Diabetes Mellitus Type 2 and Prolonged Exposure to Estrogen as Risk Factors for Development of Breast Cancer in Women of Age 35-70 in Yerevan: A Case-Control Study

Master of Public Health Thesis Project Utilizing Professional Publication Framework by

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LIST OF ABBREVIATIONS

AUA – American University of Armenia
IRB – Institutional Review Board
CHSR – College of Health Science Research and Development
NOC – National Oncology Center
AAWC – Armenian-American Wellness Center
BMI – Body Mass Index
OR – Odds Ratio
RR – Relative Risk
CI – Confidence Interval
CHBMS – Champion’s Health Belief Model Scale
NHANES – National Health and Nutrition Examination Survey
SLR – Simple Logistic Regression
MLR – Multiple Logistic Regression
AIC – Akaike Information Criterion
ROC – Receiver-Operating Characteristics
ABSTRACT

Objectives: To investigate the associations of diabetes mellitus type 2 and prolonged exposure to estrogen with the risk of breast cancer development in women of age 35-70 residing in Yerevan.

Methods: A sample of 368 cases and controls was contacted through telephone interviews. Cases (n=150) were women of age 35-70 residing in Yerevan, registered in National Oncology Center and Armenian-American Wellness Center with confirmed diagnosis of breast cancer within 2002-2008. Controls (n=152) were women of the same age group residing in Yerevan recruited through random digit dialing. The study employed a telephone-based, interviewer-administered structured questionnaire for data collection.

Results: Multiple logistic regression analyses revealed that diabetes mellitus type 2 increased the odds of developing breast cancer by factor 5.53 (95% CI 1.34-22.81) and that any birth had a protective effect on breast cancer development (adjusted OR=0.36, 95% CI 0.20-0.66). Additionally, each one year delay in age at first pregnancy was positively associated with breast cancer development (adjusted OR=1.13, 95% CI 1.01-1.27). Induced abortions increased odds of developing breast cancer by factor 2.86 (95% CI 1.02-8.04). Age and BMI were confounding factors for association between diabetes type 2 and breast cancer. Family history had no interaction with diabetes type 2 and women reproductive characteristics resulting in prolonged exposure to estrogen as risk factors for breast cancer development.

Conclusions: In this project, diabetes mellitus type 2, live births, early age first full-term pregnancy, and induced abortions were independent risk factors for development of breast cancer. The current findings serve as a basis for further investigations of global regional patterns of association between diabetes type 2 and female reproductive characteristics and risk of breast cancer development.
1. INTRODUCTION

1.1 Magnitude of Breast Cancer

Breast cancer is among the most significant chronic disease concerns among women the world over. In 2004, breast cancer incidence numbered over one million cases worldwide and, each year, more than 400,000 women die from the disease (1; 2; 3). As a public health problem, breast cancer incidence is increasing around the world. More importantly, incidence has increased as much as 5% per year in developing regions of the world (4). Globally, approximately one woman in eight (13%) has a chance to develop breast cancer (5; 6). Breast cancer accounts for about 18% of all female cancers worldwide (7), making it the most prevalent cancer in the world. There are an estimated 4.4 million survivors up to 5 years following diagnosis (8). Currently, early detection of the disease is critical to disease control and survival as approximately 96% of cases are potentially curable with early treatment (6; 9). Future containment of breast cancer rests in optimal prevention as well as early detection. Consequently, improved understanding of globally and regionally relevant risk factors is necessary to prevention and detection efforts.

1.2 Breast Cancer in the United States and in Armenia: A Comparison

Armenia - a post-Soviet society - is a developing nation with specific public health concerns that include breast cancer as well as other common conditions such as diabetes mellitus type 2 and obesity. However, little breast cancer research is specific to Armenia. What is known about breast cancer can be compared with what is known about the disease in developed nations like the United States to highlight current evidence and gaps in science that pertain to the Armenian context. An estimated 192,370 new cases of breast cancer are expected to be diagnosed in 2009 in the United States (10). Among American women, breast
cancer death rates are second only to deaths from lung cancer, as the leading cause of cancer mortality among women. An estimated 40,170 deaths are expected in 2009 (10). The age-adjusted incidence rate is 123.8 per 100,000 women per year, while the age-adjusted death rate is 24.5 per 100,000 women per year (10). In Armenia, the most current statistics show that breast cancer incidence was about 870 in 2002. Incident cases climbed to 990 in 2006 (11). Breast cancer is the leading cause of cancer morbidity and mortality among Armenian women (12). Morbidity has increased almost two-fold from 31.9 per 100,000 (1995) to 59.6 per 100,000 (2006) (13). Mortality accounted for 16.4 deaths per 100,000 in 2004 and is the eighth leading cause of death in Armenia (14; 15; 16). In summary, while breast cancer is not as pressing a concern in Armenia as it is in the United States, it presents a considerable threat to the health of Armenian women.

1.3 Background and Significance

The magnitude of the public health impact breast cancer is framed by risk factors for the disease. Substantial science exposes several important risk factors for breast cancer. The most prominent risk factors for developing breast cancer are increasing age, family history, and a variety of endogenous and exogenous sources for prolonged estrogen exposure such as reproductive patterns. More recently, diabetes mellitus type 2 has been identified as a risk factor as well. This section reviews current evidence for the risk factors to be addressed in the current study. While some literature suggests there are other risk factors (e.g. radiation, race, alcohol consumption, medication) for breast cancer, these are not apparently significant in Armenian society and thus are not reviewed here or explored in this study.

1.3a. Diabetes Mellitus Type 2

Recent literature suggests an association between diabetes mellitus type 2 and breast cancer is more recent. While the mechanism for this relationship has yet to be established,
the most likely cause is hypothesized to be hyperinsulinemia. Hyperinsulinemia is common among people with diabetes mellitus type 2. Insulin resistance is the most common cause of hyperinsulinemia (17). Insulin receptors are over-expressed in breast cancer (17). Thus, hyperinsulinemia may hypothetically stimulate growth of breast cancer cells (17-19). Several studies suggest an association between hyperinsulinemia and risk of breast cancer (17-25). Investigators found that diabetic women are 60% more likely to develop breast cancer after adjusting for age and race (20). Other authors report that insulin is associated with development of breast cancer with hazard ratios from 2.1 to 3.3 (95% CI 1.2-3.6 and 1.5-7.0) (for upper and lower quartiles of insulin respectively) thus supporting the conclusion that diabetes mellitus type 2 may be a risk factor for developing breast cancer (19). A further study reported that hyperinsulinemia is a significant risk factor (RR = 2.9, p<0.001) for breast cancer independent of general adiposity (21). These findings are corroborated by other researchers who found a moderate, direct association between diabetes mellitus type 2 and breast cancer (OR = 1.3, p<0.001) (22). This relationship appears more consistent in postmenopausal women (23). Scientists suggest that adipocytokines – biologically active peptides associated with obesity - lead to insulin resistance and, thus, are causally associated with diabetes mellitus type 2 and breast cancer (25). Investigation of the relationship of diabetes mellitus type 2 to development of breast cancer is especially important in Armenia. In 2005 1.4% of the Armenian population was found to have diabetes mellitus type 2 (26). In Armenia, morbidity of and mortality from diabetes mellitus type 2 has increased from 1309.6 and 35.83 per 100,000 population respectively in 2001 to 1607.3 and 36.29 per 100,000 population in 2006 (14). In summary, though there is evidence that suggests diabetes mellitus type 2 is a risk factor for breast cancer, the science is not yet well developed. Further investigation is needed in many societies including Armenia.
1.3b. Prolonged Exposure to Estrogen

Prolonged exposure to estrogen, through early menarche or other means, is among the most important established risk factors for breast cancer (7). The mechanism is hypothesized as prolonged exposure to estrogen which stimulates mammary cell mitogenic activity and proliferation that may represent risk of developing breast cancer (5). Early menarche (first menstruation, before age 12), late age at menopause (above age 54) and late first full-term pregnancy (above age 30) are among the best studied reproductive characteristics hypothesized as risk factors for development of breast cancer (7). Several studies reveal that early age at menarche and late age at menopause are associated with 3- and 2-fold higher relative risk for development of breast cancer (7; 27). A delay of 2 years of menarche corresponds to 10% (95% CI 6-15%) reduction in breast cancer risk, while women at menopause with each 5 year difference have 17% (95% CI 11-22%) higher risk of breast cancer (28). After adjustment for the effects of ages at interim births, the risk of breast cancer increases by about 13% for each 5 year increment in age at first birth (OR=1.13, 95% CI 1.08-1.19) (29).

Childbearing and breastfeeding practices reduce the number of menstrual cycles a woman experiences. These reproductive and childbearing practices may limit lifetime estrogen exposure (5). Some authors suggest they then having protective effect, limiting the risk of breast cancer (27). Conversely, nulliparity (30) and shorter breastfeeding period (generally less than 9 months) appear to increase risk (5). However, evidence on parity and risk of breast cancer are contradictory. Studies conducted elsewhere report no effect of parity in women with the first birth at age over 35, and higher risk at uniparous compared with nulliparous women (31). Another study reports the contrary case with a significant protective effect ($\chi^2=14.2$, p<0.001) against breast cancer observed with increasing parity (32). These contradictory findings are presented below in Table 1.
Table 1. Parity and Risk of Developing Breast Cancer

<table>
<thead>
<tr>
<th>Factors</th>
<th>Increase in risk</th>
<th>Reduction in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparity*</td>
<td>30.0%</td>
<td></td>
</tr>
<tr>
<td>Every 2 births*</td>
<td></td>
<td>16.0%</td>
</tr>
<tr>
<td>1st birth after 35 vs. before 20*</td>
<td>40.0%</td>
<td></td>
</tr>
<tr>
<td>Increasing parity**</td>
<td></td>
<td>10.0% (OR=0.9)</td>
</tr>
<tr>
<td>Parity + lactation over 25 months†</td>
<td></td>
<td>RR=0.67</td>
</tr>
<tr>
<td>High parity‡</td>
<td>RR=2.4 (in women &lt;45 years)</td>
<td>RR=0.5 (in women &gt;45 years)</td>
</tr>
</tbody>
</table>

* = reference (33), ** = reference (32), † = reference (34), ‡ = reference (35)

Two studies observe an OR of 0.85 (95% CI 0.55-1.30) for any lactation versus no lactation at all (36; 37), others report that RR of breast cancer is decreased by 4.3% (95% CI 2.9-5.8, p<0.0001) for every 12 months of breastfeeding in addition to a decrease of 7.0% (95% CI 5.0-9.0, p<0.0001) for each birth, suggesting that the longer women breastfeed the more they are protected against breast cancer (38). However, reported reduction in risk may be attributable to other factors as well.

Obesity may represent a more complex risk of breast cancer. Adipose tissue produces estrogens and is the primary endogenous source after menopause (7). In post-menopausal women, obesity has been positively associated with risk of breast cancer (39). However, increased body weight is inversely related to breast cancer risk in pre-menopausal women (39). Investigators report that obesity is an important risk factor for postmenopausal breast cancer: heavier women (BMI>31.1) have an elevated risk of breast cancer development (RR=2.52, 95% CI 1.62-3.93) compared to slimmer women (BMI = 22.6) (40). At the same time, obesity is also linked with diabetes mellitus type 2, wherein biologically active peptides called adipocytokines are associated with both obesity and insulin resistance (25). Thus, the
issue of obesity as a risk factor for both insulin resistance and breast cancer development warrants further investigation.

Along with endogenous estrogens, exogenous estrogens – consumed either as oral contraceptives or hormone replacement therapy – appear to moderately increase risk of breast cancer (7; 27). Women using contraceptives with estrogen have somewhat elevated risk (RR=1.32, 95% CI 1.14-1.54) while those using estrogen plus progestins (RR=1.41, 95% CI 1.15-1.74) have slightly higher and again significant risk. This level of risk is similar among women using hormone replacement therapy for 5-9 years (adjusted RR =1.46, 95% CI 1.22-1.74) (41). Consequently, exogenously consumed estrogens – as well as endogenously produced estrogens – may confer higher risk of developing breast cancer.

Induced abortion may hypothetically limit estrogen exposure and thus reduce risk of breast cancer. Nonetheless, induced abortion is not well studied and has only partial inconclusive evidence to support its role in breast cancer risk. Some studies suggest that induced abortions have protective effect on development of breast cancer: RR=0.93 (p<0.0002) (42). Some studies conclude that pregnancies ending with induced abortions do not increase women’s risk of breast cancer development, while others state that results substantially differ between studies with prospectively (before the diagnosis of breast cancer) and retrospectively (after the diagnosis of breast cancer) collected information on abortion (RR=0.93 vs. RR=1.0, p=0.5) (43). However, other authors report that any induced abortion results in an odds ratio of 1.3 (95% CI 1.2-1.4) while the odds ratio is 1.5 (95% CI 1.2-1.8) for induced abortion during the first trimester of pregnancy (44).

1.3c. Aging and Family history

Advanced age and family history are well-studied, non-modifiable risk factors for breast cancer development (7). These factors may also influence the role of diabetes mellitus type 2 and of estrogen exposure and confound associations. The incidence of breast cancer
approximately doubles with each decade of life (7). Thus, from age 30 to 39 the risk is only 0.43%, while it jumps to 4% by the seventh decade of life (5; Appendix 1). Similarly, breast cancer has some familial and genetic associations (7). Having first-degree relatives with breast cancer, especially those diagnosed before age 50, increases the risk of getting breast cancer (OR = 2.45, 95% CI 1.84-3.06) (5). Even women who have second- and third-degree relatives with breast cancer are at some increased risk (OR = 1.82 (95% CI 1.39-2.24) for second degree relations and 1.35 (95% CI 1.07-1.64) for third degree relations) (45).

2. RATIONALE FOR THE CURRENT STUDY

Given that breast cancer is a common malignancy among Armenian women, and that diabetes mellitus type 2 is prevalent among Armenians, the present study was conducted to explore associations between and among breast cancer, diabetes mellitus type 2 and estrogen exposure among Armenian women. No extant studies investigate estrogen exposure and diabetes mellitus type 2 and risk of breast cancer in an Armenian sample (personal communication with Executive Director of Armenian-American Wellness Center K. Hakopyan). The incidence of breast cancer and diabetes mellitus type 2 in Armenia are both increasing (12; 14; 46; 47). A variety of factors prolong exposure to estrogen, including currently low parity (1.7 births per woman in 2005); an elective abortion rate of 1.8 abortions per woman in 2005; and declining rates of exclusive breastfeeding (from 45% to 33% among children of age less than 4 months from 2000 to 2005) (13; 15). As more commonly acknowledged risk factors for prolonged estrogen exposure have increased in Armenia so too has obesity. The prevalence of women with BMI equal to and more than 25kg/m² of age over 30 accounts for 65.7% (48). Identification of associations among these factors and risk of breast cancer in both pre- and post-menopausal women (aged between 35 and 70) is then
essential for understanding the magnitude of modifiable risk of estrogen and diabetes mellitus type 2 related risk of breast cancer in Armenia.

3. PURPOSE AND RESEARCH QUESTIONS

The purposes of the study were to:

- Assess diabetes mellitus type 2 as a risk factor for development of breast cancer.
- Assess prolonged exposure to estrogen as a risk factor for development of breast cancer.
- Identify possible interaction of family history with the known risk factors in development of breast cancer.
- Provide recommendations to improve evidence for early detection of breast cancer in Armenian women at risk.

The three research questions investigated are:

1) Is there a positive association between diabetes mellitus type 2 and development of breast cancer in women of age between 35 and 70 in Yerevan?

2) Is there an association between prolonged exposure to estrogen defined by early age at menarche, late age at menopause, late age at first full-term pregnancy, nulliparity, obesity, breastfeeding practices, induced abortions and intake of exogenous hormones and development of breast cancer in women of age between 35 and 70 in Yerevan?

3) Is there an interaction between family history of breast cancer with diabetes mellitus type 2 and prolonged exposure to estrogen and development of breast cancer in women of age between 35 and 70 in Yerevan?
4. METHODS

4.1 Study Design

A case-control study design allows investigation of associations among multiple variables of interest and the single outcome of breast cancer. This design can explore aspects of relatively rare diseases. In addition, it is useful to identify multiple exposures and reveal associations and interactions among variables. A case-control design is both feasible and ethical. Further, data collection may be accomplished in a relatively short period using telephone interviews to preserve anonymity and confidentiality while incurring minimal expense (49). Potential disadvantages to this design may include recall bias and low response rates (50). Nonetheless, the Center for Health Services Research has found that, while recall bias is a concern that must be addressed in measurement, response rates among the general Armenian populace are high (averaging 85%) (51; 52). As a result, a case-control design is useful in achieving the purposes of this project.

4.2 Study Population

The target population for this project includes all women aged 35 to 70 years who reside in Yerevan, the capital of the Republic of Armenia. The study population provided both cases and controls for the project. To be eligible, both cases and controls were women aged 35 to 70 on enrollment, who speak Armenian and have documented residency in Yerevan in domiciles with operating telephones. Those agreeing to participate by telephone were enrolled for either case or control given the following criteria. Those eligible as cases were registered at the National Oncology Center (NOC) and Armenian-American Wellness Center (AAWC) between January 2002 and December 2008 with confirmed diagnosis of breast cancer. Controls should have no history of breast diseases; no previous breast surgery except for cosmetic procedures, and were identified through random digit dialing.
Women were excluded if they:

- Had busy telephone line at 3 attempts within 2 consecutive days each and 1 attempt on weekend
- Had a disconnected telephone line
- Were out of the country (for cases)
- Had an incorrect telephone number (for cases)
- Had an office telephone dialed (for controls)

### 4.3 Study Variables

The dependent variable is breast cancer. Control variables are: diabetes mellitus type 2, age, age at menarche, age at first pregnancy, age at menopause, number of pregnancies, number of induced abortions, number of live births, BMI (weight/height²), family history of breast cancer, breastfeeding duration, intake and duration of contraceptives and female hormones (Tables, Table I). The variable “diabetes mellitus type 2” was defined through a composite variable consisting of a direct question and several indirect questions. Specifically those participants diagnosed with onset of diabetes before age 35 and taking only insulin were considered to have diabetes mellitus type 1. Participants with diabetes onset after age 35 and who were taking oral hypoglycemic agents, with or without insulin, or taking insulin alone were considered to have diabetes mellitus type 2.

### 4.4 Study Instrument

A structured questionnaire for telephone use was designed for use in the study by adapting questions from instruments used in previous studies in Armenia and the United States. Thirty-three items are either closed, forced choice questions or factual reports (e.g. height and weight). The questionnaire addressed following domains: a) demographic and anthropometric data on age, education level, marital status, weight and height; b) medical
history on diabetes mellitus type 2; c) reproductive history including childbearing and breastfeeding; d) use of exogenous estrogens; e) family history of breast cancer; and f) smoking habits. Smoking habits are included in the instrument to query the tobacco use in women of the sample to augment the CHSR database to provide correspondence with other CHSR studies, although the association between smoking and breast cancer remains controversial despite over 100 epidemiologic studies (53-59). General questions as well as anthropometric, childbearing and breastfeeding questions were adapted from Champion’s instrument (CHBMS) modified for Turkish women (60; 61). Questions about diabetes and its management were adapted from questionnaire 2005-2006 NHANES for diabetes SP_DIQ (62). Questions about reproduction were adapted from instrument developed by Arakelyan (63; 64). The instrument was pre-tested in five women before proceeding with interviews. Following this pre-test, a question about induced abortions was split into two questions to query induced abortions and spontaneous abortion or miscarriage. The other 32 questions remained unchanged (Appendix 10).

4.5 Sample Size

Sample size was calculated based on proportions and OR, level of significance (type I error \( \alpha = 0.05 \), two-sided), power 80% and response rate 80%. The calculated sample projected equal numbers of participants in both case and control groups. Based on the first research question exploring diabetes mellitus type 2 and the typical range of odds ratios for developing breast cancer among diabetics (1.3 – 3.3), the most conservative OR considered for sample size calculation was 2.0 (19; 20; 22). Proportion of people exposed to diabetes mellitus type 2 was taken as 0.60 (\( p_1 = \) proportion in cases). Then \( p_2 \) (proportion of women exposed to diabetes mellitus type 2 in controls) and sample size were calculated (65; Appendix 2). Thus, \( p_2 \) was calculated as 0.43 and sample size as 147 in cases and 147 in controls. After adjusting for a response rate of 80%, a typical response rate for telephone
surveys conducted in Armenia (51; 52), the prospective sample size was increased to 184 in cases and 184 in controls to account for those declining to participate.

4.6 Data Collection

Data were collected by telephone interview during a 35-day period in early 2009. A list of 230 women with a breast cancer diagnosis and telephone numbers were obtained from AAWC and NOC by permission of the respective center directors. This list was incorporated in a sample frame and cases were selected through simple random sampling using a table of random numbers. Controls were simply identified through random digit dialing. Enrollment was recorded in a journal format (Appendix 3). The enrollment flowchart documents accrual of 150 cases and 152 controls, a sample that meets the power calculation (Appendix 4).

4.7 Statistical Analyses

Completed questionnaires were entered into and initially analyzed by SPSS 10.0. Data were cleaned (through range and spot checking) and recoding was done for some variables as appropriate. Questionnaires were considered incomplete if missing values count for more than 15% (66; 67), or five missing values in this particular case. Data were then converted for use with STATA 10.0 to complete the advanced statistical analyses. Means and standard deviations (if normally distributed) and medians and ranges (if skewed) were used for continuous variables, while frequency analyses were performed for categorical variables. T-test, chi-square and Fisher’s exact test were used for comparisons. For identification of associations between variables of interest and adjustment for interaction, confounding and effect modification, simple and multiple logistic analyses were conducted. Possible interactions between family history and all major independent variables of interest were checked and tested creating special interaction terms. In order to find independent risk factors for breast cancer, multiple logistic regression analysis was utilized with forward and
backward elimination of those variables that showed statistically significant differences in simple logistic regressions as well as including variables with marginally significant level (e.g. less than 0.100). Each model was tested against the nested model using log-likelihood ratio test and the most parsimonious model with the lowest Akaike information criterion (AIC), exact expression for bias adjustment (68), was considered as the best fitting model. The final multiple logistic regression model fit was tested for Hosmer-Lemeshow test for calibration across 10 risk groups, while for discrimination the Receiver-Operating characteristics (ROC) curve was graphed.

5. ETHICAL CONSIDERATIONS

The project, along with all study materials in English and Armenian, was approved by the Institutional Review Board (IRB) of AUA (Appendix 9). Verbal consent was obtained from all participants before the questionnaire was administered. Verbal consent included detailed information on the purpose of the study, conductor and procedure; eligibility, participant rights and voluntary involvement, and the potential risks and benefits of participation. Information obtained from participants was used only for study purposes. Only the principal investigator had access to pre-enrollment files and accrual journal with names and telephone numbers. For purposes of data management, each participant was assigned an identification number that was dissociated from enrollment and consent materials. Only the identification number was used on the questionnaire and in the database to ensure anonymity and confidentiality. The study files were maintained in a computer secured by password located in a locked room and accessible only to the principal investigator. All files with information identifying participants will be destroyed upon completion of the study and approval of the project report.
6. RESULTS

Complete questionnaires were collected from 150 cases and 152 controls for response rates of 81.5% and 82.6% respectively. Refusal rates were 3.8% (7 participants) among cases and 17.4% (32 participants) among controls. Twenty seven prospective participants in cases had died before being contacted for the study accounting for death rate of 14.7%. No incomplete questionnaires were collected. The characteristics of the study participants are presented in Table II (Tables) and graphically in Appendix 5.

Statistically significant differences (p<0.05) between cases and controls were observed in a variety of variables. Statistically significant differences (p<0.001) were observed in mean age of cases and controls (55.8 ± 7.9 vs. 51.1 ± 9.9), diabetic status in cases and controls (14.7% vs. 3.3%), also in mean age at first pregnancy (23.7 ± 4.4 vs. 21.8 ± 3.8), absence of menopause status (12.0% vs. 42.4%), as well as reported family history of breast cancer (27.3% vs. 9.9%) in cases and controls respectively. Cases were different from controls in education level (p=0.021). More interestingly, cases differ from controls in respect of a) mean overall BMI (29.0 ± 4.3 vs. 27.7 ± 4.6) as well within BMI categories (41.9% vs. 26.0% in women with BMI>30.0 kg/m²) (p=0.014 and 0.007 respectively); and b) mean age at menarche (13.5 ± 1.5 vs. 14.0 ± 1.5) (p=0.002). Parity was 1.99 ± 0.9 vs. 2.22 ± 1.02 in cases and controls with p-value equal to 0.041. Notably, there were almost three times more cases that ever used female hormones compared to controls (20.7% vs. 9.9%, p=0.009). Interestingly, controls smoked on average almost twice the number of cigarettes smoked by cases (13.4 ± 11.8 vs. 7.8 ± 6.7) (p=0.036).

Simple logistic regression analyses run for all covariates with corresponding odds ratios, 95% confidence intervals and p-values are detailed in Table III (Tables). There is a statistically significant association between development of breast cancer and age. Each one year increase in age is associated with 6% increased odds of developing breast cancer.
At that, women in age category of 45-54 and those of age 55-70 have 2.5 and 4.6 times higher odds (p=0.010 and p<0.001) respectively in comparison with women in younger age group of 35-44.

A statistically significant association between development of breast cancer and BMI exists with 7% higher odds for each unit increase in BMI. Obese women are at 2.4 higher odds versus women with normal BMI (p=0.010). Having diabetes mellitus type 2 increases the odds of developing breast cancer by a factor of 5.1 (p=0.001). Similarly menarche onset delayed by each one year decreases the odds of breast cancer development by 22% (p=0.003). Onset of menarche after 11 reduces the odds of developing breast cancer by 67% (p=0.040).

At that, late onset of menarche (after 15) reduces the odds of breast cancer development compared to early onset before 11 years by 74% (p=0.017). There is statistically significant increase of 13% (p<0.001) in odds of breast cancer associated with each year increase in age at first pregnancy. Age at first pregnancy between the ages of 21 to 30 years and that above 30 years is associated with statistically significant (p=0.003 and 0.010) increase by 2.21 (95% CI 1.32-3.69) and 4.95 (95% CI 1.47-16.71) times the odds, respectively, compared to first pregnancy before age 20 years. Further, there is a statistically significant relationship between parity and breast cancer development (24% reduction in odds, p=0.014). However, reduction in odds with each live birth or living child is not statistically significant. There is increase in odds (1.6 times) of breast cancer with lifetime induced abortions that approached significance (p=0.064). Nonetheless, the regression shows that induced abortions elevate odds of breast cancer by 77% with lifetime abortions between one and three and 95% if experienced between 4 and 10 times respectively (p=0.049 and p=0.036). Being post-menopausal increases breast cancer odds (OR=5.4; p<0.001) as does a positive family history (OR=3.5, p<0.001). Use of any estrogen also increases odds of breast cancer development (OR=2.4, p=0.010). Extended use (over 25 months) of oral contraceptives, compared to
short-time use (less than 6 months), increased odds of breast cancer (OR=10.67) but only approached significance with a p-value equal to 0.070. The graph with univariate analyses with corresponding confidence intervals is presented in Appendix 6.

As described in Section 4.7, we assessed the independent contribution of each of the candidate risk factors for the odds of breast cancer using multivariate logistic regression. While we evaluated many models in the multivariate analyses, we report the key findings from the model in Table IV (Tables) on the basis of AIC. After adjusting for BMI, we found that the linear relationship with age and the log odds of breast cancer is no longer statistically significant (OR=0.96, 95% CI 0.90-1.02). There was no evidence that the effect of BMI on breast cancer risk differed by age, nor did we find statistically significant interactions between family history and other primary independent variables and breast cancer (Table IV).

Diabetes mellitus type 2 is an independent risk factor for development of breast cancer adjusted for age, BMI, age at menarche, age at first pregnancy and age at menopause, as well as for live birth, abortion, breastfeeding duration and female hormone use. For instance, women with diabetes mellitus type 2 are 5.53 times (95% CI 1.34-22.81) more likely to have breast cancer than otherwise similar to women without diabetes mellitus type 2. Each year increment of age at first pregnancy increase the odds of developing breast cancer by factor of 1.13 (p<0.05). Giving birth to a child reduces the odds of breast cancer with OR=0.36 adjusted for other variables (p<0.05). Even one abortion increases the odds of developing breast cancer by factor 2.86 (p<0.05). Multivariate model discrimination is shown by ROC curve (Appendix 7).
7. DISCUSSION

The present case-control study investigated associations between diabetes mellitus type 2 and prolonged exposure to estrogens in risk of breast cancer among women of age 35-70 residing in Yerevan, Armenia. The present study demonstrates that diabetes mellitus type 2, BMI, aging, age at onset of menarche and at first full-term pregnancy, parity, induced abortions and female hormone use are associated with the risk of development of breast cancer. It corroborates similar findings from other studies conducted in other societies. Notably, age at menopause, breastfeeding and oral contraceptive use are not associated with the risk of breast cancer in this study.

We had reason to believe, based on analysis of the literature, that diabetes mellitus type 2 was positively associated with the risk of breast cancer development. As we expected, the results show statistically significant positive association between diabetes mellitus type 2 and breast cancer (unadjusted OR=5.05, p=0.001). This finding is consistent with those reported elsewhere (19; 22; 25). The OR increased to 5.53 after adjustment for other variables emphasizes the positive association between diabetes mellitus type 2 and breast cancer. This remarkable increase in odds of developing breast cancer in diabetic women may be due to the sample characteristics (e.g. older and heavier women among the cases), as well as other confounders and risk factors that were not considered in this study. Nevertheless, the findings warrant future research replicating the present project. Additionally, this finding may inform clinical education for primary care and specialist physicians in Armenia, encouraging better attention to screening for breast cancer among women with diabetes mellitus type 2.

We investigated female reproductive characteristics resulting in prolonged exposure to estrogen which is a risk factor for development of breast cancer. Our findings suggest that early age at onset of menarche and late age at first full-term pregnancy assuming prolonged
exposure to estrogen present risk for breast cancer (unadjusted OR= 0.33 (95% CI 0.12-0.95) and OR=4.95 (95% CI 1.47-16.71) respectively). These findings are similar to those found in other studies that suggest a protective effect of late onset of menarche and of early age at first pregnancy (7; 27; 33). The negative association found between increasing parity and risk of breast cancer is not statistically significant, contrasting published findings (29; 33-34). However, giving birth to four or more children had a marginally statistical significant protective effect for breast cancer development (OR= 0.28, p=0.071). This modest finding may be explained by the very small number of participants reporting four or more children. However, the final model adjusted for covariates shows that any birth has a protective effect on breast cancer development (adjusted OR=0.36, 95% CI 0.20-0.66). Additionally, each one year delay in age at first pregnancy is positively associated with development of breast cancer (adjusted OR=1.13, 95% CI 1.01-1.27). While these findings are intriguing, they require further investigation.

Breastfeeding and its duration had no association with breast cancer development. These findings are in contrast to literature that suggests these factors limit risk (35-38). While breastfeeding longer than 24 months was associated with reduced odds of breast cancer development (OR=0.58), this finding is not statistically significant (p=0.240). In fact, the lack of a significant association between lactation and breast cancer may be explained by almost equal number of women in the sample that breastfed their children less than and more than 9 months – the cutoff point suggested by previous studies (7).

Exogenous hormones appear to increase risk of breast cancer over time. Use of replacement hormones increased odds of breast cancer about 2.4 times (OR=2.38, p=0.010), while combined duration of female hormone use longer than 25 months shows 5.9 times greater odds when compared with use of less than 6 months. However, this increase in OR is not statistically significant (p=0.123). Similarly, overall lifetime duration of oral
contraceptive use shows marginally significant relation (OR=10.7) in the same comparison. These findings are consistent with those published elsewhere (27; 41). However, very few participants reported use of exogenous hormones for contraception or replacement and may then explain the contradiction with significance of findings from samples of women drawn from countries where use of these drugs is more common (e.g. the United States or Europe).

Age and obesity, measured as BMI, were significantly associated with increased risk of breast cancer, findings consistent with the literature (7; 39-40). As expected, simple logistic regression showed that aging, one of the major non-modifiable risk factors for breast cancer development elevate odds of disease development (unadjusted OR=2.5 and OR=4.6 in age groups of 45-54 and 55-70, p<0.010). However, in respect to the primary variables of interest – diabetes mellitus type 2 – aging turned to be a confounder, and lost its significance in the final multivariate logistic regression model (OR=0.96, 95% CI 0.90-1.02). More flexible models for relationship of age and the odds of breast cancer were similar. This suggests that much of the linear relationship with age and breast cancer may be partially explained by BMI.

Obesity was positively associated with breast cancer (unadjusted OR= 1.07, p=0.015). This finding corroborates findings of other studies (39-40). Moreover, women in the BMI category greater than 30kg/m$^2$, in other words – obese, are at 2.4 times greater odds of breast cancer development against those with normal BMI within 19.0-24.9 kg/m$^2$. Despite this association, BMI lost its significance level in the final multivariate model.

As expected, being menopausal conferred about 5.4 times greater odds (p<0.001) of developing breast cancer. About 85% of women in the sample of cases reported being menopausal, and the difference between cases and controls was significant (p<0.001). Our findings do not reveal a statistically significant relationship between late age at menopause
and development of breast cancer in contrast to published studies indicating that late age at menopause is positively associated with development of breast cancer (27-28).

The odds of breast cancer was statistically significantly greater in women who experienced 1 to 10 lifetime abortions (OR= 1.95, p=0.036) compared to women who reported no abortions. The literature reports some controversy over a possibly protective effect between induced abortions and risk of breast cancer development (42; 44). However, most evidence points to no effect (43). Interestingly, when adjusted for other covariates, induced abortions showed even higher odds of developing breast cancer (OR=2.86, p=0.046). This finding is not robust. Though induced abortions may interrupt estrogen production, thus leading to less exposure, they may also create other reproductive system alterations. Reporting bias may further jeopardize this particular finding given the sensitive nature of induced abortions. Further, the current study did not find any association between miscarriages and risk of breast cancer development; however, this finding may be explained by the few women in the sample reporting miscarriage. Future investigation is necessary to establish the actual relationship between abortion and breast cancer in the Armenian population.

### 7.1 Study Limitations

The present case-control study is limited in several ways. The psychometric properties of the questionnaire were not assessed and hence are a further constraint on the study and interpretation of the findings. Recall bias, as with all case-control studies is an important concern. Reporting bias also limits the study given the sensitive issues concerning cancer, smoking, induced abortion, and body weight addressed in the questionnaire. Latency bias could affect the results obtained from controls, since breast cancer, as any oncology problem, has a long latent period, so a number of controls could have had the problem in its earlier stages, while their reported data were considered in the light of control data. Other possible
confounding variables that were not considered or adjusted for in the current study may have altered observed associations. Finally, as this is a retrospective, population-based survey and not a biological study, the clinical relevance to the findings is limited.

### 7.2 Study Strengths

The present case-control study was the first study that focused on the role of diabetes mellitus type 2 and prolonged exposure to estrogen as risk factors for development of breast cancer among Armenian women.

### 7.3 Conclusions

In summary, the current case-control study investigated and assessed the role of diabetes type 2 and female reproductive characteristics resulting in prolonged exposure to estrogen as risk factors for development of breast cancer in women of age 35-70 residing in Yerevan. Based on the results of the final model, and addressing the research questions, a number of conclusions are made as follows:

1. Diabetes mellitus type 2 is positively associated with the risk of developing breast cancer.
2. Late age at pregnancy (after 20 years old) and nulliparity assuming prolonged exposure to estrogen are positively associated with developing breast cancer.
3. Induced abortions are positively associated with development of breast cancer.
4. Family history is an independent risk factor for breast cancer development. There is, however, no interaction apparent between the family history, diabetes type 2 and female reproductive characteristics with breast cancer development.

### 7.4 Recommendations
Based on the findings of the current case-control study, we recommend: a) conduct a cohort study to find out the incidence rate of breast cancer among the study cohort of diabetic women; b) clinical education and training of endocrinologists and mammologists to enhance their clinical collaboration to meet the needs of women with diabetes mellitus type 2 and address their risk of breast cancer and health screening needs; c) reinforcing among clinicians heightened awareness of the need for annual breast cancer screening for breast cancer among those women at risk, with the acknowledgment that diabetes mellitus type 2 likely confers risk; d) similarly reinforcing promotion of weight reduction and maintenance; e) further research replicating the present study with similar samples within and outside Yerevan; and f) prospective epidemiological and clinical studies to further explore the influence of childbearing, breastfeeding and contraceptive practices on breast cancer risk in the Armenian population.
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### TABLES

#### Table I. Study Variables (Type and Measurement)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of breast cancer</td>
<td>Dependent, binary</td>
<td>1 Case 0 Control</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Independent, continuous</td>
<td></td>
</tr>
<tr>
<td>Education level (years)</td>
<td>Independent, ordinal</td>
<td>1 School (less than 10) 2 School (10) 3 College/Professional technical 4 University 5 Postgraduate</td>
</tr>
<tr>
<td>Marital status</td>
<td>Independent, ordinal</td>
<td>1 Single 2 Married 3 Divorced 4 Widowed</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Independent, ordinal</td>
<td>Normal (19.0 – 24.9) Overweight (25.0 – 29.9) Obese (&gt;30.0)</td>
</tr>
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<td>Diabetes type 2</td>
<td>Independent, binary</td>
<td>1 Presence 0 Absence</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>Independent, ordinal</td>
<td>≤11 12-14 ≥15</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Independent, binary</td>
<td>1 Presence 0 Absence</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>Independent, continuous</td>
<td>1-5 6-15 16-35</td>
</tr>
<tr>
<td>Age at first pregnancy (years)</td>
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<td>≤20 21-30 &gt;30</td>
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<tr>
<td>Parity</td>
<td>Independent, continuous</td>
<td>0 1 2 3 4 ≥5</td>
</tr>
<tr>
<td>Abortions</td>
<td>Independent, binary</td>
<td>1 Presence 0 Absence</td>
</tr>
<tr>
<td>Number of induced abortions</td>
<td>Independent, ordinal</td>
<td>0 1-3 4-10 ≥11</td>
</tr>
<tr>
<td>Number of miscarriages</td>
<td>Independent, ordinal</td>
<td>0</td>
</tr>
<tr>
<td>Covariates</td>
<td>Cases (n=150)(%)</td>
<td>Controls (n=152)(%)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Age (y, mean ± sd)</strong></td>
<td>55.79 ± 7.89</td>
<td>51.11 ± 9.94</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 10 years</td>
<td>4 (2.7)</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>10 years</td>
<td>39 (26.0)</td>
<td>60 (39.5)</td>
</tr>
<tr>
<td>College</td>
<td>35 (23.3)</td>
<td>35 (23.0)</td>
</tr>
<tr>
<td>University</td>
<td>72 (48.0)</td>
<td>48 (31.6)</td>
</tr>
<tr>
<td>Postgraduate</td>
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<td>1 (0.7)</td>
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<td><strong>Marital status</strong></td>
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<td></td>
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<td>Single</td>
<td>11 (7.3)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>Married</td>
<td>120 (80.0)</td>
<td>129 (84.9)</td>
</tr>
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<td>Divorced</td>
<td>10 (6.7)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Widowed</td>
<td>9 (6.0)</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td></td>
<td>29.03 ± 4.28</td>
<td>27.67 ± 4.57</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>BMI (kg/m², mean ± sd)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **BMI categories** | 25 (18.4)    | 34 (27.6)    | 0.020* |
|                   | 54 (39.7)    | 57 (46.3)    |        |
|                   | 57 (41.9)    | 32 (26.0)    |        |

| **Diabetes mellitus type 2** | 128 (85.3) | 147 (96.7) | 0.001* |
|                              | 22 (14.7)  | 5 (3.3)    |        |

| **Age at menarche (y, mean ± sd)** | 13.47 ± 1.53 | 14.01 ± 1.47 | 0.002* |

| **Pregnancy** | 12 (8.0) | 9 (5.9) | 0.478 |
|               | 138 (92.0) | 143 (94.1) |        |

| **# of pregnancies (median, range)** | 5, 0-35 | 5, 0-34 | 0.278 |

| **Age at 1st pregnancy (y, mean ± sd)** | 23.71 ± 4.38 | 21.77 ± 3.78 | 0.000* |

| **Live births** | 17 (11.3) | 12 (7.9) | 0.311 |
|                 | 133 (88.7) | 140 (92.1) |        |

| **# of living children (mean ± sd)** | 1.99 ± 0.93 | 2.22 ± 1.02 | 0.041* |

| **Abortion** | 34 (22.7) | 49 (32.2) | 0.063** |
|              | 116 (77.3) | 103 (67.8) |        |

| **# of induced abortions (median, range)** | 2, 0-30 | 2, 0-30 | 0.529 |
| **# of miscarriages (median, range)** | 0, 0-6 | 0, 0-4 | 0.797 |

| **Breastfeeding** | 10 (7.5) | 6 (4.3) | 0.264 |
|                  | 123 (92.5) | 133 (95.7) |        |

| **Duration of breastfeeding (m, median, range)** | 12, 1-36 | 12, 1-72 | 0.262 |

| **Menopause** | 18 (12.0) | 64 (42.4) | 0.000* |
|               | 127 (84.7) | 83 (55.0) |        |
|               | 5 (3.3) | 4 (2.6) |        |

| **Age at menopause (y, mean ± sd)** | 48.75 ± 5.20 | 48.53 ± 5.30 | 0.765 |
## Oral contraceptive use

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>140 (93.3)</td>
<td>141 (92.8)</td>
<td>0.846</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>10 (6.7)</td>
<td>11 (7.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Duration of OC use (m, median, range)

|            | 5, 1-72 | 3, 1-60 | 0.087**       |

## Female hormone use

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>119 (79.3)</td>
<td>137 (90.1)</td>
<td>0.009*</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>31 (20.7)</td>
<td>15 (9.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Duration of FH use (m, median, range)

|            | 8, 2-72 | 6, 1-36 | 0.059**       |

## Family history of BC

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>108 (72.0)</td>
<td>137 (90.1)</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (27.3)</td>
<td>15 (9.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Smoking status

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>122 (81.3)</td>
<td>123 (80.9)</td>
<td>0.324</td>
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</tr>
<tr>
<td>Past</td>
<td>12 (8.0)</td>
<td>7 (4.6)</td>
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</tr>
<tr>
<td>Current</td>
<td>16 (10.7)</td>
<td>22 (14.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## # of cigarettes smoked (mean ± sd)

|            | 7.77 ± 6.68 | 13.44 ± 11.76 | 0.036*       |

---

*Data are presented as frequencies and percentages unless specified.

Reference for cutoff points (69)

- y=years, sd=standard deviation, #=number, BMI=body mass index, m=months, OC=oral contraceptive, FH=female hormone, BC=breast cancer, *=statistically significant, **=marginally statistically significant

### Table III. SLR Results: Odds Ratios of Developing Breast Cancer Associated with Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>150</td>
<td>152</td>
<td>1.06 (1.03-1.09)</td>
<td>0.000*</td>
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<tr>
<td>Age categories (years)</td>
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<tr>
<td>35-44</td>
<td>16</td>
<td>46</td>
<td>1.00</td>
<td></td>
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<tr>
<td>45-54</td>
<td>43</td>
<td>49</td>
<td>2.52 (1.25-5.09)</td>
<td>0.010*</td>
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<tr>
<td>55-70</td>
<td>91</td>
<td>57</td>
<td>4.59 (2.38-8.86)</td>
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<td>Education (years)</td>
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<td>1.0</td>
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<tr>
<td>School (10)</td>
<td>39</td>
<td>60</td>
<td>1.3 (0.37-4.61)</td>
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<tr>
<td>College/Professional</td>
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<td>35</td>
<td>2.0 (0.55-7.25)</td>
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</tr>
<tr>
<td>technical</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>72</td>
<td>48</td>
<td>3.0 (0.86-10.52)</td>
<td>0.086**</td>
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<td>1</td>
<td>--</td>
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<td>--------------</td>
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<tr>
<td><strong>Marital status</strong></td>
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<tr>
<td>Single</td>
<td>11</td>
<td>5</td>
<td>1.00</td>
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<tr>
<td>Married</td>
<td>120</td>
<td>129</td>
<td>0.42 (0.14-1.25)</td>
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<td>10</td>
<td>6</td>
<td>0.76 (0.18-3.27)</td>
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<td>Widowed</td>
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<td>12</td>
<td>0.34 (0.09-1.34)</td>
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<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>136</td>
<td>123</td>
<td>1.07 (1.01-1.15)</td>
<td><strong>0.015</strong>*</td>
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<tr>
<td>Normal (19.0-24.9)</td>
<td>25</td>
<td>34</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Overweight (25.0-29.9)</td>
<td>54</td>
<td>57</td>
<td>1.29 (0.68-2.44)</td>
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</tr>
<tr>
<td>Obese (≥30.0)</td>
<td>57</td>
<td>32</td>
<td>2.42 (1.24-4.75)</td>
<td><strong>0.010</strong>*</td>
</tr>
<tr>
<td><strong>Diabetes mellitus type 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>128</td>
<td>147</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>22</td>
<td>5</td>
<td>5.05 (1.86-13.73)</td>
<td><strong>0.001</strong>*</td>
</tr>
<tr>
<td><strong>Age at menarche (years)</strong></td>
<td>144</td>
<td>144</td>
<td>0.78 (0.67-0.92)</td>
<td><strong>0.003</strong>*</td>
</tr>
<tr>
<td><strong>Age at menarche categories (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11</td>
<td>14</td>
<td>5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;11</td>
<td>130</td>
<td>139</td>
<td>0.33 (0.12-0.95)</td>
<td><strong>0.040</strong>*</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>12</td>
<td>9</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>138</td>
<td>143</td>
<td>0.72 (0.30-1.77)</td>
<td>0.479</td>
</tr>
<tr>
<td><strong># of pregnancies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>55</td>
<td>58</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>6-15</td>
<td>77</td>
<td>71</td>
<td>1.14 (0.70-1.87)</td>
<td>0.591</td>
</tr>
<tr>
<td>16-35</td>
<td>5</td>
<td>14</td>
<td>0.38 (0.13-1.12)</td>
<td>0.078**</td>
</tr>
<tr>
<td><strong>Age at first pregnancy (years)</strong></td>
<td>138</td>
<td>142</td>
<td>1.13 (1.06-1.20)</td>
<td><strong>0.000</strong>*</td>
</tr>
<tr>
<td><strong>Live births</strong></td>
<td>133</td>
<td>140</td>
<td>0.76 (0.61-0.94)</td>
<td><strong>0.014</strong>*</td>
</tr>
<tr>
<td><strong>Live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>12</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>133</td>
<td>140</td>
<td>0.67 (0.31-1.46)</td>
<td>0.313</td>
</tr>
<tr>
<td><strong># of living children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>--------</td>
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<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>12</td>
<td>1.00</td>
<td>0.60 (0.20-1.78)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>13</td>
<td></td>
<td>0.83 (0.37-1.84)</td>
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<tr>
<td></td>
<td>83</td>
<td>71</td>
<td></td>
<td>0.56 (0.24-1.33)</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>44</td>
<td></td>
<td>0.28 (0.07-1.12)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abortion experience**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Ever</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34</td>
<td>49</td>
<td>1.00</td>
<td>1.62 (0.97-2.71)</td>
</tr>
</tbody>
</table>

**# of induced abortions**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1-3</th>
<th>≥11</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>34</td>
<td>49</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>53</td>
<td>1.77 (1.00-3.12)</td>
<td>0.049*</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>34</td>
<td>1.95 (1.05-3.65)</td>
<td>0.036*</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>15</td>
<td>0.48 (0.16-1.45)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

**Miscarriages**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Ever</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>115</td>
<td>115</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>37</td>
<td>0.95 (0.56-1.61)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

**# of miscarriages**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1-3</th>
<th>4-6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>115</td>
<td>115</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>35</td>
<td>0.94 (0.55-1.62)</td>
<td>0.831</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>1.00 (0.14-7.22)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**Breastfeeding experience**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Ever</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>6</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>133</td>
<td>0.55 (0.20-1.57)</td>
<td>0.268</td>
</tr>
</tbody>
</table>

**Breastfeeding duration (months)**

<table>
<thead>
<tr>
<th></th>
<th>≤9</th>
<th>10-24</th>
<th>&gt;24</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54</td>
<td>56</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>1.04 (0.62-1.74)</td>
<td>0.890</td>
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<tr>
<td></td>
<td>9</td>
<td>16</td>
<td>0.58 (0.24-1.43)</td>
<td>0.240</td>
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</table>

**Menopause**

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>64</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>132</td>
<td>87</td>
<td>5.39 (2.99-9.72)</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

**Age at menopause**

<table>
<thead>
<tr>
<th></th>
<th>≤55</th>
<th>&gt;55</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>117</td>
<td>80</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3</td>
<td>2.28 (0.61-8.54)</td>
<td>0.222</td>
</tr>
</tbody>
</table>

**Oral contraceptive use**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Ever</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>140</td>
<td>141</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>11</td>
<td>0.92 (0.38-2.22)</td>
<td>0.846</td>
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</tbody>
</table>

**Duration of OC use**
(months)
<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>8</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6</td>
<td>3</td>
<td>8</td>
<td>1.00</td>
</tr>
<tr>
<td>7-24</td>
<td>2</td>
<td>1</td>
<td>5.33 (0.34-82.82)</td>
</tr>
<tr>
<td>≥25</td>
<td>4</td>
<td>1</td>
<td>10.67 (0.82-138.22)</td>
</tr>
</tbody>
</table>

**Female hormone use**
<table>
<thead>
<tr>
<th></th>
<th>119</th>
<th>137</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>119</td>
<td>137</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever</td>
<td>31</td>
<td>15</td>
<td>2.38 (1.23-4.62)</td>
</tr>
</tbody>
</table>

**Combined duration of FH use (months)**
<table>
<thead>
<tr>
<th></th>
<th>14</th>
<th>9</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6</td>
<td>14</td>
<td>9</td>
<td>1.00</td>
</tr>
<tr>
<td>7-24</td>
<td>6</td>
<td>5</td>
<td>0.77 (0.18-3.30)</td>
</tr>
<tr>
<td>≥25</td>
<td>9</td>
<td>1</td>
<td>5.79 (0.62-53.77)</td>
</tr>
</tbody>
</table>

**Family history of BC**
<table>
<thead>
<tr>
<th></th>
<th>108</th>
<th>137</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>108</td>
<td>137</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>42</td>
<td>15</td>
<td>3.47 (1.82-6.60)</td>
</tr>
</tbody>
</table>

**Smoking status**
<table>
<thead>
<tr>
<th></th>
<th>122</th>
<th>123</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>122</td>
<td>123</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever</td>
<td>28</td>
<td>29</td>
<td>0.91 (0.66-1.27)</td>
</tr>
</tbody>
</table>

**# of daily cigarettes smoked**

<table>
<thead>
<tr>
<th></th>
<th>22</th>
<th>16</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>22</td>
<td>16</td>
<td>1.00</td>
</tr>
<tr>
<td>11-20</td>
<td>3</td>
<td>6</td>
<td>0.36 (0.08-1.68)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1</td>
<td>5</td>
<td>0.15 (0.02-1.37)</td>
</tr>
</tbody>
</table>

---

*Reference for cutoff points (70)

OR=odds ratio, BC=breast cancer, CI=confidence interval, BMI=body mass index,
#=number, OC=oral contraceptives, FH=female hormone, *=statistically significant,
**=marginally statistically significant
Table IV. Final Multiple Logistic Regression Model

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusted OR (95% CI)</th>
<th>Unadjusted OR (95% CI) from SLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus type 2</td>
<td>5.53 (1.34-22.81)</td>
<td>5.05 (1.86-13.73)</td>
</tr>
<tr>
<td>Age</td>
<td>0.96 (0.90-1.02)</td>
<td>1.06 (1.03-1.09)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.05 (0.95-1.16)</td>
<td>1.07 (1.01-1.15)</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>0.80 (0.61-1.05)</td>
<td>0.33 (0.12-0.95)</td>
</tr>
<tr>
<td>Age at 1st pregnancy</td>
<td>1.13 (1.01-1.27)</td>
<td>1.13 (1.06-1.20)</td>
</tr>
<tr>
<td>Live birth</td>
<td>0.36 (0.20-0.66)</td>
<td>0.76 (0.61-0.94)</td>
</tr>
<tr>
<td>Abortion</td>
<td>2.86 (1.02-8.04)</td>
<td>1.62 (0.97-2.71)</td>
</tr>
<tr>
<td>Breastfeeding duration</td>
<td>1.00 (0.96-1.05)</td>
<td>0.94 (0.57-1.55)</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>1.06 (0.98-1.14)</td>
<td>2.28 (0.61-8.54)</td>
</tr>
<tr>
<td>Female hormone use</td>
<td>2.88 (0.88-9.38)</td>
<td>2.38 (1.23-4.62)</td>
</tr>
</tbody>
</table>

Model characteristics: Hosmer-Lemeshow chi2(8) = 10.85, Prob > chi2 = 0.2101, number of groups = 10
Appendix 1. A Woman’s Risk of Developing Breast Cancer by Age

The risk is based on Gail model using risk factors like age at menarche, age at first live birth, number of first-degree relatives with BC etc, so the baseline age-specific hazard rate is computed as a product of observed age-specific composite hazard rate times the quantity 1 minus the attributable risk (71).

Source: NCI Surveillance Program (72)
Appendix 2. Formulae and STATA Output for Sample Size Calculation

\[ n = \left\{ \frac{z_{1-\alpha/2} \sqrt{P_1(1-P_1) + P_2(1-P_2)}}{(P_1 - P_2)^2} \right\}^2 \]

\[ P_1 = \frac{(OR)P_2}{(OR)P_2 + (1 - P_2)} \]

`. sampsi 0.60 0.43, a(0.05) p(0.8)
Estimated sample size for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1
and p2 is the proportion in population 2

Assumptions:
- alpha = 0.0500 (two-sided)
- power = 0.8000
- p1 = 0.6000
- p2 = 0.4300
- n2/n1 = 1.00

Estimated required sample sizes:
- n1 = 147
- n2 = 147

Appendix 3. Accrual Journal Form

<table>
<thead>
<tr>
<th>ID</th>
<th>Name</th>
<th>Telephone number</th>
<th>Date of interview</th>
<th>Result</th>
<th>Other</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Options for ID
- O – 122 (case from NOC # 122)
- M – 17 (case from AAWC # 17)
- C – 103 (control # 103)

Options for “Result”
- complete
- incomplete
- refusal
- absence
- busy line
- inoperable line
Appendix 4. Enrollment Flowchart

368 total participants assessed as a sample

230 eligible in frame
42 excluded
  12 out of country
  6 wrong telephone
  13 disconnected
  3 no answer
  8 busy line

98 excluded
  42 not eligible
  21 office phones
  35 busy line & no answer

184 cases
34 interviews not obtained
  27 dead
  7 refused

150 included in primary analyses

184 controls
32 interviews not obtained
  32 refused

152 included in primary analyses
Appendix 5. Box-Plots of Statistically Significant Difference (p<0.05) in Means

Figure 1. Mean Age of Cases and Controls

Notes: Mean age of cases is significantly higher than mean age of controls: 55.8±7.9 vs. 51.1±9.9 (p<0.001)

Figure 2. Mean BMI of Cases and Controls

Notes: Mean BMI of cases is significantly higher than mean BMI of controls: 29.0±4.3 vs. 27.7±4.6 (p=0.014)
Figure 3. Mean Age at Menarche of Cases and Controls

Notes: Mean age at menarche of cases is significantly lower than mean age at menarche of controls: 13.5±1.5 vs. 14.0±1.5 (p=0.002)

Figure 4. Mean Age at First Pregnancy of Cases and Controls

Notes: Mean age at first pregnancy of cases is significantly higher than mean age at first pregnancy of controls: 23.7±4.4 vs. 21.8±3.4 (p<0.001)
Appendix 6. Odds Ratios with Confidence Intervals in Univariate Analyses
Appendix 7. Receiver-Operating Characteristics Curve

Area under ROC curve = 0.8007. An area of 1.0 under the ROC curve indicates perfect discrimination, whereas an area of 0.50 indicates complete absence of discrimination. Any intermediate value is a quantitative measure of the ability of the risk predictor model to distinguish between survivors and non-survivors. The solid line represents no discrimination.
Appendix 8. Consent Forms in English and Armenian

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Oral Consent Form for Cases

Project Title: Diabetes Mellitus Type 2 and Prolonged Exposure to Estrogen as Risk Factors for Development of Breast Problems in Women of Age 35-70 in Yerevan

Hello, my name is Lilit Khachatryan. I am a Medical Doctor and a graduate student of Master of Public Health Program at the American University of Armenia. As a part of my course requirement I am conducting a study to investigate the role of diabetes and female reproductive characteristics as risk factors for development of breast problems in women of age 35-70 in Yerevan.

You have been randomly selected to participate in this study from women registered at the archive of American-Armenian Wellness Center and/or Mammology department of National Oncology Center by permission of the center director.

In case if you agree to participate in the current study, I am going to ask you a few questions concerning your medical and reproductive history. This interview will take place only once and will last no more than 10-15 minutes. You have the right to ask questions in the scope of the interview and stop it at any moment you wish with no negative consequences for you. I really appreciate your participation in the current study.

There is no any special risk and direct financial or other benefit for you being a participant for the study. The individual information you provide is of great value and will be very useful for investigation of the risk factors of breast problems. Moreover, the obtained results will be very helpful for further research in the field of breast related problems in Armenia.

The information you provide is fully confidential and will be used only for this study. Any identifying information such as your name or telephone number will not be recorded. Only I have access to the computer with names and phone numbers of study participants, and the computer is located in a locked room. All files with information identifying participants will be destroyed upon the completion of the study. Any information that you provide will be coded and held anonymous.

Your participation in the current study is absolutely voluntary. You have the right to stop the interview at any moment or skip any question you think is inappropriate with no further negative consequences for you and medical care you receive.

If you have any questions or want to obtain more information about this research project you can contact me at 091328651. If you believe that you have not been treated fairly or have been hurt by joining the study you may call the Chair of Departmental IRB Yelena Amirkhanyan at 261312 (ext. 333).
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College Of Health Sciences Subcommittee For Student Theses

Oral Consent Form for Cases (Armenian)

Institutional Review Board 

Institutional Review Board 

American University Of Armenia
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College Of Health Sciences Subcommittee For Student Theses

Oral Consent Form for Cases (Armenian)

Institutional Review Board 

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Institutional Review Board # 1/Committee On Human Research
College Of Health Sciences Subcommittee For Student Theses

Oral Consent Form for Cases (Armenian)

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Oral Consent Form for Cases (Armenian)
Project Title: Diabetes Mellitus Type 2 and Prolonged Exposure to Estrogen as Risk Factors for Development of Breast Diseases in Women of Age 35-70 in Yerevan

Hello, my name is Lilit Khachatryan. I am a Medical doctor and a graduate student of Master of Public Health Program at the American University of Armenia. As a part of my course requirement I am conducting a study to investigate the role of diabetes and female reproductive characteristics as risk factors for development of breast problems in women of age 35-70 in Yerevan.

Your telephone number has been randomly selected for this study. Is there anybody in your household who is a woman of age between 35 and 70 and has not undergone any breast surgery, except for plastic surgery, or diagnosed any breast diseases? Would you pass the telephone to her, please? (If needed, repeat the introduction for the eligible participant).

In case if you agree to participate in the current study, I am going to ask you a few questions concerning your medical and reproductive history. This interview will take place only once and will last no more than 10-15 minutes. You have the right to ask questions in the scope of the interview and stop it at any moment you wish with no negative consequences for you. I really appreciate your participation in the current study.

There is no any special risk and direct financial or other benefit for you being a participant for the study. The individual information you provide is of great value and will be very useful for investigation of the risk factors of breast problems. Moreover, the obtained results will be very helpful for further research in the field of breast related problems in Armenia.

The information you provide is fully confidential and anonymous, and will be used only for this study. Any identifying information such as your telephone number will not be recorded. Any information that you provide will be coded and held anonymous.

Your participation in the current study is absolutely voluntary. You have the right to stop the interview at any moment or skip any question you think is inappropriate with no further negative consequences for you.

If you have any questions or want to obtain more information about this research project you can contact me at 091328651. If you believe that you have not been treated fairly or have been hurt by joining the study you may call the Chair of Departmental IRB Yelena Amirkhanyan at 261312 (ext. 333).
Oral Consent Form for Controls (Armenian)
Appendix 9. IRB Approval

04 March 2009

Lilit Khachatryan, MD
Graduate Student,
Master of Public Health Program
40 Marshall Baghramian
Yerevan 0019 Armenia

RE: IRB Application Form

Dear Dr. Khachatryan:

A departmental Institutional Review Board (IRB) committee within the College of Health Sciences, reviewed your proposal entitled, "Diabetes Mellitus Type 2 and Prolonged Exposure to Estrogen as Risk Factors for Development of Breast Cancer in Women of Age 35-70 in Yerevan". The proposal was approved. Your study appears to be based on comparable prior research, is directly related to your professional duties, and is appropriate for an MPH thesis project.

In our opinion, the proposal follows widely accepted standards. We agree with you that the survey involves minimal risk because there are no patient interventions and participation is a voluntary decision.

It is our determination that this application does not need to be reviewed by the University’s IRB and approval is given to you by the College of Health Sciences to proceed with your project.

This approval does not supersede the continued advice and interactions among you and your faculty advisors. Should any change occur within the proposal, please promptly keep us informed.

Sincerely,

[Signature]

Yelena Amirkhanyan, MD, MPH
Chair, College of Health Sciences Student IRB

cc: Administrator, AUA Committee on Human Research
Student’s Thesis File
Appendix 10. Questionnaires in English and Armenian

**QUESTIONNAIRE**

Record ID ________________

Status: 1. □ Case 0. □ Control

1. How old are you? ______

2. What is the highest level of education you have completed?
   1. □ School (less than 10 years)
   2. □ School (10 years)
   3. □ College/Professional technical education (10-13 years)
   4. □ Institute/University
   5. □ Postgraduate

3. What is your current marital status?
   1. □ Single
   2. □ Married
   3. □ Divorced
   4. □ Widowed

4. What is your current weight? ______kg

5. What is your height? ______cm

***

I would like to ask you some questions now about your health history including questions about diabetes, your menstrual cycle, pregnancy, and childbirth.

6. Have you ever been told by a doctor that you have diabetes mellitus?
   0. □ No (skip to Q. 10)
   1. □ Yes

7. How old were you when a doctor first told that you had diabetes? ________________

8. Are you now taking an oral hypoglycemic agent – diabetic pills?
   0. □ No
   1. □ Yes

9. Are you now taking insulin injections?
0. □ No
1. □ Yes

***

10. At what age did you have your first menstruation? ________years old

0. □ Have never had
88. □ Don’t remember

11. How many times have you ever been pregnant (including live births, abortions, miscarriages, tubal and current pregnancy)?

__________number of pregnancies (If 0, skip to Q. 19)

12. What was your age at first pregnancy? _______years old

13. How many pregnancies ending in live birth delivery have you experienced? _______

14. How many living children do you have? _______________

15. How many induced abortions have you experienced in your lifetime? _______

16. How many miscarriages have you experienced in your lifetime? ___________

17. Did you breast-feed at least one of your children?

0. □ No (skip to Q. 19)
1. □ Yes

18. What was the longest duration of your breastfeeding? _______months/years

19. Are you currently in the menopause?

0. □ No (skip to Q. 21, then to Q. 25)
1. □ Yes
88. □ Don’t know (skip to Q. 21)

20. How long are you in the menopause? ____________________months

21. Have you ever taken an oral contraceptive?

0. □ No (skip to Q. 23)
1. □ Yes

22. What was the overall duration of taking an oral contraceptive? __________ months/years
23. Have you ever received female hormones (oral, shots, or any type) to lighten menopause symptoms?
   0. □ No (skip to Q. 25)
   1. □ Yes

24. What was the overall duration of taking female hormones? ______________ months/years

25. Have you ever used any female hormones (oral, shots, or any type) over more than a month because of other reasons/disease?
   0. □ No (skip to Q. 27)
   1. □ Yes

26. What was the overall duration of using female hormones? ____________ months/years

***

27. Among your blood related female relatives, has anybody ever been diagnosed with malignant tumor of breast?
   0. □ No (skip to Q. 29)
   1. □ Yes

28. Please, specify __________________

***

29. Are you a current smoker?
   0. □ No (skip to Q. 31)
   1. □ Yes

30. At what age did you start smoking? _______years old

31. Have you ever smoked in the past?
   0. □ No (stop the interview)
   1. □ Yes

32. How old were you when you quit smoking? _______years old

33. On average, how many cigarettes do (did) you smoke per day? _______cigarettes/day

Thank you very much for your participation.
QUESTIONNAIRE (Armenian)

Արյունագրիչ ID ———————

Այսպիսով։ 1. □ մեկ 0. □ զուգախմբ

1. Ուղղության նախատեսություն (1) ————————

2. Հույս գրանցվեցել է: 

1. □ տեքստ մեկտերի գրանցվեց
2. □ առաջին նշան (մեկ ցուցադր) 
3. □ առաջին նշան վերանցվեց (10-13 ցուցադր)
4. □ դիրք/հատորացույց
5. □ զարգացմունք/ընթացք առաջացեց

3. Հույս անցացման կարգախմբակը (1) ———————

1. □ զարգացված
2. □ մեկից զգալի
3. □ մեկից զգալի կազմ
4. □ ընդունված

4. Որոնում է փոքր վաղեր: ———————— չէ

5. Որոնում է փոքր հասարակություն: ———————— չէ

***

Այսու մեկ բոլոր հարցեր կոչում ուղեցրեն փորձ տալ կազմակերպության, ուղինով կան երկրորդական, տարածաշրջանային գրանցված, հետաքրքրվողների և բնակչությունը ունեցող բազայի: 

6. Որոնում է այս վաղեր: □ մեկ, □ զարգացած է համար չէ ընդունված և

0. □ Շ (ավելի 10-րդ հարց)
1. □ Լին

7. Ուղղության նախատեսություն (2) չէ, եթե որոնում է ավելի արագացման առաջարկ, պետք է նշվի: ————

8. Ուղղափառ բոլոր վաղերի ուղին պաշտպանող մասնակից համար նախապատրաստված է համար: 

0. □ Շ 
1. □ Լին

9. Ուղղափառ բոլոր վաղերի ուղին համար չէ ընդունված ներկայացված: 

51
10. Ընդհանուր* տարիքը ցրել, եթե այդպիսի ազդման հաշվարկում չէին: ----------- տարիքը

0. ☐ Ուն
1. ☐ Ոչ

***

11. Ընդհանուր* հիմնական տես ներկայիս (սեռավեկի, սեռիզմի ուղարկման, զարգանալիության, զարգանալիության և սեռի կապի հիմնականություն)

------------- հիմնականությունից հետո (0 թվական հերթակազմ ավագից 19-րդ հարթակ)

12. Ընդհանուր* տարիքը ցրել, եթե սարքի ազդում հեշտացել: ----------- տարիքը

13. Ընդհանուր* հիմնական է, այդպիսով դիմումը ծանրակշռություն: -------------------------------

14. Ընդհանուր* կենսագիր մրցակցություն: -------------------------------

15. Ընդհանուր* արդյունք նոր չափաստանք Ուուր որ տարրեր պարզելու: -------------------------------

16. Ընդհանուր* հիմնական է, տարանգետություն վերակօրեն: -------------------------------

17. Ուուր տրիմասահարկից գտնե մեկից կրոնի կարմիրների նկար

0. ☐ Ու (ամփույկ 19-րդ հարթակ)
1. ☐ Ոչ

18. Որոշում է, ինիցիական կրոնիներին ամբասադուրը նորից տեղադրել: -----------

19. Սեղանային Ուուր դաշնակարգահանակար միջա նկար

0. ☐ Ու (ամփույկ 21-րդ, ամփույկ 25-րդ հարթակ)
1. ☐ Ոչ
88. ☐ Չորսնս (ամփույկ 21-րդ հարթակ)

20. Որոշում մասնակցել է, որ Ուուր դաշնակարգահանակար միջա նկար: ----------- ավել/ավել

21. Հորդերը հայտարարությանը հարցի օգտագործվում էր նկար

0. ☐ Ու (ամփույկ 23-րդ հարթակ)
1. ☐ Ոչ

22. Որոշում է, հանդեսբերումների հարցի օգտագործողությունը փոխարինել տեղեկագիր: --------

52
23. Երկրին՝ օգնեցի 25-րդ հարց: (արդյունք, պատասխանը կամ այլ
տեղական) հայտարարության աղյուսակները մնացուահանվում են:

0. □ Ω (ամբողջ 25-րդ հարց)
1. □ Ու

24. Ուրախության հետևանքները օգնեցի 26-րդ հարց: -
այսից/այստեղ

25. Երկրին՝ մինչև այսօր այսպիսի ներկայացուցիչ օգնեցի 26-րդ հարց՝
(արդյունք, պատասխանը կամ այլ տեղական) սահմանափակ է

0. □ Ω (ամբողջ 27-րդ հարց)
1. □ Ու

26. Ուրախության հետևանքները օգնեցի 28-րդ հարց:

27. Ուրախության և այլ ժամանակակից մյուս հայտնչությունները դրանց
պատճառով թվով նշելուն օգնեցի 29-րդ հարց: -

0. □ Ω (ամբողջ 29-րդ հարց)
1. □ Ու

28. Ուրախության և այլ համար, օգնեցի 29-րդ հարց:

29. Որոնք, այդպիսի տվյալներ չեն: -

0. □ Ω (ամբողջ 30-րդ հարց)
1. □ Ու

30. Ուրախության և այլ համար, օգնեցի 30-րդ հարց: -

31. Ուրախության և այլ համար, օգնեցի 31-րդ հարց:

32. Ուրախության և այլ համար, օգնեցի 32-րդ հարց:

33. Ուրախության և այլ համար, օգնեցի 33-րդ հարց:

Հայտնումների համարազարդություն մասնագիտական խնդիր