College of Health Sciences
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Investigation of reproductive risk factors for endometrial cancer development among women aged 45-75 years in Yerevan, Armenia: A Case-Control study

Master of Public Health Thesis project Utilizing Professional Publication Framework

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Yerevan, Armenia
2007

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Abstract

Objectives: Endometrial cancer is one of the most common gynecologic cancers worldwide. The current study identified the reproductive risk factors of endometrial cancer among 45-75 years old women in Yerevan, Armenia and developed recommendations for early prevention of the disease.

Methods: The study utilized a case-control study design. Cases were patients aged 45-75 years with clinically and hystologically confirmed diagnosis of endometrial cancer who were registered at the National Oncology Center of Armenia from 2000 to 2006 (n=177). Controls were "healthy" women aged 45-75 years residing in Yerevan recruited through Random Digit Dialing (n=232). An interviewer-administered structured questionnaire was used during the telephone interviews with both cases and controls.

Results: Cases and controls were significantly different in several factors. According to the multiple logistic regression analyses, getting older than 55 years was associated with 2.5 times (OR=2.5, 95% CI 1.3-4.7) and 65 years with more than 9 times (OR=9.0, 95% CI 4.3-18.8) increased risk of endometrial cancer as compared to the younger age women (45-54 years). Older age at the onset of menarche (over 14 years old) was associated with threefold elevated risk of endometrial cancer. Gravidity was associated with a considerable risk reduction for endometrial cancer development (OR =0.1, 95% CI 0.03-0.38). Compared with normal weight women (BMI=19-24.9 kg/m^2), obese women (BMI >30.0 kg/m^2) had approximately 7.5 times higher risk of endometrial cancer. Oral contraceptive use and intrauterine device use was very low in this population while very high proportion of women experienced at least one induced abortion in their lifetime.

Conclusion: Older age, older age at the onset of menarche, obesity, and nulliparity were independent risk factors of endometrial cancer development. Based on the results it has been suggested to promote actively the concept of maternity and gravidity, healthy lifestyle and weight control, as well as family planning and particularly modern methods on contraception among Armenian female community.

Acknowledgments

I would like to express my deep gratitude to my advisors Lusine Abrahamyan and Lusine Poghosyan for their great contribution in preparing this project, valuable instructions and continuous support.

I am thankful to the whole MPH Program Faculty of the American University of Armenia for their encouraging attitude, support and assistance.

I would like to acknowledge the director of National Oncology Center (NOC) Prof. Galstyan H. M and the whole medical staff of NOC for making available their databases, providing valuable information and their continuous interest in the project.

I am very grateful to my family and friends for their kind attitude, patience and continuous support.

List of Abbreviations

USA	United States of America
NOC	National Oncology Center
WHO	World Health Organization
OR	Odds Ratio
RR	Relative risk
CI	Confidence Interval
OC	Oral contraceptive
IUD	Intrauterine Device
BMI	Body Mass Index
IRB	Institutional Review Board
SLM	Simple Logistic Regression
MLR	Multiple Logistic Regression
SD	Standard Deviation

1. Introduction

Endometrial cancer (EC) is a hormone-dependent neoplasm that results in malignant transformation of the inner wall of uterus [1]. It is one of the most common gynecologic cancers and accounts for 6% of all cancers in women, worldwide [2]. An estimated 199 000 incident cases were diagnosed and 50 000 died from EC in 2002, worldwide [2].

Endometrial cancer is sometimes called uterine cancer, but one should recognize that there are other cells, in particular, myometrial cells in the uterus that can become cancerous. These forms of cancers are called sarcomas, which are less common and account for less than 5% of uterine cancers [1].

Endometrial cancer is relatively uncommon among women under 45 years old representing approximately 2–14% of all cases [2]. According to the American Cancer Society, 95% of endometrial cancer affected the women age 45 and older, 60 being the average age at diagnosis making the disease a significant threat to women's health in aging population [1].

In Western industrialized countries such as United Kingdom, Spain, France the annual incidence rate as well as mortality rate from endometrial cancer is continuously increasing [1].

In United States of America (USA), for 1998, an estimated 36 000 new cases and 6 300 deaths were attributed to endometrial cancer [3]. Today's statistics is quite different. According to the American Cancer Society estimates, nearly 40 000 women receive a diagnosis of endometrial cancer each year, making it the fourth most common cancer found in women after breast cancer, lung cancer and colon cancer in USA [3]. Furthermore, about 7 400 women die from endometrial cancer each year making it the eighth leading cause of mortality among women in USA [3]. It was estimated that the chance for any woman to develop endometrial cancer during her lifetime is 1 in 40 in USA [3].

According to Canadian Cancer Statistics, in 2004 the annual endometrial cancer incidence was 3 800 which represented the ratio of 19 per 100 000 cases among women population [5]. Annual deaths attributed to endometrial cancer are 3 per 100 000 deaths or overall 700 deaths annually [5].

Australian National Mortality Database indicates that endometrial cancer accounted for 15.8 new female cases per 100 000 Australian population in 2000 encompassing 1 654 new cases of disease annually [5]. Mortality rate statistics for deaths from endometrial cancer has been estimated to be 1.6 women per 100 000 Australian population causing 261 female deaths annually [5].

Endometrial cancer is widely spread malignancy among women in Russian also; it is the second most frequent oncogynecological disease followed after cervical cancer [6]. There is an increasing trend in hormone dependent malignancies as breast cancer and endometrial cancers in Russia [6]. According the data obtained in 2000, endometrial cancer counts 6.5% in the structure of all cancers in women [6].

Armenian women historically have lower risk of endometrial cancer compared to western countries [7]. However, the incidence of endometrial cancer among Armenian women has substantially increased over the last 2 decades [7]. Nowadays, endometrial cancer is a widespread malignancy among women in Armenia and is the second most frequent oncogynecological malignancy followed cervical cancer [7]. There is an increasing trend in both morbidity and mortality from endometrial cancer in Armenia (Appendix 1, Table 1) [7]. According to the data obtained from Armenian National Oncology Center's (NOC) Statistical department, in 1997, the incidence rate of endometrial cancer was 6.9 per 100 000 population, while in 2006, the incidence rate increased to 15.1. [7]. Meanwhile, if in 1997 the mortality rate

from endometrial cancer was 3.6 per 100 000 population, in 2006 this number turned to be 7.3 [7]. However, this could possibly be attributed by the improvement of detection techniques and/or the increase of the disease incidence. On the other hand, it could be attributed by the changes of reporting of dead cases and the way state statistics are collected in Armenia [7]. Endometrial cancer mortality statistics in Armenia for 1997 and 2003 are presented in Appendix 1, Table 2. In Armenia, about 68% of endometrial cancer cases are diagnosed in the I-II stages of the disease and 32% in the III-IV stages with already existing distant metastasis [7]. It is essential to underline that five year survival rate for endometrial cancer patients followed appropriate treatment is 75-95% for I stage, 50% for II stage, 30% for stage III and less than 5% for stage IV [2,3].

1.1 Background information

The risk factors for endometrial cancer development have been under continuous investigation by researchers. It has been suggested that most endometrial cancers are "hormone-driven" underling the concept that women's hormone disbalance plays significant role in disease development [8,6]. Normally, the ovaries produce two types of female hormones: estrogen and progesterone [8,6]. The normal menstrual cycle reflects the balance between the proliferative actions of estrogen and the antiestrogenic and secretory actions of progesterone on the endometrium [8,6]. Excessive levels of estrogens lead to the uncontrolled proliferation of endometrium which further lead to the development of the endometrial hyperplasia [8,6]. If this hormonal disbalance is not corrected, simple endometrial hyperplasia may develop into a complex hyperplasia that has 25 percent risk of progressing into endometrial cancer [8,6]. Therefore, to avoid above-mentioned dysfunctional processes, the adequate levels of both estrogens and progesterone are essential [8,6].

Several studies have identified that reproductive factors such as early onset of menarche and late menopause which comprehensively lead to prolonged menstruation span, nulligravidity, miscarriages and induced abortions, age at birth, use of oral contraceptives and intrauterine devices, breastfeeding practices, obesity, tamoxifen and estrogen/hormone replacement therapies, certain ovarian diseases are related to the risk of endometrial cancer development [9-28]. Prolonged estrogen stimulation without the protection of progesterone has been suggested as the most probable mechanism for the association of reproductive factors with the risk of endometrial cancer [9; 12].

Previous research showed that having more menstrual cycles during the woman's lifetime or prolonged menstruation raises the risk of disease development [9, 10, 11]. According to a cohort study, starting menarche at the age of 10 or younger increased the risk of endometrial cancer by approximately one-third compared with those starting at the age of 15 or older [9]. Consequently, women who have gone thought menopause at the age of 55 or older have relative risk (RR) of disease 1.87 times (95% CI 1.12-3.1) greater compared to those who had undergone menopause at the age of 45 [9]. On the other hand, case-control studies carried out in Shanghai suggested that not the onset of menstruation and of menopause but the total length of menstrual span (years of menstruation , normally 32-37years) was related to the risk of endometrial cancer development indicating OR=1.99 (95% CI 1.46- 2.72) for women whose menstruation span was approximately 35 years and OR=3.21(95% CI 2.06- 5.02) for women whose menstruation span was nearly 40 years or above [10].

History of nulligravidity, defined as never being pregnant, was associated with significantly elevated risk of endometrial cancer with OR of 1.82 (95% CI 1.16-2. 85) [9, 10, 11]. Positive relationship has been shown between endometrial cancer and miscarriages and

induced abortions [9, 13]. It has been explained by the fact that during both procedures the removal of malignantly transformed epithelial cells takes place [9, 13,]. However, these associations are still the issue of great controversy.

In recent years, several articles have been written about the protective effects of oral contraceptives (OCs) (OR=0.36) and intrauterine devices (IUDs) (OR=0.4-0.7) in relation to endometrial cancer [11, 14, 15, 16, 17, 18, 19, 20].

Obesity is another risk factor for endometrial cancer development. It has been shown that gaining at least 5 kg between the ages 40 and 50 for women with BMI equal or more than 25 was associated with almost twofold increase of risk of endometrial cancer [22, 23].

Several studies have found an association between the childbearing at older age and endometrial cancer indicating that higher age at last live birth is associated with decreased risk of the cancer at a rate of about 15% per five-year delay of last birth [24]. This phenomenon has been explained by the fact of mechanical exfoliation of endometrium during each delivery which could result in removal of malignantly transformed epithelial cells [24].

Majority of studies on breastfeeding practices showed its negative association with endometrial cancer (OR 0.42 (95% CI 0.19-0.91; $p< 0.001$) despite the fact that breastfeeding increases the secretion of follicle-stimulating and luteinizing hormones [11]. On the other hand, breastfeeding is related to pregnancy and child birth that, in combination with other factors, shortens the ovulation span resulting in low level of estrogen [11].

Estrogen and hormone replacement therapy play remarkable role in endometrial cancer development [8]. Estrogen replacement therapy is offered to “menopausal women” to relieve the effects of estrogen deficiency detected during menopause [8]. A meta-analysis of 30 studies

evaluating the association between the use of estrogen and/or hormones and endometrial cancer development found a relative risk of 2.3 for estrogen users compared to non-users [25].

Certain ovarian tumors both benign and malignant produce estrogen resulting in much higher concentration of estrogen and lower concentration of progesterone which increases woman's likelihood of endometrial cancer development [1, 3, 6]. It has been shown that women with breast cancer and with family history of other location cancers have greater risk of developing cancer of endometrium [1, 3, 6]. Interestingly, several studies suggested that women who smoke had lower risk of endometrial cancer than nonsmokers and that the greatest risk reduction was observed among heavy women [27, 28]

Inconsistent and controversial results from previous studies in relation to the risk factors for endometrial cancer indicate necessity for further research in the field.

1.2 Rationale of the study

According to a leading specialist in the field of Oncogynecology in Armenia Prof. Bazikyan G. (NOC), no study has been conducted in Armenia to investigate the reproductive risk factors in the etiology of endometrial cancer development [7]. High rate of induced abortions, comparably low rate of hysterectomy and low frequency of using the hormone replacement therapy with the increase of endometrial cancer incidence highlight the existing research gap. Hence, inconsistent and controversial results from previous research, an increasing incidence of EC and the absence of any similar studies in Armenia served as the rationale for conducting the current study which aimed to investigate the importance of reproductive factors in the risk of development of endometrial cancer in Armenia.

1.3 Aims and research questions of the study

The study aims are to:

- Identify the reproductive risk factors leading to the development of endometrial cancer among 45-75 years old women in Armenia
- Develop recommendations for early prevention of the disease according to the findings of the study
- Define areas for further research in the field of Oncogynecology in Armenia

The study's primary research question is:

- Does the gravidity, defined as ever being pregnant, decrease the risk of endometrial cancer among 45-75 years old women in Yerevan?

The study's secondary research questions are:

- Does the prolonged menstruation history, defined as early age at menarche and late age at menopause, increase the risk of endometrial cancer among 45-75 years old women in Yerevan?
- Are the induce abortions, defined as interruption of pregnancy prior to the 28^{th} week, associated with the risk of endometrial cancer development among 45-75 years old women in Yerevan?

2. Methods

2.1 Study design

To investigate the association between reproductive factors such as prolonged menstruation, gravidity and induced abortion and risk of endometrial cancer, a ***case-control study design*** has been chosen. This design is appropriate for the investigation of rare diseases, rare outcomes and multiple exposure factors in a relatively short period of time with minimal financial expenditures.

2.2 Study population

The target population of the study was women aged 45-75 residing in Yerevan. The study population was women among 45-75 with both confirmed diagnosis of endometrial cancer (defined as cases) and healthy women (defined as controls) who were current residents of Yerevan, Armenia. Yerevan Marz was selected due to convenience for the investigator and the fact that National Oncology Center (NOC) is situated in Yerevan.

Cases were defined as alive women aged 45-75 with clinically and hystologically confirmed diagnosis of endometrial cancer who were registered at the National Oncology Center in period from January 2000 to December 2006. Although there was possibility for women to be diagnosed and treated in other non-specialized clinics of Yerevan, official statistical data on endometrial and other cancers from all over Armenia are collected and registered in NOC.

Controls have been chosen through Random Digit Dialing. Eligibility criteria for controls were:

- Woman aged 45-75 residing in Yerevan
- Woman who informed that she did not undergo any gynecologic surgery (for example, hysterectomy, ovary removals, ectopic pregnancy) previously.

2.3 Sample size

The sample size was calculated using the formula for a case-control study design developed by Dupont et al [29] based on the primary research question:

$$n = \frac{\left\{z_{1-\alpha/2}\sqrt{2P_2(1-P_2)} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right\}^2}{(P_1-P_2)^2} \qquad P_1 = \frac{(OR)P_2}{(OR)P_2 + (1-P_2)}$$

where P1 is proportion exposed in cases and P2 is proportion exposed in controls.

The range of estimates of proportion of controls being exposed to the risk factor of 'ever

being pregnant' (0.8-0.96) and the range for estimated Odds Ratios of developing the disease (0.25-0.5) were obtained from previous studies [9-11]. Type I error and power of the study have been specified as α equal to 0.05 and 1-β equal to 0.8 respectively. The calculated sample size was 116 for cases and 232 for controls (calculations by STATA for different values are presented in Appendix 2). The calculated sample size did not include allowance for non-respondents; therefore, replacement of study participants has been made in order to reach the desired sample size.

2.4 Data collection

Data collection procedures have launched in June, 2007 and ended in August, 2007 being carried out by one interviewer. Telephone interviews have been used as the primary method for data collection. It was a preferred methodology for current study as it gives the investigator the possibility to collect the required data in relatively short period of time and at a low cost, with the efficient coverage of target population (approximately 85% of Yerevan households possess the functioning telephones). The actual interview with the provision of oral consent form lasted about 15 minutes. Accounting the problems such as busy line, no response on phone calls or not functioning number, and refusal to participate resulted in a response rate of 89% among cases and 92% among controls. However, as planned, replacement of study participants has been made until reaching the desired sample size.

First step of data collection started at the National Oncology Center (NOC). Cases have been selected from the sample frame derived from the NOC's Registry starting backward from December 2006 till January 2000. Overall, 160 eligible cases were identified and derived from the NOC's Registry. The names and telephone numbers of eligible cases have been collected for telephone interview purposes. If missing, the medical records of eligible cases have been

obtained from NOC's archive and telephone numbers derived. Prior to data extraction, the permission had been received from the head of NOC on usage of the archive.

The telephone numbers of controls have been selected through Random Digit Dialing procedure. Identified telephone numbers have been called, and the enumeration of female residents aged 45-75 in each household have been attempted. A woman was eligible as a control if she was 45-75 years old and was without a history of a gynecologic surgery at the time of the study. Telephone interviews have been conducted with cases and controls using a structured questionnaire. Before the interview, an oral consent has been obtained from the participant.

2.5 Study instrument

An interviewer-administered structured questionnaire has been used during the telephone interviews with both cases and controls (Appendix 3 & 4). The questionnaire has been developed by the study investigators to explore the relationships between the disease status and potential risk factors. It included the questions adopted from the questionnaire used to investigate reproductive factors in relation to risk of endometrial cancer development in population based case-control study in urban Shanghai (China) as well as questions added by the investigator.

The questionnaire consisted of 31 mainly close-ended questions and included the following main domains: demographic characteristics, menstrual and reproductive history, breastfeeding experiences, contraceptive history, family history of cancer, use of hormonal medication, height and weight, and smoking status.

Before starting data collection, the developed questionnaire was pre-tested among women aged 45-75 (n=5) living in Yerevan through telephone interview. Based on the pre-test results some changes have been made in questions related to breastfeeding experiences/duration cut

offs, hormone replacement therapy, and smoking status. It was decided to consider the questionnaire incomplete if there were at least 16 missing responses.

2.6 Study variables

The dependent variable (outcome) for the current study is the presence of clinically and hystologically confirmed diagnosis of endometrial cancer (cases) or its absence as defined by study participants (controls). Main independent variables are the reproductive variables: age at onset of menarche and of menopause, number of pregnancies/deliveries, breastfeeding practices, use of OCs and IUDs, estrogen/hormone replacement therapy, BMI, family history of cancer, smoking status. A summary of the study variables is presented in Appendix 5.

2.7. Statistical analysis

Data were entered into SPSS 11.5 for Windows and checked for accuracy through range and spot checking. After cleaning and recoding procedures, the data were imported into STATA 7.0 statistical package for statistical analyses. We used means and standard deviations for description of continuous data if it was normally distributed, and medians and ranges if skewed. Continuous variables were categorized for study final analysis using cut-points from previous studies. Categorical data were described using frequencies and percentages. T-test was used for comparison of means and chi-square and Fisher's exact test for comparison of categorical data. Simple logistic regression was performed to assess the relationships between each independent variable and the outcome. Multiple logistic regression analysis was used to define the independent risk factors, potential interactions, and to control for potential confounders. The best fitting model was selected using the Log-likelihood Ratio test. The model goodness-of-fit was evaluated by Hosmer-Lemeshow (HL) chi-square test. All results with a p-value less than 0.05 were considered as statistically significant.

3. Ethical considerations

The study has been approved by the Institutional Review Board/Committee on Human Research (IRB) of the American University of Armenia. Permissions have been received from the head of the National Oncology Center as well as by the head of the Oncogynecology Department of NOC on data collection from the Cancer's Registry and use of archive to obtain medical records of patients with endometrial cancer. All participants have been provided with oral consent (Appendix 6 & 7). Risk for study participants was assessed as minimal in regards to some sensitive questions that could cause inconvenience and discomfort. They were allowed to skip the sensitive questions and stop the interview at any time. All the collected information has been kept confidential and used in the frame of current study.

4. Results

Data were collected from 117 cases and 232 controls. Refusal rate was 11% (13 participants) among cases and 8% (18 participants) among controls. However, replacement of study participants have been made to reach the desired sample sizes. No questionnaire was considered as incomplete.

General characteristics of study population were presented in **Table 1.** There was a statistically significant difference ($p<0.001$) between the mean age of cases (60.4 ± 8.1 years) and controls (54.4 ± 7.6 years). Groups were also different with respect to the distribution of marital status, BMI, experienced pregnancy, current smoking status and family history of cancer ($p<0.05$).

Table 1. Characteristics of study population*

Characteristics	Cases (n=117)	Controls (n=232)	p - value
Age (y, mean ± sd)	60.4 ± 8.1	54.4 ± 7.6	0 .000
Marital status			

Characteristics	Cases (n=117)	Controls (n=232)	p - value
Single	2 (1.7)	2 (0.8)	0.009
Married	109(93.2)	193 (83.2)	
Widowed	6(5.1)	19 (8.2)	
Divorced	0(0)	18 (7.8)	
Education (years)			
School(8)	2(1.7)	4(1.7)	0.667
School(10)	9(7.7)	17(7.3)	
College	60(51.3)	101(43.5)	
University	45(38.5)	106(45.7)	
Post-graduate	1(0.9)	4(1.7)	
BMI(kg/m^2,mean ± sd)	31.4 ± 6.4	26.2 ± 3.7	0.000
Age at menarche(y, mean ± sd)	14.2 ± 1.4	13.7 ± 1.3	0.234
Age at menopause(y, mean ± sd)	50.1 ±3.17	48.0 ±2.7	0.345
Length of menstrual cycle(d, mean ± sd)	28.4 ± 1.9	27.6 ± 2.3	0.266
Length of menstrual span(y, mean ± sd)	35.8 ± 3.3	34.6 ± 3.2	0.743
Pregnancy			
Ever	101(86.3)	227(97.8)	0.000
Never	16(13.7)	5(2.15)	
Age at first delivery (y, mean ± sd)	21.7 ± 3.4	23.0 ± 4.6	0.290
Age at last delivery (y, mean ± sd)	30.0 ±3.6	31.6 ± 5.0	0.272
Number of pregnancies (median, range)	5, 0-48	4, 0-38	0.3980
Abortion experience			
Ever	89(76.1)	174(75)	0.827
Never	28(23.9)	58(25)	
Number of abortions (median, range)	2, 0-45	2, 0-30	0.2139
Number of birth deliveries (mean ± sd)	2.3 ± 1.4	2.1 ± 1.3	0.2668
Breast-feeding experience**			
Ever	86(77.0)	188(83.0)	0.239
Never	25(23.0)	39(17.0)	
Oral contraceptive use			
Ever	3(2.6)	2(0.9)	0.339
Never	114(97.4)	230(99.1)	
Intrauterine device use			
Ever	7(5.9)	32(13.8)	0.029
Never	110(94.1)	200(86.2)	
Female hormone use			
Ever	0(0)	4(1.7)	0.723
Never	117(100)	228(98.3)	
Current smoking status			
Ever	5(4.3)	43(18.5)	0.000
Never	112(95.7)	185(79.7)	
Time to time	0(0)	4(1.7)	
Family history of cancer			

Characteristics	Cases (n=117)	Controls (n=232)	p - value
No	88(75.2)	196(84.5)	0.036
Yes	29(24.8)	36(15.5)	

** Data is presented as frequencies and percentages unless specified.*
*** Among gravid women*
BMI=Body Mass Index, d=days, y=years, sd=standard deviation

Compared to controls, cases had higher age at menarche, and age at menopause. They had longer menstrual cycle (28.4 ± 1.9 vs. 27.6 ± 2.3) and longer menstrual span. There were fewer women being ever pregnant among the cases (86.3% vs. 97.8%, $p<0.001$) than among the controls. Cases were younger at the age of first delivery and at the age of last delivery. Fewer cases ever used an intrauterine device (5.9% vs. 13.9%, $p< 0.05$), while more cases reported a family history of cancer (24.8% vs. 15.5%, $p<0.05$).

Table 2 presents the results of simple logistic regression analysis with corresponding odds ratios (ORs) and 95% confidence intervals (CIs). There was a statistically significant association between age and endometrial cancer development: for example, getting older than 65 years was associated with more than 7.7 times increased risk as compared to the younger age (45-54 years).

Table 2. Odds ratios (OR) of Endometrial cancer associated with reproductive and other risk factors

Characteristics	Cases	Controls	ORs(95% CI)	p-value
Age(years)				
45-54	28	131	1.00	
55-64	41	72	2.7(1.5-4.7)	0.001
65-75	48	29	7.7(4.2-14.3)	0.000
Marital status				
Single	2	2	1.00	
Married	109	193	0.6(.2-1.4)	0.216
Widowed	6	19	-----	
Divorced	0	18	-----	

Education(years)				
School(8)	2	4	1.00	
School(10)	9	17	1.1(0.16-6.9)	0.952
College	60	101	1.2(0.2-6.68)	0.845
University	45	106	0.8(0.15-4.8)	0.853
Post-graduate	1	4	0.5(0.03-7.9)	0.624
Age at menarche(years)				
<14	31	106	1.00	
>=14	86	126	2.3(1.44-3.79)	0.001
Length of menstrual cycle(days)				
<=28	68	161	1.00	
>28	49	71	1.6(1.03-2.6)	0.036
Age at menopause(years)				
=<45	14	35	1.00	
46-49	29	129	0.6(0.3-1.17)	0.127
50-54	61	65	2.4(1.2-4.8)	0.019
>=55	13	3	5.6(1.9-15.8)	0.001
Length of menstrual span				
<30	2	14	1.00	
30-34	35	91	2.7(0.58-12.5)	0.205
35-39	61	109	3.9(0.9-17.8)	0.077
>=40	19	18	7.3(1.4-37.2)	0.015
Pregnancy				
Never	16	5	1.00	
Ever	101	227	0.14(0.05-0.4)	0.000
Age at first delivery(years)*				
=<20	40	60	1.00	
21-25	39	123	0.6(0.4-1.0)	0.063
>=26	22	44	0.9(0.5-1.7)	0.778
Age at last delivery(years)*				
=<25	10	13	1.00	
26-29	23	39	0.9(0.4-2.2)	0.836
>=30	59	107	0.6(0.3-1.4)	0.284
Number of pregnancies*				
1	1	25	1.00	
2	10	21	0.1(0.009-0.7)	0.023
3	18	38	0.1(0.01-0.6)	0.020
4	8	29	0.1(0.016-1.2)	0.081
>=5	64	114	0.1(0.01-0.5)	0.014
Number of abortions				
Never	28	58	1.00	
1-3	53	105	1.07(0.6-1.9)	0.803
4-6	20	44	0.95(0.5-1.9)	0.903
>=7	16	25	1.3(0.6-2.9)	0.448
Number of birth deliveries*				

1	9	68	1.00	
2	42	79	0.2(0.11-0.56)	0.001
3	35	57	0.2(0.08-0.45)	0.000
>4	15	23	0.2(0.07-0.52)	0.001
Breast feeding experience*				
Never	15	39	1.00	
Ever	86	188	0.7(0.4-1.25)	0.240
Intrauterine device use				
Never	110	200	1.00	
Ever	7	32	0.39(0.16-0.9)	0.034
Current smoking status				
No	112	185	1.00	
Yes	5	47	0.2(0.7-0.5)	0.000
Family history of cancer				
No	88	196	1.00	
Yes	29	36	1.79(0.9-2.11)	0.037
Body Mass Index (kg/m^2**)**				
Normal (19.0-24.9)	20	89	1.00	
Overweight (25.0-29.9)	35	111	1.4(0.8-2.7)	0.248
Obese (>30.0)	62	32	8.6(4.5-16.4)	0.000

***** Among gravid women
---- *Insufficient observations*

There was a statistically significant *(p for trend =0.001)* association between age at menarche and endometrial cancer risk. Compared to women with age of menarche less than 14, women with menarche age above or equal to 14 had almost 2.3 times greater risk (95% CI 1.44-3.79) of endometrial cancer development. Length of menstrual cycle was significantly associated with the risk of disease: women with more than 28 days of menstrual cycle had increased risk OR =1.6 (95% CI 1.03-2.6) of getting endometrial cancer compared to women with average (>=28 days) cycle length. Older age at menopause was significantly associated with an elevated risk of endometrial cancer. Compared to women whose menopause occurred before age 40, those whose menstrual periods continued till the 55 years old had approximately 6 times (OR =5.6, 95%CI 1.9-15.8) increased risk of endometrial cancer. The risk of endometrial cancer increased significantly with the years of experienced menstruation. Compared to women

who had menstrual span for less than 30 years, women who had menstrual span for more than 40 years had 7 times elevated risk of emdometrial cancer.

Gravidity, defined as ever being pregnant, was associated with a statistically significant reduced risk of endometrial cancer (OR =0.14, 95% CI 0.05-0.4). Number of pregnancies and number of deliveries also had protective effects (OR=0.1 and OR=0.2 respectively) which did not change substantially with their increasing numbers.

Intrauterine device use was associated with the significantly reduced risk of endometrial cancer (OR = 0.39, 95% CI0.16-0.9). Smoking was related to the statistically significant reduced risk of disease development while the cancer among first degree relatives was associated with the increase risk of endometrial cancer (OR =1.79, 95% CI 0.9-2.11). Furthermore, there was statistically significant association between the BMI and endometrial cancer. Compared with normal weight women (BMI=19.0-24.9 kg/m^2), obese women (BMI>30 kg/m^2) had approximately 9 times higher risk of endometrial cancer (OR = 8.6, 95% CI 4.5-16.4). Breastfeeding experiences were not significantly related to the risk of disease development.

Multiple logistic regression analysis was used to find the independent risk factors of the outcome. All variables with significance level <0.25 were tested for the final model [29]. Each full model has been tested against the nested model using Log-likelihood Ratio Test (Appendix 8, Table 1). The best fitting model included variables of age of study participants, age at the onset of menarche, gravidity, and BMI (Table 3).

Table 3. Final logistic regression model of endometrial cancer risk factors

Risk factors	Unadjusted OR (95%CI)	Adjusted OR (95% CI)
Age(years)		
45-54	1.00	1.00
55-64	2.7(1.5-4.7)	2.5(1.3-4.7)
65-75	7.7(4.2-14.3)	9.0(4.3-18.8)

Age at menarche(years)		
<14	1.00	1.00
>=14	2.3(1.44-3.79)	3.2(1.7-5.8)
Pregnancy		
Never	1.00	1.00
Ever	0.14(0.05-0.4)	0.10(0.03-0.38)
Body Mass Index (kg/m^2**)**		
Normal (19.0-24.9)	1.00	1.00
Overweight (25.0-29.9)	1.4(0.8-2.7)	1.4(0.69-2.8)
Obese (>30.0)	8.6(4.5-16.4)	7.5(3.6-15.5)
Model characteristics: Pseudo R2=0.28; HL(chi2(8))=8.11, p=0.42), area under Receiver Operating Characteristic curve =0.841.		

Possible interactions between the variables included in the final model were checked. No statistically significant interaction was identified between the independent variables and the outcome variable. No measured confounders were identified. The model fit (calibration) was tested with Hosmer-Lemeshow goodness-of-fit test which compared the observed and model predicted probabilities of cancer development across different risk groups. For 10 risk categories the Hosmer-Lemeshow chi-square test statistics was 8.11 (df=8, prob > chi2 = 0.42) indicating good calibration. Model demonstrated also a good discrimination: area under the ROC curve was 0.841 (Appendix 8).

According to the final model, controlling for other variables in the final model getting older than 55 years was associated with 2.5 times (OR=2.5, 95% CI 1.3-4.7) and 65 years with more than 9 times (OR= 9.0, 95% CI 4.3-18.8) increased risk of endometrial cancer as compared to the younger age women (45-54 years). Older age at the onset of menarche (over 14 years old) was associated with 3 times (OR =3.2, 95% CI 1.7-5.8) elevated risk of endometrial cancer. As hypothesized, gravidity was an independent protective risk factor for this group of women: being ever pregnant was associated with a considerable risk reduction for endometrial cancer development (OR =0.1, 95% CI 0.03-0.38). Compared with normal weight women (BMI=19-

24.9 kg/m^2), obese women (BMI >30.0 kg/m^2) had approximately 7.5 times higher risk of endometrial cancer (OR = 7.5, 95% CI 3.6- 15.5).

5. Discussion

The present case-control study investigated associations between the reproductive factors and the risk of endometrial cancer development among women aged 45-75 in Yerevan. Similar to many studies conducted in western countries, this study demonstrated that gravidity, age at onset of menarche and body mass index were associated with the risk of endometrial cancer development. An interesting finding of the study was that menstrual span and induced abortions were not statistically significantly associated to endometrial cancer development.

We hypothesized that gravidity would have a protective effect on the risk of endometrial cancer development. The results of the study showed that there was a statistically significant negative association between gravidity and endometrial cancer development. It was found that women who had been ever pregnant had dramatically reduced risk of endometrial cancer (OR=0.1). The results observed in the study were consistent with those found in previous studies (OR= 0.34, 95% CI 0.13-0.92) [30] and supported the etiological hypothesis of hormonal mechanism of endometrial cancer [9, 11, 30]. Thus, nulligravidity has been linked to increased risk of disease development. Furthermore, in the present study no further risk reduction was observed in regards to increase number of full term pregnancies after controlling for age, age at menarche, gravidity and BMI risk factors. Hence, the current study suggests that even one full term pregnancy is dramatically reducing the risk of disease development underling the importance of promotion of child bearing and child birth giving among women. If the nulligravidity is associated with progesterone deficiency or an ovulation, all possible remedies

such as ovulation induction medication “fertility drugs”, intrauterine insemination, ovarian drilling, surgery, in vitro fertilization should be applied to treat the women from this condition.

According to this study results, the length of menstrual span was not statistically associated with the risk of disease development after controlling for age, gravidity and BMI risk factors. The obtained result (OR=2.3, 95% CI 0.66-7.8) was similar with results of other reports [31] and contradicts to the results of other studies that showed 3 times higher risk for women with menstrual span more than 40 years [10]. The present study indicated that the age at onset of menopause was not significantly associated with the risk of disease development while age at onset of menarche was. The results of the current study demonstrated that older age at menarche was associated with increased risk of endometrial cancer which was consistent with the results of other case-control studies demonstrating 2 times higher risk [21] and contradicts the results of prospective studies suggesting reduction in risk when the menarche starts at later age [9]. This studies demonstrated no statistically significant relationship between length of menstrual cycle (>28 days) and endometrial cancer risk (OR=1.6, 95% CI 0.9-2.7) after controlling for age and age at onset of menarche risk factors.

Several studies identified that women who experienced miscarriages and induce abortions have the half of risk of endometrial cancer as gravid women with no miscarriages and abortions [9, 13]. The current study did not find an association between the miscarriages and endometrial cancer risk development. This could be explained by the fact that very few women from study population had have experienced miscarriages, so that the study sample might be insufficient to detect that relationship.

We did not find a significant association between the induce abortions and endometrial cancer risk. High proportion of women had at least one induced abortion both among the cases

(76%) and among the controls (75%) with the median number of 2 abortions for both groups. In contrary, very few women used modern birth control methods such as OCs and IUDs. Results from similar studies showed the protective effect of oral contraceptives and intrauterine devices in relation to endometrial cancer development. The risk reduction for women who had ever used IUDs compared with women who had never used them was about 30% to 60% and the risk reduction resulted from ever contraceptive use was about 2.7. [15, 16, 17, 18, 19]. Foreign body response that results in acute and chronic inflammatory changes in the human endometrium with further removal of cancerous epithelial cells has been suggested as possible explanation of the protective effect of IUDs [14, 15, 16, 17, 18, 19]. The relationship between use of oral contraceptive or IUD use and endometrial cancer development was impossible to detect in this study due to their low utilization rate among Armenian women.

Several studies showed the positive relationship between the increased weight and endometrial cancer risk with reported OR=5.5 (95% CI 3.2–9.6) for women with BMI>30 [32, 22, 23]. The hormonal theory of endometrial cancer development states that obese women have high levels of all forms of estrogen hormones (estradiol, non-proteinbound estradiol, and estrone) being excessively converted in adipose tissue. Current study found that the risk of endometrial cancer is 7.5 times higher among obese women (BMI>30 kg/m^2) compared to that of normal weight women (BMI 19-24.9 kg/m^2). Therefore, promotion of healthy lifestyle and weight control counseling advices should be widely practiced by physicians among their patients emphasizing its imperative role in respect to cancer prevention.

The majority of the studies on breastfeeding and its relationship to endometrial cancer indicated disease risk reduction among the women who breastfed. In the current study breastfeeding was not an independent risk factor of endometrial cancer development. Several

studies have found an association between the childbearing age and endometrial cancer indicating that higher age at last live birth is associated with decreased risk of the cancer at a rate of about 15% per five-year delay of last birth [24]. However, in the case -control study conducted in China the investigators found non statistical association between the age at last pregnancy and endometrial cancer after controlling for other confounders [10]. The current study revealed no association between the age at first and last pregnancies and endometrial cancer. Some of the risk factors such as intrauterine device use, family history of cancer, and current smoking status were significantly associated with the outcome in univariable analyses and lost their significance in multivariable analyses.

The current study results must be considered in the light of several potential limitations. Recall bias could be one of the threats to validity of study findings. Cases could exaggerate some of the answers because of the underlying disease condition while controls could simply give inaccurate answers recalling events that happened several years ago. Misclassification of study participants could be a potential threat for the study, as controls might not be aware of the cancer presence at the moment of data collection. The existence of other confounders that were not been adjusted during the current study might influence on the observed associations. On the other hand, we collected data on all reproductive risk factors and potential confounders that were identified previously in other studies.

In summary, we evaluated the role of reproductive factors in relation to risk of endometrial acancer development among women aged 45-75 in Yerevan using a case-control study design. The study found that older age (>54 years), later age at the onset of menarche (>=14 years), no lifetime experience of pregnancy, and obesity (BMI>30 kg/m^2) are independent factors that increase the risk of endometrial cancer development in this population. This was the first study

in Armenia that measured the potential risk factors of endometrial cancer development in Armenian women. Future cohort studies are needed to replicate the study findings.

6. Recommendations

Based on the results of the current study the following recommendations are made:

- Gynecologists and Obstetricians should be trained to promote actively the concept of maternity/ gravidity and its importance for women health among female community. If nulliparity is related to progesterone deficiency or anovulation all possible remedies: ovulation induction medication "fertility drugs", intrauterine insemination, ovarian drilling, surgery, in vitro fertilization should be applied to treat the women from this condition.
- Health care providers should promote healthy lifestyle and effective ways of weight control among women. Patients should be informed about the roles of different factors in the risk of endometrial cancer development.
- We found a high prevalence of induced abortions and very low rates of modern contraceptive use such as oral contraceptives and IUDs. Considering the existing evidence indicating the protective effect of modern contraceptives, health care providers should promote the use of these methods with the full profile of their risks and benefits. The potential risks of induced abortions should be also discussed with the patients.

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Appendix 1. Endometrial cancer mortality statistics, Armenia

Table 1. Incidence and mortality rates for endometrial cancer from 1997 to 2006, Armenia

Indicators	1997	2000	2003	2006
Number of incident cases	89	102	116	194
Incidence rate/ per 100 000 population	6.9	7.9	9.0	15.1
Mortality rate/ per 100 000 population	3.6	4.0	4.1	7.3

Data source: National Oncology Center of Armenia

Table 2. Endometrial cancer mortality statistics: comparative data for 1997 and 2003, Armenia

Cancer localization	1997		2003		Mortality change %
	Total	**%**	**Total**	**%**	
Female reproductive organs	263	100.0%	324	100.0%	+23.2%
Uterine corpus	83	31.5%	106	32.7%	+27.7%
Uterine cervix	91	34.6%	101	31.1%	+11%

Data source: National Oncology Center of Armenia

Appendix 2. Sample size calculation

Estimated sample size for two-sample comparison of proportions (unequal samples). STATA results

Test Ho	Estimated proportions/ OR(0.25-0.5)	Required sample size
$p_1=p_2$ where p_1 is the proportion in cases and p_2 is the proportion in controls	OR=0.5 alpha = 0.05 (two-sided) power = 0.80 p_1 = 0.920 p_2 = 0.960* n_2/n_1 = 2.00	n_1 =433 n_2 =866
$p_1=p_2$ where p1 is the proportion in cases and p2 is the proportion in controls	OR=0.49 alpha = 0.05(two-sided) power = 0.80 p_1 = 0.6 p_2 = 0.8** n_2/n_1 = 2.00	n_1 =4934 n_2 =9868
$p_1=p_2$ where p1 is the proportion in cases and p2 is the proportion in controls	OR=0.25 alpha =0.05(two-sided) power = 0.80 p_1 = 0.7 p_2 = 0.89*** n_2/n_1 = 2.00	n_1 =116 n_2 =232

Sources of proportions and Odds ratios
** Reference # 10*
*** Reference # 9*
**** Reference # 11*

Appendix 3. Questionnaire (English version)

QUESTIONNAIRE

Interviewer ID_____

Date of the interview: _ _ _ _ /_ _ _ _ /_ _ _ _
(day) (month) (year)

Record ID_____

Status: 1. □ Case
0. □ Control

1. How old are you? _____

2. What is your completed educational level?

1. School (8 years or less)	□
2. School (10 years)	□
3. College	□
4. Institute/ University	□
5. Post-graduate	□

3. What is your current marital status?

0. Single	□
1. Married	□
2. Widowed	□
3. Divorced	□

4. What is your current weight? _____kg

5. What is your height? _____cm

The following are some questions related to your menstrual, pregnancy, and childbirth history.

6. At what age did you have your first menarche?

_____years old
10. □ Have never had
88. □ Don't remember

7. Have you had regular menstrual cycles for the most periods of your life? (Excluding times of pregnancy, breast feeding or contraceptive use)

0. □ No

1. □ Yes
2. □ Sometimes

8. What is the length of your typical menstrual cycle? (excluded the time when you used hormonal contraceptives, if any) _____days

9. How many times have you ever been pregnant? (including live births, abortions, miscarriages, tubal or other pregnancies, current pregnancy)

_____number of pregnancies
0. □ Never been pregnant

10. What was your age at first pregnancy? _____years old

11. What was your age at last pregnancy? _____years old

12. Are you currently pregnant?

0. □ No
1. □ Yes

13. Have you had any menarche in the past 12 months?

0. □ No
1. □ Yes
88. □ Don't remember

14. If you have not been pregnant, the reason was:

0. Never married	□
1. You are infertile	□
2. Your husband is infertile	□
3. Did not want to have a baby	□
4. Do not want to have a baby at present	□
88. Unknown/Don't know	□
9. Other	□

Specify other_____

15. How many miscarriages have you experienced in your life? _____

16. How many abortions have you experienced? _____

17. How many pregnancies ending in live birth delivery have you experienced? _____

18. Did you breast-feed at least one of your children? (If no, skip to Q.20)

0. □ No
1. □ Yes

19. If breast-feed, what was the longest duration? _____months

20. Why you did not breast feed?

1. □ No milk
2. □ Unwilling
3. □ Not allowed by the doctor
9. Other _____

21. Are you in the menopause?

0. □ No
1. □ Yes, _____ duration
88. □ Don't know

22. Have you ever taken an oral contraceptive?

0. □ No
1. □ Yes, _____overall duration

23. Have you ever used any type of Intrauterine devices (IUD)?

0. □ No
1. □ Yes, _____overall duration

24. Have you ever received female hormones (oral, shots, or any type) to lighten menopause symptoms?

0. □ No
1. □ Yes, _____overall duration

25. Have you ever used any hormones (oral, shots, or any type) over more that a month because of other reasons/disease?

0. □ No
1. □ Yes, _____overall duration

26. Are you a current smoker? (If no skip to Q.29)

0. □ No
1. □ Yes

27. At what age did you start smoking? _____years old

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

29. Have you ever smoked in the past?

0. □ No

1. □ Yes, _____ years

30. How old were you when you quit smoking? _____years old

31. Among your blood related relatives, has anybody ever been diagnosed with malignant tumor? (If yes, specify)

0. □ No
1. □ Yes, _____

Thank you for your participation!

Appendix 4. Questionnaire (Armenian version)

Հարցաշար

Հետազոտող _____

Հարցման ամսաթիվ: _ _ _ _ /_ _ _ _ /_ _ _ _
(օր) (ամիս) (տարի)

Հարցաթերթիկ _____ Կարգավիճակ: 1. □ Դեպք
0. □ Կոնտրոլ

1. Քանի՞ տարեկան եք _____

2. Ինչ՞ կրթություն ունեք

1. Դպրոց (8 տարի)	□
2. Դպրոց (10 տարի)	□
3. Քոլեջ/ Ուսումնարան/ Տեխնիկում	□
4. Ինստիտուտ/ Համալսարան	□
5. Հետդիպլոմային	□

3. Ամուսնական ինչ՞ կարգավիճակում եք

0. Ամուսնացած չեմ	□
1. Ամուսնացած եմ	□
2. Այրի	□
3. Բաժանված	□

4. Ինչպիսին՞ է Ձեր քաշը _____կգ

5. Ինչպիսին՞ է Ձեր հասակը _____սմ

Հետևյալ հարցերը կլինեն Ձեր դաշտանային ցիկլի, հղիությունների և ծննդաբերությունների վերաբերյալ:

6. Քանի՞ տարեկանում եք առաջին անգամ տեսել դաշտան
_____տարեկանում
10. □ Երբեք չեմ տեսել
88. □ Չեմ հիշում

7. Մեծամասամբ Ձեր դաշտանային ցիկլերը եղել՞ են կանոնավոր (հաշվի չառնելով հղիությունների, կրծքով կերակրելու, կամ հակաբեղմնավորիչների օգտագործման ժամանակաշրջանները)

0. □ Ոչ
1. □ Այո
2. □ Երբեմն

8. Որքան՞ է Ձեր դաշտանային ցիկլի տևողությունը (հաշվի չառնելով հորմոնալ հակաբեղմնավորիչների օգտագործման ժամանակաշրջանը) _____օր

9. Քանի՞ անգամ եք հղիացել (ներառելով ծննդաբերությունները, արտարգանդային հղիությունները, հղության արհեստական ընդհատումների, վիժումները, ներկա հղիոնությունը եթե այդպիսիք եղել են)

_____հղիություն
0. □ Երբեք չեմ եղել հղի (անցիր հարց 13)

10. Որ՞ տարիքում եք հղիացել առաջին անգամ _____տարեկանում

11. Որ՞ տարիքում եք հղիացել վերջին անգամ _____տարեկանում

12. Ներկայումս Դուք հղի՞ եք

0. □ Ոչ
1. □ Այո

13. Պարզել եք Ձեր չհղիանալու պատճառը՝

0. Ամուսնացած չեմ	□
1. Չբերություն	□
2. Չբերություն ամուսնու մոտ	□
3. Չեմ ցանկացել երեխա ունենալ	□
4. Չեմ ցանկանում երեխա ունենալ ներկայումս	□
88. Չեմ կարող պատասխանել	□
9. Այլ	□

Այլ_____

14. Վերջին 12 ամիսների ընթացքում Դուք դաշտան տեսել՞ եք

0. □ Ոչ
1. □ Այո

88. □ Չեմ հիշում

15. Ձեր հղիությունների ընթացքում վիժումներ եղել՞ են

0. □ Ոչ
1. □ Այո, _____

16. Քանի՞ հղիության արհեստական ընդհատում (աբորտ) եք ունեցել Ձեր կյանքում _____

17. Քանի՞ անգամ եք ծննդաբերել_____

18. Կրծքով կերակրել՞ եք Ձեր երեխաներից առնվազն մեկին (եթե ոչ,անցիր հարց 20)

0. □ Ոչ
1. □ Այո

19. Եթե կրծքով կերակրել եք, ապա ինչքան՞ է եղել ամենաերկար տևողությունը_____

20. Ինչումն՞ է կրծքով չկերակրելու պատճառը՝

1. □ Կաթի բացակայություն
2. □ Ցանկության բացակայություն
3. □ Բժշկական ցուցումներով
9. Այլ_____

21. Դուք դաշտանադադարի մեջ՞ եք

0. □ Ոչ
1. □ Այո, _____ ժամանակ
88. □ Չեմ կարող ասել

22. Դուք երբևիցե հակաբեղմնավորիչ օգտագործել՞ եք դեղահաբի ձևով

0. □ Ոչ
1. □ Այո, _____ընդհանուր տևողություն

23. Դուք երբևիցե ներարգանդային զսպատակ օգտագործել՞ եք

0. □ Ոչ

1. □ Այո, _____ ընդանուր տևողություն

24. Դուք երբևիցե օգտագործել՞ եք կանացի հորմոններ դաշտանադադարի սիմպտոմները թեթևացնելու համար

0. □ Ոչ
1. □ Այո, _____ ընդանուր տևողություն

25. Դուք երբևիցե օգտագործել՞ եք հորմոնային դեղամիջոցներ հիվանդությունների կամ այլ պատճառների համար մեկ ամսից ավել տևողությամբ

0. □ Ոչ
1. □ Այո, _____ ընդանուր տևողություն

26. Դուք ծխում՞ եք (եթե ոչ, անցիր հարց 29)

0. □ Ոչ
1. □ Այո
2. □ Ժամանակ առ ժամանակ

27. Որ՞ տարիքու եք սկսել ծխել _____տարեկան

28. Միջինում քանի՞ հատ ծխախոտ եք ծխում կամ ծխել օրվա ընթացքում _____ծխախոտ/օր

29. Դուք ծխախոտ ծխել՞ եք անցյալում

0. □ Ոչ
1. □ Այո, _____ տարի

30. Քանի՞ տարեկանում եք թողել ծխելը _____տարեկանում

31. Ձեր բարեկամներից որևիցե մեկի մոտ երբևիցե չարորակ նորագոյացություն հայտնաբերվել՞ է (Եթե այո, մանրամասնեք տեղակայումը)

0. □ Ոչ
1. □ Այո,

_____

Շնորհակալություն մասնակցության համար

Appendix 5. Study variables

Table 3: Description of study variables

Variable name	Type	Measure
Presence of endometrial cancer	Dependent/Binary	Measured as 1 case 0 control
Marital status	Independent/Ordinal	Measured as 1 Single 2 Married 3 Widowed 4 Divorced
Education (years)	Independent/Ordinal	Measured as 1 School(8) 2 School(10) 3 College 4 University 5 Post-graduate
Pregnancy	Independent/ Binary	Measured as 1 presence 0 absence
Number of pregnancies	Independent/Ordinal	Measured as 1 2 3 4 >=5
Age at first delivery (years)	Independent/Ordinal	Measured as =<20 21-25 >=26
Age at last delivery (years)	Independent/Ordinal	Measured as =<25 26-29 >=30
Miscarriage	Independent/ Binary	Measured as 1 presence 0 absence
Number of miscarriages	Independent/Ordinal	Measured as 0 1-3 4-6 >=7
Induced abortion	Independent/ Binary	Measured as 1 presence 0 absence
Number of induced abortions	Independent/Ordinal	Measured as 0 1-3 4-6 >=7
Length of menstrual cycle (days)	Independent/Ordinal	Measured as <=28 >28
Age at menarche (years)	Independent/Ordinal	Measured as <14 >=14
Menopause (years)	Independent/ Binary	Measured as 1 presence

		0 absence
Age at menopause (years)	Independent/Ordinal	Measured as =<45 46-49 50-54 >=55
Breastfeeding/duration	Independent/Binary/Ordinal	Measured as 1 presence 0 absence
Use of oral contraceptives/duration	Independent/Binary/Ordinal	Measured as 1 presence 0 absence
Hormone replacement therapy	Independent/ Binary/Ordinal	Measured as 1 presence 0 absence
Family history of cancer	Independent/ Binary	Measured as 1 presence 0 absence
Use of Intrauterine Device/ duration	Independent/Binary/Ordinal	Measured as 1 presence 0 absence
Smoking habits/per day	Independent/Binary/Ordinal	Measured as 1 presence 0 absence
Body Mass Index kg/m^2	Independent/Ordinal	Measured as Normal (19.0-24.9 kg/m^2) Overweight (25.0-29.9 kg/m^2) Obese (>30.0 kg/m^2)

Appendix 6. Consent forms (English versions)

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

ORAL CONSENT FORM (for cases)

Title of Research Project: **Investigation of reproductive factors for endometrial disorders among women aged 45-65 in Yerevan, Armenia**

Hello, my name is Stella Arakelyan. I am a Medical doctor and a graduate student of Master of Public Health Program at the American University of Armenia. I am conducting a study to investigate the reproductive risk factors for endometrial diso

rders' development among women aged 45-65 in Yerevan.

You have been selected to participate in the study because you had been registered at the Oncogynecology department of National Oncology Center (NOC). Permission to collect your contact information has been received from the head of NOC.

In case you are willing to participate in the current study, I will ask you few questions concerning your reproductive history. This interview will take place only once and last no more than 10-15 minutes. You have right to ask questions in the scope of the interview and stop it at any moment you want. I really appreciate your participation in the current study.

There is no special risk for you being a participant for the study. The information provided by you is of great value and will be very useful for investigation of the risk factors of endometrial disorders. Moreover, the obtained results will be very helpful for further research in the field of Gynecology in Armenia.

The information you provided is fully confidential and will be used only for the study. Summary report of the study will be submitted to the College of Health Sciences of the American University of Armenia with the further possibility being published in the professional journal.

Your participation in the current study is 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 and will not affect medical care you receive.

If you want to obtain more information about this research project you can contact Lusine Abrahamyan at lusine_abrahamyan@yahoo.com. If you believe that you have not been treated fairly or have been hurt by joining the study you may call MPH Program Coordinator Yelena Amirkhanyan (3741) 51-25-68.

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

ORAL CONSENT FORM (for controls)

Title of Research Project: **Investigation of reproductive factors for endometrial disorders among women aged 45-65 in Yerevan, Armenia**

Hello, my name is Stella Arakelyan. I am a Medical doctor and a graduate student of Master of Public Health Program at the American University of Armenia. I am conducting a study to investigate the reproductive risk factors for endometrial disorders' development among women aged 45-65 in Yerevan.

Your telephone number has been selected randomly for the current study. Do you have someone in your household who is a 45-65 years woman and who did not undergo any gynecologic surgery? Would you please pass the phone? *(If needed, repeat the introduction for the eligible participant).*

In case you are willing to participate in the current study, I will ask you few questions concerning your reproductive history. This interview will take place only once and last no more than 10-15 minutes. You have right to ask questions in the scope of the interview and stop it at any moment you want. I really appreciate your participation in the current study.

There is no special risk for you being a participant for the study. The information provided by you is of great value and will be very useful for investigation of the risk factors of endometrial disorders. Moreover, the obtained results will be very helpful for further research in the field of Gynecology in Armenia.

The information you provided is fully confidential and will be used only for the study. Summary report of the study will be submitted to the College of Health Sciences of the American University of Armenia with the further possibility being published in the professional journal.

Your participation in the current study is 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.

If you want to obtain more information about this research project you can contact Lusine Abrahamyan at lusine_abrahamyan@yahoo.com. If you believe that you have not been treated fairly or have been hurt by joining the study you may call MPH Program Coordinator Yelena Amirkhanyan (3741) 51-25-68.

Appendix 7. Consent forms (Armenian version)

Հայաստանի Ամերիկյան Համալսարան
“Հանրային Առողջապահության” Ֆակուլտետ
Վերարտադրողական գործոնների ուսումնասիրությունը արգանդի խոռոչի փոփոխությունների ձևավորման գործում Երևան քաղաքի 45-65 տարեկան կանանց շրջանակներում:
Բանավոր Համաձայնագիր (դեպքերի համար)

Բարև ձեզ, իմ անունը Ստելլա Առաքելյան է: Ես բժիշկ եմ և Հայաստանի Ամերիկյան Համալսարանի “Հանրային Առողջապահության” Ֆակուլտետի ավարտական կուրսի ուսանող: Ես անց եմ կացնում հետազոտություն,որի նպատակն է բացահայտել վերարտադրողական գործոնների դերը արգանդի խոռոչի փոփոխությունների ձևավորման գործում Երևան քաղաքի 45-65 տարեկան կանանց շրջանակներում:
Դուք ընտրվել եք որպես այս հետազոտության մասնակից, քանի որ դուք ունեք առողջության հետ կապված մեզ հետաքրքրող խնդիր: Ձեր տվյալները վերցվել են Ազգային Ուռուցքաբանության Կենտրոնի Օնկոգինեկոլոգիայի բաժանմունքից՝ տնօրենի համաձայնությամբ:
Եթե դուք տաք Ձեր համաձայնությունը մասնակցել այս հետազոտությանը, ես Ձեզ կտամ հարցեր կապված Ձեր վերարտադրողական անցյալի հետ: Այս հարցազրույցը տեղի կունենա մեկ անգամ և կտևի մոտավորապես 10-15 րոպե:
Հարցազրույցի ընթացքում Դուք իրավունք ունեք հարցեր տալ ինձ և դադարեցնել հարցերին պատասխանելը եթե գտնեք դրա անհրաժեշտությունը: Ես գնահատում եմ Ձեր պատրաստակամությունը մասնակցել այս հարցազրույցին:
Հետազոտությանը մասնակցելով դուք ոչ մի վտանգի չեք ենթարկվում:
Ձեր կողմից տրամադրված տեղեկությունները կլինեն շատ օգտակար բացահայտելու վերարտադրողական գործոնների դերը արգանդի խոռոչի փոփոխությունների ձևավորման գործում, և կնպաստեն Հայաստանում ինեկոլոգիայի ասպարեզում գիտելիքների ընդլայնմանը:
Ձեր կողմից տրամադրված տեղեկությունները կպահվեն գաղտնի և կօգտագործվեն միայն հետազոտության նպատակով: Ձեր կողմից տրամադրած տվյալները հասանելի կլինեն միայն ծրագրի հետազոտողի համար: Ամփոփված պատասխանների փաթեթը մատչելի կլինի միայն Հայաստանի Ամերիկյան Համալսարանի “Հանրային Առողջապահության” Ֆակուլտետի համար:
Ձեր մասնակցությունը այս հետազոտությանը լրիվ կամավոր է և կախված է Ձեր ընտրությունից: Դուք կարող եք ցանկացած պահին դադարեցնել հարցազրույցը կամ խուսափել ցանկացած հարցին պատասխանելուց, եթե գտնեք դրա անհրաժեշտությունը:
Ձեր հրաժարվելը մասնակցելու այս հետազոտությանը բացասականորեն չի անդրադառնա Ձեր հետագա կյանքի և տրամադրվող բուժ օգնության որակի վրա:
Եթե Դուք ինչ-որ հարցեր ունեք կամ ցանկանում եք խոսել որևէ մեկի հետ հետազոտության վերաբերյալ, կարող եք դիմել Լուսինե Աբրահամյանին հետևյալ էլ. փոստի հասցեյով: lusine_abrahamyan@yahoo.com.
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ հատազոտության մասին, քանի որ գտնում եք, որ Ձեզ հետ անարդար են վարվել համ Ձեզ վնաս է հասցվել հետազոտությանը մասնակցելու հետևանքով, կարող եք դիմել Ելենա Ամիրխանյանին հետևյալ հեռախոսահամարով (3741) 51-25-68.

Հայաստանի Ամերիկյան Համալսարան
“Հանրային Առողջապահության” Ֆակուլտետ
Վերարտադրողական գործոնների ուսումնասիրությունը արգանդի խոռոչի փոփոխությունների ձևավորման գործում Երևան քաղաքի 45-65 տարեկան կանանց շրջանակներում:

Բանավոր Համաձայնագիր (կոնտրոլ խմբի համար)

Բարև ձեզ, իմ անունը Ստելլա Առաքելյան է: Ես բժիշկ եմ և Հայաստանի Ամերիկյան Համալսարանի “Հանրային Առողջապահության” Ֆակուլտետի ավարտական կուրսի ուսանող: Ես անց եմ կացնում հետազոտություն,որի նպատակն է բացահայտել վերարտադրողական գործոնների դերը արգանդի խոռոչի փոփոխությունների ձևավորման գործում Երևան քաղաքի 45-65 տարեկան կանանց շրջանակներում:
Ձեր հեռախոսի համարը ընտրվել է պատահականորեն: Եթե Ձեր ընտանիքում կա 45-65 տարեկան կին, որը երբևիցե չի վիրահատվել կանացի օրգանների կապակցությամբ, կխնդրեի նրան փոխանցել լսափողը:
(Անհրաժեշտության դեպքում կրկնել ներածության մասը կոնտրոլ խմբի հատկանիշներին համապատասխանող անձի համա)
Եթե դուք տաք Ձեր համաձայնությունը մասնակցել այս հետազոտությանը, ես Ձեզ կտամ հարցեր կապված Ձեր վերարտադրողական անցյալի հետ: Այս հարցազրույցը տեղի կունենա մեկ անգամ և կտևի մոտավորապես 10-15 րոպե:
Հարցազրույցի ընթացքում Դուք իրավունք ունեք հարցեր տալ ինձ և դադարեցնել հարցերին պատասխանելը եթե գտնեք դրա անհրաժեշտությունը: Ես գնահատում եմ Ձեր պատրաստակամությունը մասնակցել այս հարցազրույցին:
Հետազոտությանը մասնակցելով դուք ոչ մի վտանգի չեք ենթարկվում:
Ձեր կողմից տրամադրված տեղեկությունները կլինեն շատ օգտակար բացահայտելու վերարտադրողական գործոնների դերը արգանդի խոռոչի փոփոխությունների ձևավորման գործում, և կնպաստեն Հայաստանում ինեկոլոգիայի ասպարեզում գիտելիքների ընդլայնմանը:
Ձեր կողմից տրամադրված տեղեկությունները կպահվեն գաղտնի և կօգտագործվեն միայն հետազոտության նպատակով: Ձեր կողմից տրամադրած տվյալները հասանելի կլինեն միայն ծրագրի հետազոտողի համար: Ամփոփված պատասխանների փաթեթը մատչելի կլինի միայն Հայաստանի Ամերիկյան Համալսարանի “Հանրային Առողջապահության” Ֆակուլտետի համար:
Ձեր մասնակցությունը այս հետազոտությանը լրիվ կամավոր է և կախված է Ձեր ընտրությունից: Դուք կարող եք ցանկացած պահին դադարեցնել հարցազրույցը կամ խուսափել ցանկացած հարցին պատասխանելուց, եթե գտնեք դրա անհրաժեշտությունը:
Ձեր հրաժարվելը մասնակցելու այս հետազոտությանը բացասականորեն չի անդրադառնա Ձեր հետագա կյանքի վրա:
Եթե Դուք ինչ-որ հարցեր ունեք կամ ցանկանում եք խոսել որևէ մեկի հետ հետազոտության վերաբերյալ, կարող եք դիմել Լուսինե Աբրահամյանին հետևյալ էլ. փոստի հասցեյով: lusine_abrahamyan@yahoo.com.
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ հատազոտության մասին, քանի որ գտնում եք, որ Ձեզ հետ անարդար են վարվել համ Ձեզ վնաս է հասցվել հետազոտությանը մասնակցելու հետևանքով, կարող եք դիմել Ելենա Ամիրխանյանին հետևյալ հեռախոսահամարով (3741) 51-25-68.

Appendix 8. Details of multiple logistic regression analyses

Table 4.Results of Log Likelihood Test for Alternate Multiple Logistic Regression Models

	cc	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]	Log LL test
Model 1	Iagect_2	2.664187	.7611682	3.43	0.001	1.521854	4.663974	---
	_Iagect_3	7.743842	2.4324	6.52	0.000	4.183961	14.33261	
Model 2	_Iagect_2	2.907608	.8531887	3.64	0.000	1.635931	5.167811	chi2(1)=16.1
	_Iagect_3	8.932248	2.930212	6.67	0.000	4.69597	16.99011	p=0.0001
	agem	2.851022	.7737775	3.86	0.000	1.674871	4.853105	(compared with Model 1)
Model 3	_Iagect_2	2.897123	.8718187	3.53	0.000	1.60627	5.225349	chi2(1)=14.78
	_Iagect_3	8.705951	2.922488	6.45	0.000	4.508973	16.8095	p=0.0001
	agem	3.065929	.8620381	3.98	0.000	1.766983	5.319758	(compared
	pregnancy	.1324037	.0757654	-3.53	0.000	.0431338	.4064276	with Model 2)
Model 4 (Final)	Iagect_2	2.465534	.8046118	2.77	0.006	1.300549	4.674072	chi2(1)=14.01
	_Iagect_3	9.037475	3.387726	5.87	0.000	4.334824	18.84181	p=0.0001
	agem	3.167933	.9749736	3.75	0.000	1.733035	5.790881	(compared
	pregnancy	.101665	.068209	-3.41	0.001	.0272951	.3786686	with Model 3)
	_IBMIcut_2	1.385036	.4894706	0.92	0.357	.6928626	2.768694	
	_IBMIcut_3	7.472945	2.780464	5.41	0.000	3.603999	15.49526	

Variables in the model: agect=age categories, agem=age at onset of menarche, pregnancy= childbearing experience, BMIcut=Body Mass Index categories

Assessment of the final model fit (Model 4)

1. Goodness-of-fit (calibration)

. *lfit, group (10)*

number of observations = 342

number of groups = 10

Hosmer-Lemeshow chi2(8) = 8.11

Prob > chi2 = 0.4230

2. Model discrimination

. *lroc*

Logistic model for cc

number of observations = 342

area under ROC curve = 0.8407

Area under the ROC curve