risk Ratio=1.27; 95% CI: 1.06-1.52, p-value for trend<0.002). [57]

Sieri and colleague (2004) [58] also investigated the association between dietary patterns and breast cancer risk in a cohort study conducted in Northern Italy, from 1987 to 1992. This cohort included 8984 women with an average follow up of 9.5 years and 207 incident breast cancer cases. Authors used the exploratory factor analysis on 34 food groups from validated 107 FFQ-food items, to identify dietary patterns. Four major dietary patterns were found (explained 30% of the variance) as follow: “salad vegetables” (mostly includes; raw vegetables and olive oil); “Western diet” (potatoes, red meat, eggs and butter); “canteen” (pasta and tomato sauce); and “prudent” (cooked vegetables, pulses, and fish, with negative loading on wines and spirits). After adjusting for potential confounders there was no significant association between “Western”, “prudent” or “canteen” dietary patterns and breast cancer risk (RR=0.9 with 95% CI: 0.58-1.41, P-trend=0.705; RR=0.95 with 95% CI: 0.63-1.45, P-trend=0.935 and RR=1.28 with 95% CI: 0.9-1.83, P-trend=0.169, respectfully, comparing the highest with the lowest food intake tertile). Only the “salad vegetables” pattern showed a significant protective effect on breast cancer risk (RR = 0.66 with 95% CI: 0.47- 0.95, p-value for trend<0.016, comparing highest with lowest tertile). When data were stratified by body mass index (BMI), “salad vegetables” pattern was very protective for the women with BMI <25 (RR = 0.39 with 95% CI: 0.22–0.69, p-value for trend < 0.001), and it was no longer associated significantly with breast cancer risk in the women with BMI ≥25 (RR = 0.99 with 95% CI: 0.60–1.61, p-value for trend=0.997).[58]

Fung and colleagues (2005) [59] examined the association of the food patterns and breast cancer risk in postmenopausal women from the Nurses' Health Study (NHS) which began in 1976 in 11 U.S states. Baseline FFQ was collected in 1984 and additional waves of FFQ were sent to these women every 2-4 years. 3,026 incident cases of postmenopausal breast cancer occurred during the 16 years of follow up (1984-2000). Factor analysis was used on 38 food groups (based on 61 food items) and two major dietary patterns were identified as follow; "prudent pattern" (fruits, vegetables, whole grains, low-fat dairy products, fish and poultry) and "Western" pattern (red and processed meats, refined grains, sweets and desserts and high-fat dairy product). After adjusting for the potential confounders, neither "prudent" nor "Western" dietary pattern were associated significantly with breast cancer risk in female postmenopausal population (RR=0.97; 95% CI: 0.86-1.11, p-trend=0.43 and RR=0.97; 95% CI: 0.83-1.14, p-trend=0.88, respectfully; comparing highest to the lowest quintile). However, while authors looked at the association between breast cancer risk and these two dietary patterns by smoking status at baseline, "Western" pattern increased the breast cancer risk in smokers (RR = 1.44; 95% CI = 1.02–2.03; p-value for trend< 0.03, comparing the highest to lowest quintile intake). When data were stratified by estrogen receptor status, the "prudent" pattern was protective for the estrogen receptor-negative breast cancer (RR = 0.62; 95% CI = 0.45–0.88; p-value for trend< 0.006).[59]

Another cohort study (Nurses' Health Study II) [60] based on 8 years follow-up of 90,638 premenopausal women (26- 46 years old at baseline), ascertained 710 cases of invasive breast cancer. Participants completed FFQ in 1991(with 133 food items) and in 1995(with 142 food items). Foods reported from both waves were grouped into 39 food variables. Using factor analysis (principal component) on food groups, two major dietary patterns were found and labeled as: the ‘‘prudent’’ pattern (mainly consumption of vegetables, fruit, legumes, whole grain, fish, and poultry and low-fat dairy products) and ‘‘Western’’ pattern (mainly consumption of red and processed meats, refined grain, and high-fat dairy products) dietary patterns. Findings showed the same results for the premenopausal women as postmenopausal women in the Nurses' Health Study (NHS I). After adjusting for potential confounders, none of the patterns was associated significantly with overall breast cancer risk (RR=0.90; 95% CI: 0.68-1.18, p-value for trend = 0.54 and RR=0.97; 95% CI: 0.71-1.33, p-value for trend = 0.97 for the “prudent” dietary pattern and “Western” dietary pattern respectfully, comparing highest to lowest quintiles of cumulative average score). However “prudent” dietary pattern was protective for breast cancer risk in the never smokers subgroup when data were stratified by smoking status (RR=0.57; 95% CI: 0.36-0.88, p-value for trend<0.01).[60]

Mannisto et al (2005) [61] evaluated the risk of breast cancer with dietary pattern in three prospective cohort studies with follow-up time varying between 7 to 13 years; Netherlands (NLCS), Sweden (SMC), and Italy (Italy-ORDET), with a total of 3271 breast cancer cases. FFQs contained 150, 107 and 67 food items in NLCS, ORDET and SMNC respectfully.[61] Foods were classified into 49, 31 and 42 food groups based on validated FFQ's for each of the 3 countries. Principal component analysis method was used separately in each country to achieve dietary pattern. In NLCS, five major dietary patterns were identified as: “vegetables”, “fat dairy”, “pork, processed meat, potatoes”, “brown/white bread substitute” and “sweet and savory snacks”; in ORDET study, four dietary patterns emerged: “vegetables”, “pork, processed meat, potatoes”, “other cooked vegetables” and “alcohol”; and in SMC study, again four dietary patterns were characterized: “vegetables”, “pork, processed meat, potatoes”, ”alcohol”, ”margarine/butter substitution.” Within each cohort, the specific identified patterns, explained

23.2%, 29.0% and 21.8% of the total variance in NLCS, ORDET and SMC cohorts respectfully. Two major dietary patterns were common in all three studies as follow; “vegetables’ and “pork, processed meat, potatoes”. After adjusting for potential confounders the findings showed no significant association between “vegetables” pattern and breast cancer risk in all three cohort studies (RR =0.9; 95% CI: 0.67-1.20, p-value for trend=0.31 in NLCS study, RR=0.79; 95% CI: 0.5-1.27, p-value for trend=0.32 in SMC study and RR=0.91; 95% CI: 0.79-1.05, p-value for trend=0.19 in Italy-ORDET study, comparing the highest versus lowest quartile). However "pork, processed meat, potatoes" pattern was protective in the NLCS study (RR = 0.69; 95% CI: 0.52-0.92; p-trend<0.02, comparing the highest versus lowest quartile) but there was no significant association between “pork, processed meat, potatoes” pattern and breast cancer risk in SMC or ORDET studies (Relative Risk=1.07; 95% CI:0.58-1.98, p-trend=0.95 in SMC, and Relative Risk=0.92; 95% CI:0.78=1.09, p-trend=0.47, comparing the highest versus lowest quartile).[61]

Velie and her colleagues investigated food patterns and breast cancer risk among postmenopausal women. This was a prospective cohort study (conducted in US) of 40,559 women(follow up from 1987 to1998) with 1186 postmenopausal breast cancer cases. Using factor analysis on 61 food items, three main dietary patterns were identified: “vegetable-fish/poultry-fruit”,”beef/pork-starch”, and “traditional southern”.[62] Based on data in these analysis, after adjusting for the potential confounders, no significant association between breast cancer risk and the “vegetable-fish/poultry-fruit” pattern (relative hazard=1.04; 95% CI: 0.87-1.26, p-value for trend=0.77) or “beef/pork-starch” pattern (relative hazard=1.04; 95% CI: 0.87-1.23, p-value for trend trend=0.53) was observed. However, the” traditional southern” pattern reduced invasive breast cancer risk (relative hazard=0.78; 95% CI; 0.65- 0.95, p-value for trend<0.003). When authors stratified their data based on family history, BMI, history of breast disease and smoking status," traditional southern" dietary pattern was protective for the women without a family history of breast cancer (relative hazard=0.83; 95% CI: 0.68-1.01, p-value<0.05), for the postmenopausal women with BMI < 25 (relative hazard=0.79; 95% CI: 0.63-0.99, p-value for trend <0.02). In addition, authors also looked at this dietary pattern by tumor receptor status. The "traditional southern" diet was protective for postmenopausal estrogen receptor positive breast tumors (adjusted relative hazard =0.75; 95% CI: 0.59-0.96, p-value for trend< 0.01) and progesterone receptor positive tumors (adjusted relative hazard =0.69; 95% CI: 0.53-0.89, p-value for trend< 0.003). All relative hazards were calculated by comparing the highest versus the lowest quintile of intake. [62]

Moreover, Cottet et al (2009) assessed the association between dietary patterns and breast cancer risk in a large French cohort study of 2,381 postmenopausal invasive breast cancer cases (follow-up 1993–2005) from 65,374 women. Using factor analysis (principal component) on 69 food groups, two major dietary patterns were identified which explained 10% of variance of food consumption.[63] Dietary patterns labeled as: ‘‘alcohol/Western’’ (mainly meat products, French fries, appetizers, rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, alcoholic beverages, cakes, mayonnaise, and butter/cream) and ‘‘healthy/Mediterranean’’ (mainly vegetables, fruits, seafood, olive oil, and sunflower oil). After adjusting for the potential confounders the "alcohol/Western" pattern increased the invasive breast cancer risk in the postmenopausal women (HR=1.20, 95% CI: 1.03- 1.38; p-value for linear trend <0.007, comparing the highest vs. the lowest quartile), whereas "healthy/ Mediterranean" pattern was protective for postmenopausal invasive breast cancer women cases (HR=0.85, 95% CI: 0.75-0.95; p-value for linear trend < 0.003, comparing the highest vs. the lowest quartile). When authors stratified the postmenopausal invasive breast cancer women by estrogen receptor/progesterone receptor (ER/PR) status, “alcohol Western” dietary pattern had only positive significant association in subgroup of estrogen receptor-positive/progesterone receptor-positive (ER+/PR+) postmenopausal invasive breast cancer women (HR=1.33, 95% CI: 1.07- 1.65; p-value for linear trend <0.005, comparing the highest vs. the lowest quartile). Also, “healthy/ Mediterranean” dietary pattern was only protective in subgroup of estrogen receptor-positive/progesterone receptor-negative (ER+/PR-) postmenopausal invasive breast cancer cases (HR=0.65, 95% CI: 0.49-0.87; p-value for linear trend < 0.001, comparing the highest vs. the lowest quartile) [63]

The last cohort study in meta-analysis was Black Women’s Health Study, a prospective cohort study of 50,778 participants followed-up every other year from 1995 to 2007. This study, conducted in US, ascertained 1094 incident breast cancer cases during the 12 years of follow-up. FFQ was completed in 1995 based on 69 food items and then aggregated in 29 food groups.[64] A factor analysis was used to derive food patterns based on these food groups. Two major dietary patterns were identified in this study as: “Western” (mainly consumption of refined grains, processed meat, and sweets) and “prudent” (mainly consumption of whole grains, vegetables, fruit, and fish). After adjusting for the potential confounders, the “prudent” dietary pattern was inversely associated with overall breast cancer risk (Incidence Rate Ratio (IRR) =0.86 with 95% CI: 0.68-1.08, p-value for trend < 0.06), however “Western” dietary pattern was not associated significantly with overall breast cancer risk (IRR =1.06 with 95% CI: 0.81-1.37, p-value for trend=0.86). When authors stratified women by BMI and menopausal status; the “prudent” dietary pattern was protective for the women with 25≤ BMI <30 (IRR= 0.64; 95% CI: 0.43, 0.93, p-value for trend < 0.01) and also for the premenopausal women (IRR= 0.70; 95% CI: 0.52-0.96, p-value for trend< 0.01). Furthermore, when authors stratified women by estrogen receptor and progesterone receptor status, the “prudent” dietary pattern was protective for the estrogen receptor–negative breast cancers (IRR= 0.52; 95% CI: 0.28- 0.94, p-value for trend <0.01), progesterone receptor-negative (IRR=0.66; 95% CI:0.39-1.09, p-value for trend<0.03) and for the combination of estrogen-negative/progesterone-negative (IRR=0.66; 95% CI:0.34-1.26, p-value for trend<0.04) (all IRR were calculated by comparing highest quintile with the lower quintile). [64]

Below is a discussion of the two new cohort studies published after the 2010 meta-analysis.

United Kingdom Women’s Cohort Study (2010) is another large cohort study of 35,372 women (35-69 years old) that examined the relationship between breast cancer risk and common dietary patterns.[65] During 9 year follow-up, 330 premenopausal and 453 postmenopausal invasive breast cancers were observed. FFQ was used at baseline for assessing diet and included 217 food items. Authors looked at the association between four common dietary patterns based on a hierarchy consumption of meat and fish, identified as: “vegetarians” (mainly based on consuming red meat, poultry, or fish less than once a week); “fish eaters” (mainly based on consuming of fish at least once a week but not poultry or red meat); “poultry eaters” (mainly based on consuming poultry at least once a week and may eat fish but not red meat); and “red meat eaters” (mainly based on consuming red meat at least once a week and may or may not consume poultry and fish). In this study red meat was defined as beef, pork, lamb, offal, and processed meat. After adjusting for potential confounders, none of dietary patterns were associated significantly with breast cancer risk in the whole cohort. When authors looked at the data stratified by menopausal status, again none of dietary patterns were associated significantly with premenopausal breast cancer women, but in postmenopausal women “fish eaters” pattern was protective as compared to “red meat eaters”(Adjusted Hazard Ratio=0.60, 95% CI: 0.38–0.96). The remaining dietary patterns were not associated significantly with risk of postmenopausal breast cancer. [65]

The most recent publication by Baglietto et al (2011) is based on a study conducted in Melbourne, Australia (Melbourne Collaborate Cohort Study, MCC).[66] This study contained 41,514 participants and included 20,967 women aged between 27 to 76 years at baseline, recruited from 1990 to 1994. During an average of 14 years follow-up (1994-2007), 815 women developed invasive breast cancer. Study population based on place of birth summarized participants as: 79% Australia, New Zealand or United Kingdom, and 21% Italian or Greece. For diet assessment, authors used 121 food item FFQ .Using principal factor analysis four major dietary factor emerged; “vegetables”, “fruit and salads”, “traditional Australian” and “meat”. After adjusting for the potential confounders, “fruits and salad” dietary pattern had reduction of breast cancer risk (Hazard Ratio=0.81, 95% CI: 0.63-1.03; p-value for linear trend<0.03, comparing the highest vs. lowest quintile), remaining patterns were not associated significantly with breast cancer risk (adjusted HR=0.98, 95% CI:0.76-1.28; p-value for trend=0.97, adjusted HR=1.25, 95% CI:0.90-1.74; p-value for trend=0.24 and HR=1.12, 95% CI:0.76-1.28; p-value for trend=0.45, comparing the highest vs. lowest quintile) for ‘vegetables”, “traditional Australian”, and “ meat” dietary pattern respectfully. When women were stratified by ER/PR status, ‘fruit and salad” dietary pattern was protective in both estrogen receptor negative(ER-) and progesterone receptor negative (PR-) (adjusted HR=0.55, 95% CI: 0.32-0.93; p-value for trend<0.004 and adjusted HR=0.67, 95% CI: 0.46-0.98; p-value for trend<0.01; respectfully, comparing the highest vs. lowest quintile). However, this pattern was not associated significantly in both estrogen receptor positive(ER+) and progesterone receptor positive (PR+) tumor subtypes (HR=0.92, 95% CI: 0.69-1.22; p-value for trend=0.47 and HR=0.92, 95% CI: 0.66-1.28; p-value for trend=0.58; respectfully, comparing the highest vs. lowest quintile) after adjusting the possible confounders. The remaining dietary patterns were not associated significantly with any tumor subtypes. [66]

2.3.2) Case Control Studies

Nkondjock and Ghadirian et al (2005) evaluated the role of dietary patterns on breast cancer in two simultaneous case-control studies of French-Canadians conducted in Montreal with 616 cases (414 breast cancer & 202 colon cancer) and 429 population-based controls , frequency matched in age (5 years) and place of residence.[67] Food consumptions' data were obtained by FFQ and grouped into 41 food groups. Using factor analysis three main dietary patterns were identified as: "chocolate-cereal" pattern (was characterized by a high intake of chocolate-based products, breakfast cereals, water, and fruits), "pork and processed meat" pattern (was characterized by a high intake of pork, white bread and processed meat products) and "drinker" pattern (was identified by a high intake of wine, liquor, and beer). There were no significant associations of breast cancer risk with any dietary pattern. The ORs were: 1.14 (95% CI: 0.76–1.71, p-trend=0.26) for the "chocolate–cereal" pattern; 0.85(95% CI: 0.54–1.34, p-trend=0.39) for the "pork and processed meat" pattern, and 0.92 (95% CI: 0.62–1.38, p-trend =0.95) for the "drinker" pattern. These ORs were based on comparing the highest to the lowest quartile of dietary pattern scores after adjusting the potential confounders. Authors concluded that breast cancer risk may not have any association with a food patterns in French-Canadian women. [67]

Another case-control study that evaluated the relationship between eating pattern and breast cancer risk was conducted by Roco et al (2006) [68] in Montevideo, Uruguay. The study included 442 breast cancer cases and the same number of hospitalized controls, with non-neoplastic diseases. Dietary intake was assessed by 64 food items FFQ which represented Uruguayan diet. Through exploratory factor analysis (principal component) in controls based on 15 food groups, six major factors were derived : “traditional”, “healthy”, “Western”, “stew”, “high-fat” and ”drinker” and explained 58.3% of the total variability. Odds ratios for the association between dietary factors and breast cancer risk were calculated by two methods: 1) when scores on dietary pattern was divided into quartiles, and 2) for increment of one standard error of factor score. For analysis using quartiles, a significant reduction of breast cancer risk was observed for both “traditional” (OR=0.53; 95% CI: 0.35-0.79, p-value for trend<0.009) and “healthy” patterns (OR=0.46;95% CI: 0.31-0.69, p-value for trend<0.0001). “Western” pattern increased breast cancer risk (OR=2.16; 95% CI: 1.46-3.20, p-value for trend<0.0004), while the remaining patterns didn’t have any significant association with breast cancer risk (stew pattern: OR=0.71; 95% CI:0.47-1.06, p-value for trend=0.14; high-fat pattern: OR=1.31; 95% CI:0.92-2.08, p-value for trend=0.31; drinker pattern: OR=1.06; 95% CI:0.72-1.57, p-value for trend=0.92) (all ORs comparing high vs. low quartile after adjusting the potential confounders). When analysis were performed calculating OR’s for unit change in standard error of the factor score, effect of dietary patterns differed by menopausal status. For example, “traditional” diet was protective in postmenopausal women (OR=0.73; 95% CI: 0.59-0.90) and not protective in premenopausal women (OR=0.80; 95% CI: 0.57-1.12, p-value of heterogeneity between pre- and postmenopausal status<0.04). Also “healthy” diet was protective in postmenopausal women (OR=0.72; 95% CI: 0.61-0.85) but it increased breast cancer risk in premenopausal women (OR=1.49; 95% CI: 0.97-2.29 p-value of heterogeneity between pre- post menopausal status<0.0001). “Western” diet which had significant association with breast cancer risk (OR=

1.31; 95% CI: 1.13-1.51, when stratified, was not significant in premenopausal women (OR=1.17 95% CI: 0.83-1.65), but remained significant in post-menopausal women (OR=1.38; 95% CI: 1.17-1.63) “Stew” dietary pattern was protective for overall breast cancer risk (OR= 0.83; 95% CI: 0.71-0.98), however this association was not significant in premenopausal women (OR=0.88; 95% CI: 0.61-1.00. although the p-value of heterogeneity between pre- post menopausal status=0.28 was not significant). “High-fat” and “drinker” diets didn’t have any significant association with breast cancer risk .All OR’s were calculated for the increment of one standard error of each score, therefore each scored pattern was entered into the model as a continuous term.[68]

Another case-control study was conducted in Chinese women in Shanghai by Cui et al (Cui *et al* 2007).[69] This study included 1,446 cases and 1,549 frequency matched controls (in 5 years). FFQ was based on 76 food items which covered more than 85% food consumed in Shanghai. Using principal component analysis, two patterns were obtained: a ‘‘vegetable-soy’’ pattern (which was characterized by tofu, cauliflower, beans, bean sprouts, green leafy vegetables) and a ‘‘meat-sweet’’ pattern (which was characterized by shrimp, chicken, beef, pork, candy, desserts). Though “vegetable-soy” pattern was not associated with breast cancer risk (OR=1.0; 95% CI: 0.8-1.2; p-value for trend=0.61), ‘meat-sweet’ pattern increased breast cancer risk (OR= 1.3; 95% CI: 1.0- 1.7; P-value < 0.03) comparing low vs. high quintile after adjusting the possible confounders. When authors stratified women by menopausal status and also estrogen receptor status, the association between ‘meat-sweet’ pattern and breast cancer risk was significant only in postmenopausal women, (OR= 1.6; 95% CI: 1.0-2.2; p-value for trend<0.04), and specifically among those with estrogen receptor–positive tumors (OR= 1.9

;95% CI: 1.1-3.3; P-value for trend <0.03). Authors concluded that a “meat-sweet” dietary pattern increases breast cancer risk in postmenopausal Chinese women. [69]

Kaoru and colleague (2007) [70] evaluated the association between food patterns and breast cancer risk in Japanese women. This case–control used data from hospital based research program at Aichi Cancer center, contained information for 1885 cases and 22,333 controls. Factor analysis (principal component) was used for the 31 food items and four major dietary patterns emerged included: “prudent”, “fatty”, “Japanese” and “salty’. After adjusting of potential confounders, “prudent” diet was protective for breast cancer in all women (OR=0.73; 95% CI: 0.63–0.84, p-value for trend < 0.0001, comparing the highest vs. lowest quartile), whereas there was no significant association between the “fatty”, “Japanese” or “salty” dietary patterns and breast cancer risk. Furthermore, when authors stratified women by BMI, “fatty’ diet and “Japanese” diet increased breast cancer risk for the women with a BMI ≥25 (fatty: OR=1.58; 95% CI: 1.14-2.19, p-value for trend<0.027; Japanese: OR=1.45; 95% CI: 1.05-1.99, p-value for trend< 0.031) comparing highest vs. lowest quartile but the remaining dietary patterns didn’t have any association with breast cancer risk. For the women with BMI<25 same result as for all women were obtained; “prudent” diet reduced breast cancer risk (OR=0.7; 95% CI: 0.6-0.82, p-value for trend<0.0001, comparing highest vs. lowest quartile) whereas the remaining dietary patterns didn’t have any significant association with breast cancer risk.

Decarli and colleague (2008) [71] looked at the associations between dietary patterns and breast cancer in two multicentre case-control studies conducted in Italy with 2,569 breast cancer cases hospitalized in four Italian regions during 1991-1999, and 3,413 controls that were chosen from the same hospital. FFQ contained 78 food items representing Italian diet. Using principal component factor analysis four major dietary patterns were identified that explained 76% of total variance of nutrient intakes, labeled as: “animal products”, “vitamins and fiber”, “unsaturated fats” and “starch-rich”. After adjusting for possible confounders, the “animal products” and the “unsaturated fats” patterns were protective (OR = 0.74; 95% CI: 0.61-0.91, p-value for trend<0.01 and OR = 0.83; 95% CI: 0.68-1.00 p-value for trend<0.03, respectively, comparing the highest vs. lowest quartile), whereas the starch-rich pattern increased breast cancer risk (OR = 1.34; 95% CI: 1.10-1.65, p-value for trend<0.01). Vitamins and fiber didn’t have any significant association with breast cancer risk (OR = 0.87; 95% CI: 0.73-1.04, p-value for trend=0.2). [71]

Maurtaugh et al (2008) [72] also evaluated the association between breast cancer risk and dietary patterns in a case-control study of Hispanic women (757 cases, 867 controls) and non-Hispanic white women (1524 cases, 1598 controls) from the Four-Corners Breast Cancer Study (FCBC). Using factor analysis for the 69 food groups, five dietary patterns emerged and were labeled as: “Western”, “prudent”,”Native Mexican”, “dieter” and “Mediterranean”. In all women, a significant increase in risk was observed for “Western” and” prudent” dietary patterns (OR=1.32 95% CI: 1.04-1.68 p-value for trend<0.01 and OR=1.42 95% CI: 1.14-1.77, p-value for trend<0.01, respectfully, comparing the highest vs. lowest quartile) whereas “Native Mexican” and “Mediterranean” dietary patterns were protective (OR=0.68 95% CI: 0.55-0.85 p-value for trend<0.01 and OR=0.76 95% CI:0.63-0.92, p-value for trend<0.01, respectfully, comparing the highest vs. lowest quartile). When authors stratified the women by ethnicity and menopausal status, the results were not consistent across ethnic and menopausal status. For example, in white non-Hispanic women, “Western” dietary pattern increased breast cancer risk in both pre and postmenopausal women (OR=1.87; 95% CI: 1.10-3.19, p-value for trend<0.01 and OR=1.47; 95% CI: 1.01-2.14, p-value for trend<0.01, respectfully, comparing the highest vs. lowest quartile) but it was not associated with breast cancer risk in Hispanic women, neither in premenopausal or postmenopausal women (OR=1.44;95% CI: 0.75-2.75, p-value for trend= 0.51 and OR=1.08; 95% CI: 0.65-1.81, p-value for trend=0.77, respectfully, comparing the highest vs. lowest quartile). "Native Mexican" pattern was protective in all strata except for Hispanic postmenopausal women [72]

Anna Wu et al (2009) [73] conducted a population-based case-control study among Asian American women residing in Los Angeles. The study included 1248 new breast cancer cases (known as Chinese, Japanese, or Pilipino) aged 25-74 years old who were ascertained between 1995 to 2001, and 1148 controls (matched in age, ethnicity, and neighborhood) . Authors used factor analysis (principal component method) on controls' food intake based on 174 FFQ-food items to assess dietary patterns. Three main dietary patterns were identified and labeled as: "Western-meat/starch", "ethnic-meat/starch" and "vegetables/soy" explaining 21% of the total variance. In this study, authors looked at effect of each of these three patterns separately as well as at the effect of combined patterns on breast cancer risk. The results are as follow; after adjusting the known confounders "Western-meat/starch" dietary pattern was not associated significantly with breast cancer risk (OR= 1.14, 95% CI:0.83-1.56; p-value for trend=0.27), "ethnic-meat/starch" dietary pattern increased the breast cancer risk (OR= 1.46, 95% CI:1.09-1.95; p-value for trend<0.008) and "vegetables/soy" dietary pattern decreased breast risk (OR= 0.69, 95% CI:0.52-0.91; p-value for trend<0.013) comparing highest vs. lowest quartile intake. When authors considered combined "Western meat/starch" pattern and "ethnic-meat/starch" pattern, breast cancer risk increased significantly after adjusting for the potential confounders(OR=1.61, 95% CI: 1.08-2.39; p-value for trend<0.008, comparing the highest vs. lowest intake of both diets). Furthermore by considering all three diets together, breast cancer risk was increased significantly by increasing diet scores. For instance women with a high intake of both “Western meat/starch” diet and “ethnic-meat/starch” diet, also low intake of the “vegetables/soy” diet (combined score≥6) had a two-fold increase in breast cancer risk, compared to women with a low intake of both “Western meat/starch” diet and “ethnic-meat/starch” diet, also high intake of the “vegetables/soy” diet (Adjusted OR= 2.19, 95% CI:1.40-3.42; p-value for trend<0.0005). Hence authors concluded that the diet with low consumption of meat/starches and high consumption of vegetables/soy reduces breast cancer risk in American Asian women. [73]

De Stefani et al 2009 also examined the role of dietary patterns in etiology of various cancer sites such as mouth and pharynx, esophagus, stomach, colon, rectum, lung, breast, bladder and kidney.[74] This study was population-based multisite case-control study conducted in Uruguay that included 3,528 cases (461 breast cancer cases) and 2,532 controls. Using factor analysis (principal component method) on 17 food groups; four dietary patterns emerged: “prudent”, “Western”, “traditional” and “drinker” explaining 36.3 % variance of total food intake. “Western” dietary pattern significantly increased breast cancer risk (OR=1.81 95% CI: 1.32-2.50, p-value for trend<0.0001). “Drinker” pattern also increased breast cancer risk (OR=1.40 95% CI: 1.05-1.87, p-value for trend<0.002) whereas “prudent” and “traditional” diets were protective (OR=0.63 95% CI:0.47-0.85, p-value for trend<0.005 and OR=0.53 95% CI:0.86-0.77, p-value for trend<0.002, respectfully) (all OR compared the highest vs. lowest tertile). [74]

Results from the two new case-control studies are discussed below.

Two additional case-control studies were published after the 2010 meta-analysis, which examined the effect of dietary patterns on breast cancer risk. The first one is by Young et al, 2010, conducted in Korea.[75] This study included 357 cases and 357 age-matched controls. Food intakes were assessed by FFQ based on 103 food items which were subsequently grouped into 39 food variables. Through principal component analysis on controls two dietary patterns were derived, and labeled as: “vegetable-seafood” and “meat-starch”. After adjusting for potential confounders, “vegetable-seafood “dietary pattern was protective in breast cancer risk (OR=0.14; 95% CI: 0.08-0.25, p-value for trend<0.001) but no significant association was observed between “meat-starch” dietary pattern and breast cancer risk (OR=0.78; 95% CI: 0.53-1.13, p-value for trend=0.171) (all ORs comparing the highest vs. lowest intake). While authors stratified the women by menopausal status, the results didn’t modify substantially; “vegetable-seafood” dietary pattern was inversely associated with breast cancer risk in both pre and postmenopausal women (OR=0.18; 95% CI: 0.09-0.36, p-value for trend<0.0001 and OR=0.08; 95% CI: 0.03-0.25, p-value for trend<0.0001 respectfully). Also “meat-starch” dietary pattern didn’t have any significant association in either premenopausal or postmenopausal breast cancer (OR=0.96; 95% CI: 0.49-1.88, p-value for trend=0.854 and OR=0.45; 95% CI: 0.17-1.20, p-value for trend<0.009 respectfully); these ORs were based on comparing the highest to the lowest intake after adjusting the potential confounders. [75]

The most recent paper published on the role of dietary patterns and breast cancer risk, was done by Zhang et al (2010). This is a population based case-control study of Chinese women, and includes 438 new primary breast cancer cases and 438 controls, frequency matched on age (5-years) and resident (rural/urban).[76] Diet was assessed by FFQ and grouped into 13 food variables. Using factor analysis on 13 food groups of controls, two major dietary patterns were obtained which explained 27.9% of total variance. Dietary factors were labeled as: “vegetable-fruit–soy–milk–poultry–fish” pattern and “grain–meat–pickle” pattern. After adjusting for the potential confounders, “vegetable-fruit–soy–milk–poultry–fish” dietary pattern was inversely associated with breast cancer risk (OR =0.26, 95% CI = 0.17–0.42; p-value for trend<0.001) whereas “grain–meat–pickle” pattern was positively associated with breast cancer risk (OR = 2.58, 95% CI: 1.53- 4.34; p-value for trend<0.001) comparing the highest vs. lowest quartile. Authors also examined the association between breast cancer risk and combined score on these two patterns: score of ≥ 6 (high intake of vegetable-fruit–soy–milk–poultry–fish pattern and a low intake of the grain–meat–pickle pattern) compared to the women with combined score ≤ 3 (low intake of vegetable-fruit–soy–milk–poultry–fish pattern and a high intake of the grain–meat–pickle pattern). Women in the high intake of vegetable-fruit category, and low intake of “grain-meat-pickle” pattern had similar reduction in breast cancer risk as those that had only a high score on “vegetable-fruit–soy–milk–poultry–fish” dietary pattern (OR =0.26, 95% CI = 0.17–0.41; p-value for trend<0.001). When authors stratified the women by ER/PR status, results remained same as for the whole sample, “vegetable-fruit–soy–milk–poultry–fish” dietary pattern was protective in ER+, ER-, PR+, PR- , ER+/PR+ and ER-/PR-, whereas “grain–meat–pickle” dietary pattern increased breast cancer risk in all subtypes. Moreover results didn’t change considerably when data was further sub-grouped by menopausal status; “vegetable-fruit–soy–milk–poultry–fish” dietary pattern was protective in both pre- postmenopausal women, and “grain–meat–pickle” dietary pattern increased breast cancer risk in both pre- postmenopausal women. Again results didn’t change considerably when authors stratified by BMI status (<25 vs. >=25). “Vegetable-fruit–soy–milk–poultry–fish” dietary pattern was inversely associated with breast cancer risk for the women with BMI <25 and also BMI ≥25 , again “grain–meat–pickle” dietary pattern was positively associated with breast cancer risk in both subgroups as well. [76]

Chapter 3: Methods

3.1) Design and Participants

3.1.1) Study Design

This study consists of two parallel population-based case-control studies, one conducted among Polish-migrant women in Cook County (Chicago) and Detroit Metropolitan Area, and one in Poland in 4 centers: Katowice, Gliwice, Poznan and Bialystok.

3.1.2) Dataset

The analysis for this thesis is based on the US component of the Polish Women's Health Study. The study was designed to evaluate the effects of diet and other lifestyle factors on breast cancer risk in Polish immigrants to the United States and Polish natives. The study was funded by the National Institute of Health/ National Cancer Institute (NIH/NCI), in 1997 with Dr. Dorothy R. Pathak as the Principal Investigator (PI). The data collection for the study started in 2000 concurrently in Poland and the United States.

3.1.3) Study Population

The main challenge in identifying both cases and controls was confirmation that the women were born in Poland and currently residing in the two study areas. Cases were identified by the Illinois State Cancer Registry (ISCR) for the Cook County area and by the SEER Registry located at Karmanos Cancer Institute/Wayne University for the Detroit Metropolitan Area. Cases had to be histologically or cytologically confirmed incident invasive breast cancer diagnosed between January 1st 1994 and December 31st 2001 in the age group 20 -79 years. As a first step in case identification and recruitment, a letter was sent out to the physician asking for permission to contact the patient to evaluate their eligibility for the study. All White cases with unknown place of birth were first screened for being Polish-born. All Polish-born cases were then approached about participation in the study. This involved an introductory letter describing the study and letting them know that an interviewer will contact them to answer any questions and set-up a time for an interview if they agree to participate.

Controls were frequency matched to cases on age (within 5-year age groups) and area of residence. Random Digit Dialing (RDD) approach was used to identify controls under the age of 65, and controls between the ages 65-79 were selected from the Medicare records of the Health Care Financing Administration (HCFA) for the female population at the two sites. All controls were screened for place of birth. If a Polish-born female between ages 20-79 was identified, the additional exclusion criteria were previous diagnosis with any other cancer except squamous or basal cell carcinoma.

3.1.4) Data Collection

In order to capture the traditional Polish diet, information on diet was collected retrospectively from all subjects (migrants in US and natives in Poland) for the time period 1985-1989, the last 5 years period prior to introduction of market economy in Poland. Food frequency questionnaire (FFQ) was used to capture the usual dietary intake for that time period.

3.1.5) Dietary Assessment

To evaluate the role of diet on caner, which develops over a long time period, ideally one would conduct a cohort study, where dietary intake was collected prospectively over time.

However, given that this was a case-control study, and our goal was to capture a traditional Polish diet, we chose to use the FFQ for the time period 1985-1989, rather than over last year as it is frequently done in case-control studies. Although diet in US did not undergo such drastic changes as diet in Poland after 1990, we chose to ask migrant women in US to recall their diet during the same time period (1985-89) in order to have similar recall bias between Poland and US. Our FFQ was modeled on the FFQ used in Nurses' Health Study and included 142 food items that were common to both Polish and American diets. Frequency of consumption was assessed in times per days, week, month, or year. The whole interview, including the FFQ was administered by trained interviewers at in-person home visits. Given that the usual dietary intake was for the time period 1985-1989, the 1986 Nurse's Health Study (Dr. Willett's data base) was used for nutrient information for foods available in US, and was supplemented by data obtained from the Polish nutrient database, DIET 1, for foods that were specifically Polish, available to migrants in Polish delicatessens in Chicago and Detroit.

3.1.6) Food Grouping

The food grouping was based on the similarity of nutrient profiles and was similar to that used in other articles.[57,68,77] Some of food items were considered individually either because it was inappropriate to put them into other food groups (such as eggs, margarine, tea, coffee, diet soft drink, etc) or because they potentially could represent different dietary patterns (such as wine, beer, vodka, etc). 40 food groupings were developed, and only margarine was eliminated after the first stage of factor analysis. Therefore, 39 food groupings were retained for the final analysis. See Appendix for details (Table 7)

3.1.7) Risk Factors of Questionnaire

Information on other established and potential risk factors such as age, age at first full term pregnancy, parity, age at menarche, age at menopause, use of oral contraceptive pills, hormonal replacement therapy, family history of breast cancer, height, weight, and physical activity were also collected for the same time period. Each participant provided information on the date of migration to the US allowing for the calculation of the duration of stay in the US.

3.2) Description of Variables

3.2.1) Dependent Variable

Our outcome variable was the breast cancer case/control status.

3.2.2) Independent Variables

Main Exposure of Interest

Food Groups' Consumption: The main exposure of interest was 39 food groups of consumption. Consumption was assessed in terms of daily, weekly, monthly or yearly frequencies. Then all consumption frequencies were converted into daily consumption by an appropriate conversion factor. Food consumption was further standardized to represent frequency of consumption/1000 calories/day.

Covariates

Age at Menarche: Age at menarche was assessed by the onset of natural menstruation. Median age at menarche was 14 years. Age at menarche was divided into 3 categories as follows: less than 13 years, 13 to less than 15, and 15 years and older.

Menopausal Status and Age at Menopause: Subjects who reported having menstrual cycles were considered as pre-menopausal. Subjects who provided age at natural menopause were considered post-menopausal. Subjects who were uncertain about their menopausal status were categorized as follows: women, who had hysterectomy without removal of ovaries, were considered pre-menopausal if their age was less than 50 and postmenopausal if they were 50 years or older and their age at menopause was assigned to be 50. Women who reported that they were post-menopausal but did not provide information about their age at menopause, were assigned age 50 for their age at menopause.

Age at First Full Term Pregnancy: Full term pregnancy was defined as any pregnancy with gestational age more than 24 weeks or 6 months, irrespective of the outcome. Age at first full term pregnancy was divided into 3 categories: less than 22, equal to 22 to less than 30 and equal to and greater than 30 years. We also included nulliparous as a separate group.

First Degree Family History: History of breast cancer in the mother, sister or daughter was considered as positive first degree family history. This was analyzed as a binary variable (0=no family history, 1=with family history).

Alcohol: Alcohol consumption was assessed by total intake of beer, wine and hard liquor during 1985 -1989. Among those who consumed alcohol, the median consumption was 0.5 drinks per week, which is equivalent approximately to 6 grams of alcohol per week (1 drink is approximately equivalent to 12 grams of alcohol).[29] This variable was divided into 3 categories: non drinkers, drinkers with less than 0.5 drinks per week and equal/greater than 0.5 drinks per week.

BMI (1985-1989): Body Mass Index (BMI) was calculated from height and weight in 1985 - 1989 using the following formula - weight (kg)/ $[\text{height}]^2$ (m). BMI was considered as 4 categories: under-weight (<18.5), normal (18.5-<25), overweight (≥25-≤30) and obese (>30). If height was available, but weight in 1985-1989 was missing, weight at age of 18, 30, 40, 50 or 60, based on subject's age range in 1985 was used for BMI calculation. Thus, if age in 1985-1989 was less than 25 years, then weight at 18 was used for calculations, similarly if age in 1895-89 was between any one of these age categories, 25-<35, 35-<45, 45-<55, 55-70 then weight at respective closest age decade 30, 40, 50 and 60 were used respectively. If weight for the closest decade as described above was missing (13 participants), mean weight specific to case/control status, for a particular age range in 1985 was used for BMI calculation for these individuals. If height was missing, the BMI remained as missing. If the individual's age in 1985 was lower than the age at which maximum height was attained, their 1985 BMI was also assigned to a missing category. Totally, information on BMI in 1985-1989 was missing for 13 participants.

Duration Living In the US by 1985: During interview each participant provided information on date of migration from Poland to the US. Using this information we calculated the duration of stay in the US prior to 1985. We considered three categories for this variable as follows: recently moved (moved after 1985), less than 10 years prior to 1985, and moved more than 10 years prior to 1985.

Hormone Replacement Therapy: All subjects were asked if they have ever used hormone replacement therapy in form of pills or skin patches, creams, suppositories or injectables for relief of menopausal symptoms and/or prevention of bone loss. The response was recorded as yes/no and analyzed as a binary variable.

Oral Contraceptive Use (OC): Use of hormonal preparations for birth control was asked for all subjects and recorded as ever used / never used. This was analyzed as a binary variable.

Physical Activity: Physical activity during 1985-1989 was assessed using a questionnaire modeled on validated physical activity questionnaires which included daily activities like sitting, reclining and household activities such as sweeping, gardening, cooking, stair climbing and sleeping. It also included recreational activities such as recreational sports, walking, bicycling, aerobic exercise as well as job activity. Intensity of activity was expressed in terms of MET's (Metabolic Equivalent), which were extracted from the Compendium of Physical Activities.[29] To calculate total MET-hs per day, the hours spent on each type of activity that has its own unique MET-hs value are multiplied by that value and added together. Total MET-h/day was divided into quartiles as follows: (0 - ≤47.33), (>47.33 - ≤54.41), (>54.41- ≤63.23), (>63.23). Information on physical activity was missing for 2 participants, as they were unable to recall their activity in 1985-1989.

3.3) Statistical Analyses

We used a factor analysis to obtain food patterns based on 40 food groups in controls (Appendix, Table7). Then we excluded 1food group (margarine) from our analysis because it had very small factor loading across all factors in the initial analysis. Subsequent analyses were performed on 39 food groups. Dietary patterns were derived based on patterns of consumption for controls. SAS software (Version 9.2) was used for all analyses. Proc factor in SAS with option Method=Principal was used. The orthogonal transformation was used for the rotation of the factor by using function Rotate= Varimax (orthogonal) function in order to obtain a simpler structure with greater interpretability.[59] The Scree plot was used to assess the number of factors that should be retained in the analyses (a combination of Eigen-values>1). Positive factor loadings indicate that the food group is associated directly to the pattern, whereas the negative loadings indicate an inverse association with the factor. Factor loadings close to zero indicate that variables are unrelated to a factor. Labeling of the factors was based on our interoperation of which foods carried high loading on that specific factor. Food patterns with a loading higher than 0.29 on a given factor were considered to contribute importantly to that dietary pattern (Table3). For calculating the score for a woman on a dietary pattern, the subjects' frequency of consumption on each food group, standardized/1000calories, was multiplied by the pattern weight for that food group. The sum of these products for all food groups is the factor score for each dietary pattern. Quartiles of scores were used to assess the associations of the food group/food patterns with breast cancer risk and to estimate the risk of breast cancer associated with each score quartile. Relative risks were approximated by odds ratios. We used the unconditional multiple logistic regression to obtain odds ratios and 95% CIs for the quartiles of scores of the dietary patterns. To account for the matching variables, we always included in our models the matching categories of age, area of residence and menopausal status. In addition to to these factors we also included the following potential risk factors for breast cancer in multivariate analyses: age at menarche, age at first term pregnancy, family history of breast cancer among first degree relatives, use of contraception, use of hormonal replacement therapy, alcohol consumption, physical activity, BMI in 1985-1989 and duration of stay in US. The dependent variable was binary (case/control) in the logistic regression model In the multivariate analyses the covariates were considered as follow: family history (no/yes), age at full term pregnancy (categorical, 4 strata), age at menarche (categorical, 3 strata), duration in US (categorical, 3 strata), oral contraceptive use (no/yes),BMI (categorical, 4 strata), physical activities (categorical, 4 strata), hormone replacement therapy (no/yes), alcohol use(categorical, 3 strata).

To assess if dietary pattern have the same effect on pre vs. post menopausal breast cancer risk, analysis were carried out for all women, adjusting for menopausal status, as well as separately for pre and post menopausal women. Therefore, estimates of odds ratios were based on information for the whole data, pre- and postmenopausal women respectfully (Table4, Table5, and Table6).

Chi-square test was used to compare the distribution of demographic factors and selected characteristics of the study population (Table 1). Table 2, provides univariate analyses of well-known risk factors, using logistic regression, and adjusting only for the two matching factors, age and area of residence.

Table1- Distribution of Cases and Controls by Demographic Factors and Selected Risk Factors

Variable	No. of Cases (%)	No. of Controls (%)	P-Value
Age (years)			**0.1942**
20-34	6(4.3)	16(5.6)	
35-44	26(18.8)	42(14.8)	
45-54	44(31.9)	79(27.8)	
55-64	28(20.3)	47(16.6)	
>=75	7(5.1)	33(11.6)	
Residence			**0.55**
Detroit	29(21.0)	67(23.6)	
Chicago	109(79.0)	217(76.4)	
Menopausal Status			**0.1345**
Premenopausal	64(46.4)	110(38.7)	
Postmenopausal	74(53.6)	174(61.3)	
Family History of Breast Cancer			**<0.0567**
No	118(85.5)	260(91.5)	
Yes	20(14.5)	24(8.5)	
Age at full term pregnancy			**<0.0445**
Nulliparous	16(11.6)	26(9.1)	
<22	30(21.7)	81(28.5)	
22 – 29	69(50.0)	153(53.9)	
>=30	23(16.7)	24(8.5)	

Table1 (cont'd)

Variable	No. of Cases (%)	No. of Controls (%)	P-Value
Age at menarche			**0.1499**
<13	35(25.3)	59(20.8)	
13-15	72(52.2)	136(47.9)	
>15	31(22.5)	89(31.3)	
Duration stayed in US in1985			**0.9383**
Recent Moved	61(44.2)	127(44.7)	
Less than 10 years	33(23.9)	71(25)	
More than 10 years	44(31.9)	86(30.3)	
Total caloric intake			**<0.0454**
<1882.22 calories /day	48(34.8)	67(23.6)	
1882.22-2257.39	27(19.6)	73(25.7)	
2257.40-2735.19	38(27.5)	72(25.4)	
>2735.19	25(18.1)	72(25.3)	
Body mass index (BMI)			**0.2644**
Underweight (<18.50	2(1.4)	5(1.7)	
Normal (18.5-24.9)	64(46.4)	103(36.3)	
Overweight (25-29.9)	51(37.0)	124(43.7)	
Obese (>29.9)	21(15.2)	52(18.3)	
Alcohol use			**0.2114**
Non-drinker	12 (8.7)	42(14.8)	
<0.5 g alcohol/week	66(47.8)	125(44)	
>=0.5 g alcohol/week	60(43.5)	117(41.2)	

Table1 (cont'd)

Variable	No. of Cases (%)	No. of Controls (%)	P-Value
Physical activity (MET-h/day)			**<0.0318**
0-47.33	45(32.6)	67(23.6)	
47.34-54.41	42(30.4)	72(25.3)	
54.42-63.23	30(21.8)	72(25.4)	
>63.23	21(15.2)	73(25.7)	
Number of full term pregnancy			**0.2281**
0	16(11.6)	26(9.2)	
1	33(23.9)	56(19.7)	
2	52(37.7)	106(37.3)	
3	27(19.6)	54(19.0)	
4	10(7.2)	42(14.8)	
Hormone replacement therapy			**0.6738**
Never	120(87)	251(88.4)	
Ever	18(13)	33(11.6)	
Oral contraceptive use			**0.1856**
Never	115(83.3)	250(88.0)	
Ever	23(16.7)	34(12.0)	
Total women	**138 (100.0)**	**284(100.0)**	

Table2- Univariate Analysis for Selected Risk Factors

Variable	OR *	95 % CI **
Menopausal Status		
Premenopausal	Reference	
Postmenopausal	1.30	0.63-2.66
Family History of Breast Cancer		
No	Reference	
Yes	1.90	0.99-3.61
Age at full term pregnancy		
Nulliparous	1.71	0.80-3.66
<22	Reference	
22 – 29	1.29	0.77-2.15
>=30	3.05	1.45-6.42
Age at menarche		
<13	Reference	
13-15	0.90	0.4-1.51
>15	0.58	0.32-1.05
Duration stayed in US in1985		
Recent Moved	Reference	
Less than 10 years	1.02	0.59-1.75
More than 10 years	1.72	0.95-3.11
Oral contraceptive use		
Never	Reference	
Ever	1.40	0.77-2.56

Table2 (cont'd)

Variable	OR *	95 % CI **
Hormone replacement therapy		
Never	Reference	
Ever	1.27	0.67-2.42
Total caloric intake		
<1882.22 calories /day	Reference	
1882.22-2257.39	0.52	0.29-0.93
2257.40-2735.19	0.74	0.43-1.29
>2735.19	0.5	0.28-0.91
Body mass index (BMI)		
Underweight (<18.5)	0.64	0.12-3.48
Normal (18.5-24.9)	Reference	
Overweight (25-29.9)	0.65	0.40-1.04
Obese (>29.9)	0.66	0.35-1.22
Physical activity (MET-h/day)		
0-47.33	Reference	
47.34-54.41	0.84	0.48-1.44
54.42-63.23	0.58	0.32-1.03
>63.23	0.40	0.21-0.76
Alcohol use		
Non-drinker	Reference	
<0.5 g alcohol/week	1.61	0.77-3.37
>=0.5 g alcohol/week	1.59	0.77-3.30

Table2 (cont'd)

Variable	OR [*]	95 % CI [**]
Number of full term pregnancy		
0	Reference	
1	0.94	0.44-2.02
2	0.81	0.40-1.67
3	0.85	0.38-1.86
4	0.43	0.16-1.09

[*]ORs adjusted for the two matching factors, age and area of residence. - [**] Confidence Interval.

Table3- Rotated Factor Loading Matrix for the Six Factors Retained Among Controls*

Food Groups	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6	Communalities
Whole grains	0.14894	0.10351	**0.30681**	0.00646	0.04373	0.05226	0.13171551
Refined grains	-0.26677	**-0.49085**	**-0.32203**	-0.06682	-0.05119	0.21302	0.46826563
Butter_smalec	-0.11291	**-0.47751**	0.04924	-0.06576	0.11251	0.20394	0.30175541
Nuts	0.07026	**0.36153**	-0.13679	0.14824	-0.16691	**-0.30235**	0.29559740
Desserts	-0.18396	0.19314	-0.26283	-0.14335	-0.00634	-0.13883	0.18008595
Snacks	-0.00361	**0.47244**	-0.08635	-0.05107	0.07661	-0.00474	0.23916402
Cooked_cereals	0.02222	-0.10485	0.16537	-0.02459	-0.02885	**-0.29621**	0.12801307
Cold_cereals	-0.07433	**0.34803**	0.00199	-0.01206	0.03683	-0.22340	0.17805977
Eggs	-0.10191	-0.07008	-0.01982	0.16846	0.04375	0.18847	0.08150095
Processed_meats	0.01992	-0.14918	-0.06218	0.04449	-0.18543	**0.33398**	0.17442109
Highfat_dairy	-0.10955	0.03331	-0.06987	-0.02979	**0.58381**	-0.09369	0.36848969
Lowfat_dairy	0.13865	0.08428	-0.03501	-0.01486	-0.09023	**-0.33445**	0.14777476
Fresh fruits	**0.38596**	0.02929	0.02737	-0.13494	-0.07635	-0.25318	0.23870821
High sugar	-0.07998	-0.21869	-0.05083	-0.08735	**0.59277**	0.01841	0.41614495
Soups	-0.02568	-0.06685	**0.34690**	-0.08578	0.05557	0.08687	0.14345975
Raw_cabbage	0.16021	-0.21123	**0.29584**	-0.07305	0.03446	-0.10846	0.17609746
Boiled_cabbage	-0.12480	-0.06814	**0.38716**	-0.06077	-0.05505	0.00252	0.17684009
Cooked_cabbage	0.04848	- 0.17771	**0.53984**	-0.02722	-0.23165	-0.07937	0.38606199
Dark-yellow_veg	**0.54850**	0.07722	0.11959	0.04979	0.02971	-0.20311	0.36572712
Beets	0.10170	-0.28402	**0.43207**	0.08404	-0.09565	-0.03631	0.29521769
Cruciferous_veg	**0.36049**	-0.19249	0.10888	0.00209	-0.06980	0.05502	0.18676690
Other_veg	**0.38500**	**0.50104**	0.21823	0.01815	0.05779	-0.01861	0.45090742
Alliums_veg	**0.36338**	0.03603	0.23352	0.00588	0.06410	-0.03928	0.19355873
Tomato	**0.55634**	0.05283	-0.18036	0.01501	0.03542	-0.09288	0.35493771
Salads	**0.58435**	-0.00713	-0.01278	-0.05869	-0.00722	0.10482	0.35616518
Potatoes	-0.09041	-0.13344	0.27508	-0.15711	0.05770	**0.32190**	0.23328633
Pasta	-0.04218	0.12902	0.25089	-0.01482	0.01848	-0.10726	0.09343609
Fast food	-0.00249	**0.47729**	-0.16521	-0.05001	-0.03942	0.17183	0.28868517
Pork_beef_veal	-0.03453	-0.01200	0.12481	-0.12147	-0.17191	**0.56131**	0.37629304
White_meat	**0.29824**	0.27031	-0.03901	0.03896	0.08068	-0.06236	0.17545063
Fish	**0.34790**	0.06695	0.25651	0.16077	-0.06209	-0.11371	0.23394911
Organ_meat	-0.10384	-0.00302	0.25824	-0.02971	-0.17785	0.13236	0.12751090
Salad dressing	**0.41625**	**0.46202**	-0.23279	0.03094	0.02822	0.03231	0.44372496
Beer	-0.06668	-0.01395	-0.14841	**0.74691**	0.01361	0.02509	0.58536148
Wine	0.13159	0.09755	0.06545	**0.52300**	- 0.08356	-0.10113	0.32185161
Vodka	-0.05214	-0.02930	-0.09990	**0.82105**	- 0.02824	0.02369	0.68903989
Coffee	0.15984	**0.30358**	-0.03746	0.07529	**0.64635**	0.03398	0.54370865
Tea	0.05985	**-0.29493**	0.05408	-0.05491	0.27197	0.09516	0.17952745
Dietsoftdrinks	**0.35441**	0.03514	-0.12807	-0.00197	-0.06331	-0.04923	0.14967403
Variance (%)	0.23	0.16	0.12	0.10	0.8	0.7	0.76**

*Loadings higher than 0.29 are typed in bold. - **Total communality explained by the model: 76%

Table4- Adjusted Odds Ratios (ORs)* of Breast Cancer by Quartile (Q) of Dietary Patterns among All Polish Women

Dietary Pattern	Adjusted OR (%95 CI) Q1**	Q2	Q3	Q4	P for Linear Trend***
Healthy Western					
No. Cases/Controls	36/71	48/71	26/71	28/71	
Multivariate OR	1.00(Ref)	1.40(0.77,2.54)	0.69(0.36,1.32)	0.72(0.38,1.37)	0.0912
Unhealthy Western					
No. Cases/Controls	31/71	45/71	24/71	38/71	
Multivariate OR	1.00(Ref)	1.41(0.76,2.61)	0.69(0.32,1.50)	0.99(0.44,2.24)	0.6860
Polish					
No. Cases/Controls	41/71	37/71	40/71	20/71	
Multivariate OR	1.00(Ref)	0.89(0.49,1.61)	1.08(0.59,1.97)	0.49(0.25,0.98)	0.1109
Alcohol Drinker					
No. Cases/Controls	29/71	38/71	30/71	41/71	
Multivariate OR	1.00(Ref)	1.42(0.74,2.70)	1.06(0.53,2.14)	1.59(0.74,3.43)	0.3679
High Fat/Sugar					
No. Cases/Controls	23/71	33/71	44/71	38/71	
Multivariate OR	1.00(Ref)	1.42(0.74,2.76)	1.69(0.89,3.23)	1.43(0.73,2.78)	0.2744
Meat/Potatoes					
No. Cases/Controls	22/71	33/71	47/71	36/71	
Multivariate OR	Reference	1.53(0.77,3.03)	2.08(1.07,4.05)	1.49(0.74,3.02)	0.2106

*ORs were adjusted for the following covariates: age, residence, menopausal status, age at menarche, age at first term delivery, family history of breast cancer among first degree relatives, use of contraception, use of hormonal replacement therapy, alcohol consumption, physical activity, BMI in 1985-1989, and duration of stay in US

**Reference Category

***Wald Test for Linear Trend

All Breast Cancer Cases (138)

All Controls (284)

Table5- Adjusted Odds Ratios (ORs)* of Breast Cancer by Quartile (Q) of Dietary Patterns among Premenopausal Polish Women

Dietary Pattern	Adjusted OR (%95 CI) Q1**	Q2	Q3	Q4	P for Linear Trend***
Healthy Western					
No. Cases/Controls	17/32	24/27	12/24	11/27	
Multivariate OR	1.00(Ref)	1.96(0.78,4.94)	0.79(0.28,2.20)	0.73(0.26,2.05)	0.2766
Unhealthy Western					
No. Cases/Controls	17/39	28/28	10/28	9/15	
Multivariate OR	1.00(Ref)	2.74(1.12,6.67)	0.58(0.17,1.99)	0.88(0.20,3.80)	0.7858
Polish					
No. Cases/Controls	17/29	17/31	19/24	11/26	
Multivariate OR	1.00(Ref)	0.75(0.29,1.95)	1.11(0.42,2.95)	0.48(0.16,1.43)	0.3376
Alcohol Drinker					
No. Cases/Controls	12/28	17/28	14/29	21/25	
Multivariate OR	1.00(Ref)	1.52(0.54,4.27)	0.92(0.29,2.94)	1.50(0.47,4.81)	0.6126
High Fat/Sugar					
No. Cases/Controls	8/34	20/21	22/28	14/27	
Multivariate OR	1.00(Ref)	6.02(1.99,18.23)	3.10(1.08,8.93)	2.26(0.75,6.87)	0.3099
Meat/Potatoes					
No. Cases/Controls	5/14	16/28	27/26	16/42	
Multivariate OR	1.00(Ref)	2.30(0.55-9.55)	5.22(1.24,21.92)	1.45(0.35,6.00)	0.9241

*ORs were adjusted for the following covariates: age, residence, age at menarche, age at first term delivery, family history of breast cancer among first degree relatives, use of contraception, use of hormonal replacement therapy, alcohol consumption, physical activity, BMI in 1985-1989, and duration of stay in US

**Reference Category

***Wald Test for Linear Trend

Breast Cancer Cases (64)

Controls (174)

Table6- Adjusted Odds Ratio (OR)* of Breast Cancer by Quartile (Q) of Dietary Patterns among Postmenopausal Polish Women

Dietary Pattern	Adjusted OR (%95 CI) Q1**	Q2	Q3	Q4	P for Linear Trend***
Healthy Western					
No. Cases/Controls	19/39	24/44	14/47	17/44	
Multivariate OR	1.00(Ref)	1.16(0.49,2.74)	0.52(0.21,1.31)	0.61(0.24,1.54)	0.1131
Unhealthy Western					
No. Cases/Controls	14/32	17/43	14/43	29/56	
Multivariate OR	1.00(Ref)	0.61(0.23,1.63)	0.57(0.19,1.74)	0.61(0.19,1.92)	0.4893
Polish					
No. Cases/Controls	24/42	20/40	21/47	9/45	
Multivariate OR	1.00(Ref)	0.79(0.34,1.85)	0.97(0.42,2.26)	0.29(0.11,0.81)	0.0499
Alcohol Drinker					
No. Cases/Controls	17/43	21/43	16/42	20/46	
Multivariate OR	1.00(Ref)	1.21(0.50,2.92)	0.86(0.34,2.21)	1.08(0.36,3.32)	0.9441
High Fat/Sugar					
No. Cases/Controls	15/37	13/50	22/43	24/44	
Multivariate OR	1.00(Ref)	0.52(0.20,1.32)	0.81(0.32,2.01)	0.87(0.35,2.15)	0.9240
Meat/Potatoes					
No. Cases/Controls	17/57	17/43	20/45	20/29	
Multivariate OR	1.00(Ref)	1.24(0.52,2.96)	1.15(0.49,2.67)	2.02(0.81,5.05)	0.1935

*Ors were adjusted for the following covariates: age, residence, menopausal status, age at menarche, age at first term delivery, family history of breast cancer among first degree relatives, use of contraception, use of hormonal replacement therapy, alcohol consumption, physical activity, BMI in 1985-1989, and duration of stay in US

**Reference Category

***Wald Test for Linear Trend

Breast Cancer Cases (74)

Controls (248)

Chapter 4: Results

The analytical data set for this thesis consisted of 138 cases and 284 controls. Table1 shows the distribution of demographic characteristics for cases and controls. Among the cases, 109 were from Chicago and 29 from Detroit. Also 217 controls were from Chicago and 67 controls from Detroit. As a result of the frequency matched design, distribution of age and area of residence were very similar for cases and controls. (Table1). Several of previously observed risk factors for breast cancer were confirmed in this study. We observed higher proportion of cases with family history of breast cancer as well as having older age at first birth. A protective effect of higher levels of physical activity was also observed. To adjust for the observed lower caloric intake among cases, for our subsequent analysis of dietary patterns, we used standardized frequency of consumption/1000 calories/day. Table 2 provides results from univariate analysis for selected risk factors. Since controls were frequency matched to cases on age and area of residence, ORs and 95% CIs in Table 2, are adjusted for these two matching factors.

First degree of family history of breast cancer was reported by 14.5 % of cases and 8.5 % of controls (p-value<0.0567) (Table1). Females with family history of breast cancer tend to have increased risk of breast cancer, though the result did not reach α=0.05 level of significance (OR=1.90 95% CI: 0.99-3.61) (Table2).

Age at first full term pregnancy differed significantly between cases and controls (p-value<0.0445) (Table1). Older age at first birth increased breast cancer, especially in the last strata (comparing age at first birth >31 vs. <20). The observed breast cancer risk increased more than three folder (OR=3.05; 95% CI: 1.45-6.42) (Table 2). Nulliparous females were also at an increased risk of breast cancer compared to females with age at first birth at age<22, though the difference was not statistically significant (OR=1.71; 95% CI: 0.80-3.66) (Table2).

The distribution of physical activity also differed significantly between cases and controls (P-value<0.0318) (Table1). Furthermore we observed that women with higher level of physical activities (>63.23MET-h/day) had significantly decreased risk of breast cancer when compared to the women with physical activity of (0-47.33 MET-h/day) (OR=0.40; 95% CI: 0.21-0.76) (Table2).

Factor loading matrix among controls is shown in Table3. The procedure retained six major dietary patterns. Factor 1 was labeled as “healthy Western” dietary pattern which presented high positive loadings for fresh fruits, dark yellow vegetables, cruciferous vegetables; other vegetables, alliums vegetables, tomato, salads, white meat, fish, salad dressing and diet soft drinks. It explained 23% of the common variance. Factor 2 was labeled as “unhealthy Western “ dietary pattern which was characterized by high positive loadings of nuts, snacks, cold cereals, other vegetables, fast foods, salad dressing, coffee and high negative loading of refined grains and tea and accounted for 16% of the common variance. Factor 3 was labeled as “Polish” dietary pattern characterized by high positive loading of whole grains, soups, raw cabbage, boiled cabbage, cooked cabbage, beets and high negative loading of refined grains accounting for 12% of the common variance. Factor 4 was labeled as “alcohol drinker” dietary pattern with high positive loadings for beer, wine and vodka accounting for 10% of the common variance. Factor 5 was labeled as “high fat dairy products and high sugar” dietary pattern which displayed very high positive loading in high fat dairy products, high sugar, and coffee accounting for 8% of common variance. And finally factor 6 was labeled as “meat/potatoes” dietary pattern and displayed high positive loading in processed meats, potatoes, pork _beef _veal and high negative loading in desserts, cooked cereals and law fat dairy products and accounted for 7% of common variance. Thus six factors in our model accounted for 76% of the common variance.

Odds ratios and 95% CI for breast cancer risk in quartiles of each factor score are shown in Table4, Table5 and Table6. Each dietary factor was entered into the model as a categorical variable (quartiles). Table4 represents odds ratios and 95% CI when all women were included in the model, with adjustment for menopausal status. Table5 and Table6 show ORs and 95% CI for the pre and postmenopausal women respectfully.

Based on Table4,Table5 and Table6 , after adjustment for potential confounders, as well as age and area of residence the "healthy Western" pattern provides some reduction in breast cancer risk especially in postmenopausal women, however this inverse association did not reach statistical significance (OR=0.72; 95% CI: 0.38-1.37; OR=0.73; 95% CI: 0.26-2.05 and OR=0.61; 95% CI: 0.24-1.54 for all women, pre and postmenopausal women respectfully; comparing the highest vs. the lowest quartile). The "unhealthy Western" dietary pattern was not associated with breast cancer risk neither in whole data nor in any stratum (pre- and postmenopausal women) (OR=0.88; 95% CI: 0.20-3.80 for premenopausal; OR=0.61; 95% CI: 0.19-1.92 for postmenopausal; and OR=0.99; 95% CI: 0.44-2.24 for all women; after adjusting for the potential confounders, comparing the highest vs. the lowest quartile). "Polish" dietary pattern, comparing the highest vs. lowest quartile, significantly reduced breast cancer risk for all women (OR=0.49; 95% CI: 0.25-0.98) and when stratified by menopausal status, especially in postmenopausal women (OR=0.29; 95% CI: 0.11-0.81). No significant reduction in risk was observed for pre-menopausal women (OR=0.48; 95% CI: 0.16-1.43), although the OR estimate is of the same magnitude as for all women. Lack of observed significance is potentially due to larger variability in that group as well smaller sample size. "Alcohol drinker" pattern although showed increased risk, was not significantly associated with breast cancer risk neither in the total sample, nor when stratified on menopausal status (OR=1.50; 95% CI: 0.47-4.81 for premenopausal; OR=1.08; 95% CI: 0.36-3.32 for postmenopausal; and OR=1.59; 95% CI: 0.74-3.43 for all women; after adjusting for the potential confounders, comparing the highest vs. the lowest quartile). After adjusting for the potential confounders “high dairy fat/ sugar” pattern was not significantly associated with breast cancer risk in all women. However, when data were stratified on menopausal status, for pre-menopausal women, a significant increase in risk was observed for second and third quartile as compared to first (OR=6.02; 95% CI: 1.99-18.23, OR=3.10; 95% CI: 1.08-8.93, respectively), but not for the highest quartile (OR=2.26; 95% CI: 0.75-6.87). No increase in risk was observed for post-menopausal women. Finally “meat/potatoes” pattern increased breast cancer risk; however the results were not statistically significant (OR=1.49; 95% CI: 0.74-3.02; OR=1.45; 95% CI: 0.35-6.00 and OR=2.02; 95% CI: 0.81-5.05 for all women, pre and postmenopausal women respectfully; after adjusting for the potential confounders, comparing the highest vs. the lowest quartile).

Chapter 5: Discussion/Conclusions

The present analyses identified six major dietary patterns that explained about 76% of the common variance represented by the latent dietary patterns. This compares favorably with other studies, though many studies report percentage of total variance explained by dietary factors, rather than percentage of the common variance shared by the food groups.[57-75] We used Principal Axis Factor Analysis, where factors are extracted based on a correlation matrix where diagonal values of 1.0 in the correlation matrix (Principal Component Analysis) are replaced by multiple R-square of the respective food group with all the other food groups. This approach assumes that there are few latent factors (dietary patterns) which represent what was measured by the many food groups

Our dietary patterns analysis identified several dietary patterns similar to those observed in the other studies. [57-75] The high loadings on these factors were for food groups or specific foods that had similar high loadings in previous articles. However, because of the uniqueness of this population, foods such as beets, boiled sauerkraut, boiled or steamed fresh cabbage, cabbage rolls, etc, loaded on what we named as "Polish" dietary pattern that is specific to the Polish population.

Only the "Polish" dietary pattern emerged as significantly reducing breast cancer risk. The foods that loaded on this pattern have been previously observed to decrease breast cancer risk in other epidemiological studies. Specifically, cabbage is a member of Brassica vegetables which contain glucosinolates (GLS- glucobrassicin, glucotropaeolin, glucoraphanin, sinigrin and others). The break-down products of GLS include indole-3-carbinol (I3C) and its digestive derivative 3, 3'-diindolylmethane (DIM), and isothiocyanates, all of which have been shown to have anti-carcinogenic properties both *in vitro* and *in vivo* studies. Murillo G and Mehta RG, in their review article entitled: Cruciferous Vegetables and Cancer Prevention, provide several mechanisms of action of the micronutrients found in cruciferous vegetables. [80] For example, these micronutrients act as scavenger of free radicals, increase expression of tumor suppressor genes such as E-cadherin and BRCA-1, detoxify carcinogens by induction of Phase II enzymes such as glutathione S-transfarases, and decrease DNA adducts. Given the systemic impact of these micronutrients, cruciferous vegetables have been observed to decrease cancer risk at other cancer sites as well, such as lung and stomach. The primary hypothesis for the Polish Women's Health Study, was that reduction in consumption of cabbage foods by Polish migrant women to the US contributes to the observed increase in breast cancer risk in the migrating generation. Therefore, the observed protection offered by "Polish" dietary pattern, confirms the original hypothesis.

The "healthy/Western" dietary pattern, characterized by high positive scores for healthy foods such as fresh fruits, all types of vegetables, salad dressing, white meat and fish, also offered reduction in breast cancer risk, but the results were not statistically significant at $\alpha=0.05$ level. However, "healthy /Western" dietary pattern was inversely associated with breast cancer risk in all women at level of 10% (p-value for trend <0.0912). This pattern labeled as "salad vegetables", "vegetables fish" and "prudent pattern" in previous studies was observed to decrease breast cancer risk, especially in postmenopausal women. [51,57-61,63-65,68,70,74-76] The direction of association was consistent in all studies though the results were not always statistically significant.[57-62] Thus, our results for this dietary pattern are consistent with the other studies, since odds ratios indicate trend towards reduction in risk.

"Unhealthy Western" pattern, was identified by high positive score of unhealthy foods such as: snacks, fast foods and coffee. However it included some healthy foods such as nuts and other vegetables. This pattern was labeled in other studies as "Western" and "unhealthy." We did not observe an increase in risk due to this pattern and results from previous studies have been inconsistent.[57-60,63,64,69,72-74]

The "alcohol drinker" pattern was characterized by a very high factor loading of the alcohol drinks such as wine, beer and vodka. This pattern was obtained in many articles; however the results were not always consistent.[57,63,67,68,74] As discussed before, several biologically plausible mechanisms have been proposed for the association between breast cancer and alcohol consumption. Acetaldehyde, metabolite of alcohol has been shown to be carcinogenic and also, known to destruct folate and induce secondary hyperproliferation.[31] In addition, it has been proposed that the increased risk for breast cancer from alcohol consumption can also be partly explained by higher estrogen levels in heavy drinkers. [32] In our study "Alcohol drinker" pattern showed trend towards increased breast cancer risk in all women as well as pre- and postmenopausal women. Thus, our results are similar to those observed previously in the literature.[67,68]

The "high in dairy fat/sugar" pattern was defined by high positive loading for dairy fat, high sugar, and coffee. This pattern was identified in some studies and labeled as "fatty" but the results were again inconsistent.[43-48,70] In our analysis for the total sample, odds ratios for second through fourth quartile relative to first quartile were all greater than 1.0, yet none reached statistical significance. When data were stratified by menopausal status, a significant increase in risk was observed for pre-menopausal women, but not in post-menopausal. Therefore our results replicate findings from some of the other studies reported in the literature. [44-48,70].

Finally the "meats/potatoes" pattern was characterized by a very high factor loading of the processed meats, potatoes, pork - beef- veal. Meats, especially processed meats have been hypothesized to play a role in increasing breast cancer risk. Processed meat is a source of carcinogens such as heterocyclic amines, nitrous compounds, and polycyclic aromatic hydrocarbons. All of these compounds have been shown to increase mammary tumors in animal models and have been hypothesized to increase breast cancer risk. This pattern with a trend towards increasing breast cancer risk was observed in many articles; however the results were not always consistent. [44-48, 68, 69,71,73,75] In our study "meats/potatoes" showed trend towards increased risk of breast cancer in all women, as well as in pre-menopausal women. No such trend was observed for post-menopausal. Thus our results are consistent with what has been observed in the literature. [67,73,75]

One of the limitations of this study is the potential for recall bias of the usual dietary habits, since women were asked to recall their usual diet during 1985-89, which was approximately 15 years prior to the time of interview. However, we do not believe that this bias is differential for cases vs. controls. To enhance recall of the dietary habits for that time period, women were asked to fill out events calendar that helped them to recall where they lived, as well as any other major events that were occurring in their life during that time. Since the Chernobyl nuclear accident occurred in April 1986, women commented that they could easily remember where they lived and what they ate during that time period.

In addition, the concept of using factor analysis has certain limitations as well. Dietary patterns are derived based on correlation structure between the food groups/foods; yet, these dietary patterns may not be suitable for predicting disease status.[78] Patterns are defined as linear function of food groups and are not chosen to reflect theoretical consideration for potential mechanism in the development of disease.

To our knowledge, this is the first case-control study evaluating the association between dietary patterns and breast cancer risk in Polish immigrant women to the US.

In conclusion, based on these findings, dietary patterns may play role in breast cancer risk in Polish migrant women to the US. This study provides support for the protective effect of "Polish" traditional diet that includes high consumption of cabbage foods. Therefore, this dietary pattern has a potential to reduce breast cancer risk.

Ethical Considerations:

The study was reviewed and approved by the Institutional Review Board (IRB) at Michigan State University. The approval was renewed in 2008-2013.

APPENDIX

Table7- Food Grouping Used in the Dietary Pattern Analysis

Foods or Food Grouping	Food Items
Whole grains	Dark bread like whole wheat, dark rye or pumpernickel
Refined grains	White bread, Polish white bread, hard rolls, English muffins, bagels
Butter, animal fat	Butter, animal fat
Margarine	Margarine
Nuts	Nuts, peanut butter
Desserts	Cookies, donuts, other sweets, cakes or pies, cheesecake, Chocolates
Snacks	Potato chips, corn chips, popcorn, crackers
Cooked breakfast cereals	Oatmeal, cream of wheat, rice, barley, cooked noodles
Cold cereals	Cold high-fiber cereals, highly fortified cereals, other cereals: Corn Flakes, Rice Krispies, Cheerios
Eggs	Eggs
Processed meats	Bacon, cold cuts (ham, ham sausage, Canadian bacon, Kielbasa, poultry liverwurst, head cheese
High fat dairy products	Cream cheese, yellow cheese, sour or whipping cream, whole milk, ice cream, non-dairy creamer, milk in coffee
Low fat dairy products	Cottage cheese, white cheese, yogurt, low fat milk or skim milk
Fresh fruits	Apples, banana, orange, tangerine, grapefruit, pears, grapes, peaches, plums, strawberries, cherries, cantaloupe
High sugar	Fruit preserves, jams, jellies, sugar in cereals; coffee; tea, all juices, kompot, , regular soft drink
Soups	Vegetables soups, soups from legumes, chicken soups, pickle soup;
Raw cabbage	Salads made from raw sauerkraut, salads from raw cabbage,
Boiled cabbage	Boiled sauerkraut, boiled or steam fresh cabbage
Roll cabbage	Hunter's stew, cabbage rolls, season Pierogi, nalesniki, lazanki with sauerkraut or mushrooms, cabbage soup
Dark yellow vegetables	Carrots, cooked carrots not in soups, bell paper green, yellow or red, sweets potatoes, yams
Beets	Beets cooked, red borsch
Cruciferous vegetables	Turnips or rutabaga, cauliflower, Brussels sprouts, radishes in season, mustard, horseradish
Other vegetables	String beans, spinach cooked, corn cooked beans , peas or lima beans excluding those in soups , green peas
Alliums vegetables	Raw onion, fried, sauté or stuffed onion, green onions, chives, leeks, garlic
Tomato	Fresh tomato, tomato sauce, tomato juice or V8 juice, ketchup, tomato soup
Salads	Fresh cucumbers, pickled , tossed leafy salads from any type of lettuce, other green leafy vegetables eaten raw
Pasta	Macaroni, spaghetti, or other pasta, buckwheat, rice as a side, pierogi with any filling, nalesniki , pizza;

Table7 (cont'd)

Foods or Food Grouping	Food Items
Fast food	Fast food
Pork beef veal	kotlety mielone, meat loaf, meat balls, pork, beef, veal, sausage fried , hotdogs or frankfurters
W hit meat	Chicken, turkey
Fish	Fish, tuna, sardines, Heming
Organ meat	Liver-beef, calf, or pork, liver-chicken, turkey, or goose, other organ meats (giblets)
Salad dressing	Mayonnaise, on sandwich or salad dressing, , any salad dressing such as ranch, French or vinaigrette
Beer	Beer
Wine	Wine
Vodka	Vodca
Coffee	Coffee
Tea	Herbal tea, regular tea
Diet soft drink	Diet soft drinks

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