

CASE INVESTIGATION AND CASE - CONTROL STUDY OF BREAST CANCER IN YOUNG WOMEN

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Executive summary

Breast cancer is a major public health problem for women all over the world. It is the most common form of malignancy affecting women in Armenia as well. A number of factors play a role as determinants of the risk of breast cancer. The different effect of some risk factors can be traced in younger premenopausal woman comparing with older premenopausal women. Thus, there is considerable interest in the reasons of women susceptibility to breast cancer at younger age, particularly at ages under 35 in Armenia because such a study has not been conducted in Armenia. Hence, the aims of this study were: 1) to investigate the main and specific risk factors that are involved in developing of breast cancer among premenopausal women under the age of 35 living in Yerevan; 2) to assess the knowledge about prevention of breast cancer such as breast self-examination and mammography among women under age of 35 with the history of breast cancer compared with those at the same age but without disease and 3) to study the access to health care facilities for breast cancer screening.

Case investigation method and case-control study design were used as tools for identification of specific risk profile of the factors that could be involved in the development of breast cancer in women under the age of 35. In all, 20 (77%) breast cancer cases and 31(78%) controls at the same age but without disease were interviewed. The data were collected using a questionnaire done by the interviewer at home for both cases and controls. Odds ratio (OR) and its 95% confidence interval (95% CI) for each exposure variable were estimated by using EpiInfo computer program. The method of average percent discordance estimation was used for statistical analysis of some variables. This method was used because of small number of cases and controls.

Of all factors that were included in this investigation for their possible role in breast cancer etiology in younger women, only few of them stand out as being of particular importance in women under age of 35 living in Yerevan. Positive family history, benign breast diseases have special significance as determinants of breast cancer risk in younger women. Monthly income is a factor that is also associated with increased risk in women under the age of 35. Other factors that were investigated in this study also revealed important associations, but these associations were not statistically significant.

Taking into account the epidemiological findings of the study, some recommendations about preventive strategies for breast cancer can be suggested: educational programs, screening programs for target population and further epidemiologic investigations.

Introduction

Background

Cancer of the breast is the most frequent tumor in females and a major public health problem for women all over the world. The American Cancer Society estimated that thirty-two percent of all incident cancers in women are breast cancers. The incidence curve for breast cancer rises with age from 30 to 70 years, but there is an inflection at around 45-54 years, after which rates increase much more slowly [1].

Breast cancer is the most common form of malignancy affecting women in Armenia as well. According to statistical data 28 percent of all incident cancers in women in Republic of Armenia and 33 percent in Yerevan in 1995 and respectively 26 percent and 29 percent in 1996 are breast cancer.

Breast cancer is generally divided into pre- and postmenopausal cases. Age is used as a surrogate measure of menopausal status dividing into two age ranges: 0-49 (premenopausal) and 50 and older (postmenopausal). Premenopausal cases of breast cancer are also divided into breast cancer in younger (before age 35) and older (after age 35) women [2].

Statistical data of the Third National Cancer Survey done in the US in 1975 shows that according to menopausal status 27 percent of breast cancer cases are in premenopausal and 73 percent in postmenopausal women and 2.7 percent of women with breast cancer are under age 35 [3].

Statistical data of breast cancer incidence in women according to menopausal status, in Armenia, in 1995 and 1996 can be seen in Table 1a.

Table 1a. Distribution of breast cancer in women by Menopausal Status; 1995 and 1996

Menopausal status by age, y	1995		1996	
	Republic of Armenia	Yerevan	Republic of Armenia	Yerevan
Premenopausal 0-49	273 (44 %)	127 (42%)	246 (43 %)	92 (37%)
Postmenopausal ≥ 50	346 (56 %)	172 (58%)	331 (57 %)	155 (63 %)
Total	619	299	577	247

The age distribution of breast cancer incidence in women under age 35 compared with incidence in women older than 35 years can be seen in Table 1b.

Table 1b. Age distribution of breast cancer in women; 1995 and 1996

Age, y	1995		1996	
	Republic of Armenia	Yerevan	Republic of Armenia	Yerevan
< 35	36 (5.8 %)	14 (4.7%)	19 (3.3 %)	6 (2.4%)
≥ 35	583 (94.2 %)	285 (95.3%)	558 (96.7 %)	241 (97.6%)

A number of factors play a role as determinants of the risk of breast cancer. Most epidemiological studies for breast cancer have been conducted in populations of older, largely postmenopausal women as more specific and common age group for the development of breast cancer. There is considerable interest in the reasons of women susceptibility to breast cancer at younger age, particularly at ages under 35. Such a study has not been conducted in Armenia.

Risk factors for breast cancer

Some epidemiological studies of breast cancer done in the world that have included younger, premenopausal women in their populations have found that factors that predict altered risk of breast cancer after menopause can have different or even reversed effects before menopause. The different effect of same risk factors can be traced in younger premenopausal women under age of 35 comparing with older premenopausal women [4,1].

The general risk factors for breast cancer for women at all ages are positive family history of breast cancer; reproductive variables such as early age at menarche, late age at first full-term pregnancy, low parity, shorter duration of menstrual cycle, high number of spontaneous and induced abortion, breast feeding, use of oral contraceptives; nutrition (high fat intake); history of proliferative benign breast disease; high level of endogenous and exogenous (especially progestines) hormones; active smoking and habitual alcohol consumption [5,1,4].

A number of case-control studies have been conducted to determine the association between family history and the risk of developing breast cancer. Conclusions of all studies are that women who have had a mother or sister diagnosed with breast cancer are at greater risk themselves. The risk has been estimated as almost three times as high as those women with no family history of the disease [5]. The fraction of inherited breast cancer cases may be as low as 5% of all breast cancer patients, but may be as high as 25 % among women who are diagnosed with breast cancer before age of 35. Furthermore, a family history of early-onset breast cancer is estimated to be 23 times more common among the younger breast cancer cases than the older ones [2].

Genetic analysis of breast cancer in the cancer study done in Department of Epidemiology and Public Health of Yale University in 1991 provide evidence for the existence of a rare autosomal dominant allele leading to increased susceptibility to breast cancer. The effect of genotype on the risk of breast cancer is shown to be a function of a woman's age. The risk of breast cancer for women who carry the susceptibility allele is predicted to be the highest among women aged 20-29 years [6].

There is a high association between breast cancer and ovarian cancer in same families. The lifetime risk of developing breast cancer for a woman with one or two first degree relatives affected with ovarian cancer is estimated to be approximately 31% compared with 13% in controls [7].

Epidemiological studies on reproductive variables showed that early age at first birth is associated with a decreased risk for breast cancer. Women who have no pregnancy or have their first pregnancy after the age of 30 have almost a threefold increase in risk as compared to those giving birth the first time at the age 20 or younger [1,5].

Many case-control studies were done to evaluate the association between abortions, whether spontaneous or induced, and breast cancer risk. The association observed were stronger among the youngest women aged less than 30 [8,9,1].

Age at menarche and parity were found to be a risk factors among the young premenopausal women. Younger age at menarche was suggestive of an increase in risk [7]. Some studies have reported that the protective effect of a late age at menarche on breast cancer risk appears stronger in younger premenopausal women [10,11].

A younger age at first lactation is significantly associated with a reduction in the risk of young premenopausal breast cancer [12].

Benign breast disease plays a role as a determinant of the risk of breast cancer. The relative risk has been estimated as 2.7 for those having a history of benign disease as compared to women without disease [5]. In some studies that have examined the association of benign breast disease with development of breast cancer within strata of age, the magnitude of the relative risk for atypical hyperplasia has been doubled or more in younger women compared with older premenopausal women [1,5].

Some epidemiological studies showed that women who have never been married are at greater risk than women who have been married, and nulliparous women are at higher risk than women who have born children [13,1,2,5].

Many studies found that the relationship between the risk of breast cancer and oral contraceptive (OC) use appeared to vary by the age at diagnosis. Among women aged 20-34 years at diagnosis, those who had ever used oral contraceptives had a slightly increased risk of breast cancer (odds ratio [OR] 1.4; 95% confidence interval [CI], 1.0-2.1) compared with women of the same ages who had never used OC. Among women aged 35-44 years, there was no association between OC use and breast cancer. Among women aged 45-55 years, those who used OC had a slightly decreased risk of breast cancer [14,11,1].

Some epidemiological case-control studies conducted to examine the relationship between cigarette smoking and breast cancer showed no association between ever smokers versus never smokers and breast cancer risk and no association was found with risk and age started smoking, age stopped smoking, amount smoked or total years smoked [15]. Only in few studies, smoking has been associated with a small increase in breast cancer risk and only one study found a larger increase in risk for women who began smoking at younger ages compared to other smokers [4].

Epidemiological analysis on the body weight - breast cancer controversy showed that excess weight may be related to the initiation of breast cancer in young premenopausal women through its effect on menstrual cycles. But heavy status at any time is more strongly associated with elevated risks for postmenopausal breast cancer [16,11].

In conclusion, of all the factors that have received much research attention for their possible role in breast cancer etiology, some stand out as being of particular importance in younger premenopausal women. Parity, body size, oral contraceptives use at early ages or of long duration may have opposite effects on breast cancer in younger and older women. Other factors of particular significance in the etiology of early-onset breast cancer include a late age at first birth, never having lactated and history of proliferative benign breast disease. Family history has special significance as a determinant of breast cancer risk in younger premenopausal women.

Some case-control studies described the effectiveness of breast self-examination. The risk of developing advanced breast cancer was found to be slightly higher in women who did, compared with those who did not report that they practiced breast self-examination. Based on studies the American Cancer Society has recommended breast self-examination as a method of detecting breast cancer early for relatively young women [1].

Many studies showed that the early detection and treatment of breast cancer based on screening that includes mammography reduces mortality from the disease [17,1].

Objectives.

Taking into consideration the interest and importance of investigation of risk factors for breast cancer in young women under age of 35 as an unusual age group for developing breast cancer and the fact that no attempt has been done to elucidate the role of risk factors of breast cancer particularly of women at young age in Armenia, the objectives of this study were:

- to investigate the main and specific risk factors that are involved in developing of breast cancer among premenopausal women under the age of 35 living in Yerevan.
- to assess the knowledge about prevention of breast cancer such as breast self-examination and mammography among women under the age of 35 with the history of breast cancer compared with those at the same age but without disease.
- to study the access to health care facilities for breast cancer screening.

Subjects and Methods

Study design

Case investigation method was used as a tool for identification of specific risk profile of the factors that could be involved in the development of breast cancer in women under the the age of 35. Since this age group is not common for women to have breast cancer and only 26 women diagnosed with breast

cancer in 1995, 1996, and by August of 1997 whose residence is Yerevan were under the age of 35, it has not been possible to accumulate large numbers of young breast cancer cases for study. Thus, it was more useful for investigation to do an in-depth study of each woman with the history of breast cancer and gather information from a variety sources: from the cases and from medical records obtained from the Oncology Dispensary. For these reasons the case investigation method was the most appropriate one to conduct the study and to try to explain why premenopausal women developed breast cancer at such an early age and understand some of the determinants of this problem.

Case-control design was used for conducting study with 20 cases of breast cancer and 33 controls.

Study Population

Cases

The eligibility criteria of the cases were: 1) age under 35, 2) residence in Yerevan, 3) first diagnosed as having breast cancer in 1995, 1996 and by August of 1997, 4) availability for interview.

Cases were identified from individual patient records in the Records Department of Oncology Dispensary. Breast cancer were histologically confirmed for all cases.

Out of 26 breast cancer cases under the age of 35 detected by the Oncology Dispensary registry 1(4%) woman refused to participate, 2 (8%) were not reached due to problems with finding addresses, 2 (8%) women were out of Armenia and 1(4%) woman had died. In all, 20 (77%) breast cancer cases were interviewed.

Five cases had breast cancer of clinical stage I (by TNM (Tumor, Nodus, Metastasis) classification proposed in VII International Oncological Congress in London, 1958 [18]), ten of these 20 cancers were of clinical stage II and five of clinical stage III. 19 cases had undergone an operation on the breast and 1 had only symptomatic treatment due to metastasis.

Controls

Two types of control subjects were randomly selected: neighborhood controls and controls selected from among friends, colleagues of cases. Random selection was done by asking each case to list 3 women among neighbors and 4 among friends or colleagues at the same age as they were and then one control subject from each group was randomly (by using random-number table) picked up for both control groups. For each case 2 control subjects had to be selected and interviewed. Thus, the total number of controls had to be 40. To be eligible, the control subjects had to be women matched to cases for year of birth; who had no previous malignancy and who had residence in Yerevan. A total of 33(82%) women were interviewed as controls, while 2(5%) women declared reluctance; 3(8%) neighborhood controls and 2(5%) controls among friends, colleagues of cases that had to be at the same age as cases were not found. Two women were excluded from the final analysis because they had had cancer of uterus and ovarian cancer. Thus, 31(78%) women constituted the control group.

Data collection

The data were collected using a questionnaire done by the interviewer at home for both cases and controls. The interview took about 15 minutes; information was recorded using a structured questionnaire (Annex II) that covered the following items: basic demographic characteristics (occupation, education, marital status, socio-economic status); menstrual and reproductive experience; contraceptive history; family history; smoking and drinking habits.

Assessing questions about knowledge and about access to health care facilities for breast cancer screening were also included in the questionnaire.

Age at menarche was taken as age when the first menses appeared. The total number of years married was calculated by taking the years from getting married to date of interview in cases if interviewee is still married or to date when marital status changed.

Data Processing and Analysis

Odds ratio (OR) and its 95% confidence interval (95% CI) for each exposure variable were estimated by using EpiInfo computer program. Knowledge and access to primary health care related variables were analyzed by using the same computer program.

The method of average percent discordance was used for statistical analysis of some variables because of small number of cases and controls. The method is based on the concept of discordant cases and controls: when the case is exposed to particular factor and the control is not and vice versa. The proportion of exposed and not exposed controls for each factor was estimated. Next, the percent discordance of the factor was estimated in the following way: percent of exposed controls to particular factor was multiplied by number of non exposed cases to the same factor and added to percent of non exposed controls multiplied by number of exposed cases to the same factor. Thereupon, average percent discordance of 20 cases was estimated for that factor. Then, variables were listed beginning from the largest average percent discordance because: the higher the average percent discordance for factor the greater the influence of this factor on breast cancer risk.

Results

Demographic Characteristics

Table I. shows the effect on breast cancer risk of factors related to demographic characteristics. Education, occupation and marital status grouped into two categories for cases and for controls were not related to the risk of breast cancer in this study. Positive association with late age at marriage (≥ 25) and inverse association with total number of years married were observed among cases and controls. Low income (≤ 10.000 drams) increased, statistically significantly, the risk of breast cancer for cases compared with controls.

TABLE I. Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) of Demographic Characteristics of the Study Population for Breast Cancer.

Characteristic	Cases number and %	Controls number and %	OR	95 % CI
Education				
- primary school/college	10 (50%)	18 (58%)	0.72	0.2-2.26
- university/postgraduate	10 (50%)	13 (42%)		
Occupation				
- factory workers	4 (22%)	5 (23%)	0.97	0.16-5.53
- office workers/teachers/ public workers	14 (78%)	17 (77%)		
Marital status				
- single	2 (10%)	5 (23%)	0.58	0.07-4.05
- married/widowed/divorced	18 (90%)	26 (84%)		
- single/widowed/divorced	4 (20%)	10 (32%)	0.53	0.11-2.35
- married	16 (80%)	21 (68%)		
Age at marriage (y)				
≥ 25	3 (17%)	3 (10%)	1.53	0.21-11.42
≤ 24	15 (83%)	23 (88%)		
Total no. of years married				
≤ 10	7 (39%)	11 (42%)	0.87	0.21-3.5
≥ 11	11 (61%)	15 (58%)		
Monthly income				
≤ 10.000 drams	12 (60%)	8 (26%)	4.31*	1.1-17.6
> 10.000 drams	8 (40%)	23 (77%)		

(* - here and in following data -the results are statistically significant)

Reproductive factors

Table II. demonstrates the ORs with 95% CIs of the reproductive variables for breast cancer. A positive association with early age at menarche, late age at first full-term pregnancy and having at least one pregnancy was observed in the study, but this association was not statistically significant. An inverse, but not significant association with low number of pregnancies (≤ 5) was also found.

The more the number of abortions (≥ 4), the higher was the risk of breast cancer. The odds ratio for average months of breast feeding was suggestive of an increase in risk of breast cancer related to lower number of months of breast feeding. The breast cancer risk associated with nulliparity differ from parous women. Among parous women, the risk decreased with increasing parity.

Data on menstrual regularity showed that only 4 cases did not have menstrual cycles at the time of interview which were terminated due to surgery. Other cases and controls reported regular menstrual cycles.

Estimation of usual cycle length demonstrated that shorter cycles (cycle length ≤ 25 days) have slight positive association (OR=1.35) with breast cancer risk.

Data related to use of oral contraceptives are not shown because 99% of cases and 98% of controls have never used oral contraceptives.

TABLE II. Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) of Reproductive Variables for Breast Cancer.

Factor	Cases number and %	Controls number and %	OR	95 % CI
Age at menarche (y)				
≤ 12	7 (35%)	7 (23%)	1.85	0.44-7.77
≥ 13	13 (65%)	24 (77%)		
Length of menstrual cycle (days)				
≤ 25	7 (44%)	9 (29%)	1.9	0.33-5.22
≥ 26	9 (56%)	22 (71%)		
Age at first full-term pregnancy (y)				
≥ 26	3 (19%)	1 (3.5%)	6.46	0.42-96.08
≤ 25	13 (81%)	28 (96.5%)		
Pregnancy				
- Yes	18 (90%)	24 (77%)	2.63	0.41-21.21
- No	2 (10%)	7 (23%)		
No. of pregnancies				
≤ 5	8 (44%)	17 (71%)	0.33	0.07-1.41
≥ 6	10 (56%)	7 (29%)		
Abortion				
- Yes	15 (75%)	21 (68%)	1.43	0.34-6.16
- No	5 (25%)	10 (32%)		
No. of abortions				
≥ 4	10 (67%)	7 (33%)	4.00	0.81-21.22
≤ 3	5 (33%)	14 (67%)		
Average months of breast feeding				
≤ 4	8 (53%)	10 (48%)	1.26	0.27-5.85
≥ 5	7 (33%)	11 (52%)		
Parity				
0	3 (15%)	8 (26%)	1.00	
≥ 1	17 (85%)	23 (74%)	1.97	0.39-13.08
1	5 (25%)	4 (13%)	3.33	0.37-32.25
2	7 (35%)	12 (39%)	1.59	0.25-11.9
≥ 3	5 (25%)	7 (23%)	1.9	0.25-16.58

Benign Breast Diseases and Family History

TABLE III. Effect of Benign Breast Diseases and Family History of Cancer on the risk of Breast Cancer

Factor	Cases number and %	Controls number and %	OR	95% CI
Benign breast diseases - Yes - No	13 (65%) 7 (35%)	7 (23%) 23 (77%)	6.10 *	1.5-25.7
Breast cancer among relatives (maternal grandmother or mother or sister) - Yes - No	5 (25%) 15 (75%)	1 (3%) 30 (97%)	10	0.95-488.8
Breast, ovarian and uteri cancer among relatives of cases - Yes - No	12 (60%) 8 (40%)	5 (16%) 26 (84%)	7.8 *	1.79-36.53
History of other type of cancer among relatives of cases - Yes - No	13 (65%) 7 (35%)	5 (16%) 26 (84%)	9.66 *	2.18-45.54

ORs and 95% CIs of benign breast diseases presented in Table III. show positive, statistically significant association of benign breast diseases with breast cancer in cases compared with controls.

An excess risk of breast cancer was found in patients who had at least one first- or second-degree relative (maternal grandmother or mother or sister) with a history of breast cancer and statistically significant association was found among cases who had relative with a history of other cancer (breast, ovarian, uteri). These cases had an increased risk of breast cancer. Among relatives maternal grandmothers were diagnosed with cancer at 45 years of age, mothers were diagnosed at ages between 36 and 49 and sisters at ages between 27 and 32 (data not shown).

Smoking and drinking habits

In Table IV. current cigarette smoking showed a small positive association with breast cancer (OR=1.21; 1.38 for those smoking < 20 cigarettes per day). The OR of alcohol drinkers versus non-drinkers was 0.26 (95% CI=0.06-0.97) and showed the protective effect of drinking on the risk of breast cancer. Dose response relationship was also implied.

TABLE IV. Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) of Habitual Smoking and Drinking for Breast Cancer.

Factor	Cases number and %	Controls number and %	OR	95% CI
Smoking				
- Never smoke	13 (65%)	21 (68%)	1.00	
- Ex-smoker	1 (5%)	2 (6%)	0.81	0.01-17.1
- Current smoker	6 (30%)	8 (26%)	1.21	0.29-5.11
< 20 cigarettes/day	6	7	1.38	0.32-6.06
≥ 20 cigarettes/day	0	1	0.00	0.00
Drinking				
- Nondrinker	13 (65%)	10 (32%)	1.00	
- Drinker	7 (35%)	21 (68%)	0.26	0.06-0.97
< 3 drinks/day	6	19	0.24	0.06-0.97
> 4-9 drinks/day	1	2	0.38	0.01-8.7

Knowledge related questions

Knowledge related questions for cases were prefaced with “Before you were diagnosed with breast cancer”, asking them to recall the information that they had before facing the problem related to breast. Thus, as it presented in Table V (Annex I), 7 (35%) of cases and 16 (52%) of controls have heard about breast self-examination. Out of these cases and controls 5 (71%) cases and 11 (69%) controls acquired this information from magazines, newspapers, television and other sources; only 4 (25%) controls received the information about breast self-examination from physicians or nurses and 5 (31%) from friends, relatives and neighbors.

Thirteen (57%) of those cases and controls who know about breast self-examination think that a woman should start breast self-examination at ages 20-29, 6 (26%) at ages 30-39 and only 3 (13%) persons think that a woman should start breast self-examination before 20 years of age. Ten (44%) of them think that breast self-examination should be performed every 3 months and 6 (26%) think about every 6 months.

Only 7 (35%) cases and 18 (58%) controls have heard about mammograms. Mostly the information about mammograms was received from magazines, newspapers, television or from friends, relatives,

neighbors. Twelve (48%) of these cases and controls think that a woman should start to have mammograms at ages 20-39, 9 (36%) cases and controls believe that ages 40-59 are the most appropriate time for starting to be screened by mammography. Eight (32%) of interviewed cases and controls consider that mammograms should be performed every 6 months, 9 (36%) of them think about once a year and 3 (12%) of them think about once in two years.

Access to Medical Care Facility

Analysis of variables related to access to Medical Care Facilities for breast screening, presented in Table VI (Annex I), showed that 13 (65%) cases out of 20 and 12 (38%) controls out of 31 are aware of breast cancer screening services offered by any health department in Armenia. Having known about existence of such kind of services the only reason mentioned by cases and controls for inaccessibility of these services to them was the cost. Eleven (55%) cases, before being told that they had breast cancer, have been screened by physician for breast cancer at a medical care facility, 5 (45%) of them got this breast exam following the doctor recommendation, 4 (36%) of them by self-motivation, 1 (9%) case had previous breast problem and 2 (18%) cases mentioned other reasons. These cases mostly had the breast examination at hospital and oncology dispensary. Only 3 (10%) controls have been screened by physician for breast cancer. These screenings were performed at polyclinic, hospital and oncology dispensary. The reasons for screening were the doctor recommendation, self-motivation and one control mentioned the breast problem. One of the reasons for not being screened for breast cancer mentioned by 4 cases and 22 controls was that it is not necessary. Three cases and one control think that they are too young to be screened for breast cancer. Other reasons mentioned by cases and controls were: “not recommended” and cost.

Four (20%) cases and no controls have done a mammogram. The reasons of not getting a mammogram named by cases were 1) they did not know about it; 2) not recommended, 3) cost and 4)

not necessary. The most frequent reasons of not getting a mammogram mentioned by controls were that they did not know about mammography; their belief that it is not necessary and then the cost.

Results of Average Percent Discordance Estimation.

Analysis of collected data by using the method of average percent discordance estimation presented in Table VII. (Annex I) showed that the largest average percent discordance and therefore the most elevated risk for developing breast cancer has the positive family history of any cancer. Second factor is benign breast disease, followed by average monthly income.

Number of pregnancies, number of abortions and average months of breast feeding have the same average percent discordance. Thus, these factors can be considered as having equal influence on breast cancer risk in youngest women. The lowest average percent discordance and thus the weakest risk or no risk at all has alcohol consumption.

Discussion

In this study the number of cases was relatively small. Recruitment method was intended to gather all of the available breast cancer cases. The possibility of bias of selection of cases should not be considered in this study because first of all, there was no selection done for interview of cases and second, all cases had undergone diagnostic procedures with histologically confirmation of breast cancer before the beginning of the study.

In this study the selection of non-cancer individuals as the control group was done by matching controls to each case by age. Thus, the age distribution of cases as well as controls was between 25 and 35 years of age as it was aimed by the objective of the study.

The residence of all cases and controls was the Yerevan City. The district residence distribution of neighborhood controls within Yerevan was similar to that of the breast cancer cases. Controls selected

from among friends and colleagues of cases can be to some extent considered as representatives of the same socio-economic status as cases.

The small number of cases and controls in this study did not allow to reveal many statistically significant associations of breast cancer with different risk factors. Nevertheless, the analysis of collected data showed some relationships between breast cancer and factors which are of particular significance in the etiology of early-onset breast cancer. However, due to a possible lack of power, it will be better to consider the results of this study in light of the literature for an adequate appraisal of discovered relationships.

In the present study not much difference was revealed between cases and controls in respect of the level of education and type of occupation, and no association was found between these factors and the risk of breast cancer.

Many epidemiological studies have shown a protective effect of being married and early age at marriage which is explained by certain hormonal changes. This study did not reveal any protective effect of being married, but the late age of marriage (≥ 25) showed the positive association (OR = 1.65) with breast cancer risk, which can be indirectly related to late first full-term pregnancy.

Some epidemiological investigations have suggested a positive relation between breast cancer and high socioeconomic status (one of the indicators of socioeconomic status was taken as monthly income) [19]. Nevertheless, in this study an increased risk of breast cancer was observed among cases with low monthly income ($\leq 10,000$ drams). Trying to elucidate this relationship the difficult economic situation that exists in Armenia should be taken into consideration, because this economic situation is reflected in low monthly income of the overwhelming majority of Armenian population. This fact can be considered as a possible explanation of epidemiological finding in this study.

In the present study, positive association between reproductive variables and breast cancer risk were noted and these findings are consistent with those in other studies conducted in different countries. In both this study and those of other investigations, the decrease in the risk associated with a late age at

menarche was observed. Many authors suggest that in discussion of the possible influence of age at menarche, error of recall of age at menarche must be kept in mind [20]. Recall of age at menarche is less likely to be the reason for bias in this investigation because study population was comparatively young while error of recall is considered to be an issue of concern if the study population is older women.

Shorter menstrual cycles have been shown in this study to confer slightly increased risk of breast cancer. It has been pointed out in many studies that women with shorter cycles spend more of their reproductive years in the luteal phase, when estrogen and progesterone levels are both high and when mitotic activity appears to reach its peak, than do women with longer cycle lengths [1].

In agreement with some studies, positive association between late age at first full-term pregnancy, number of parities and breast cancer was also found in this study. These factors are probably related to hormonal changes affecting breast tissue proliferation during a full-term pregnancy [20]. In this study analysis was done for high parity in comparison with low parity and the statement can be made that women in all birth categories were at decreased risk in comparison with nulliparous women. However, it should be noted and taken into consideration that some of the youngest women in this study population may not have completed the reproductive phase of their life.

The positive association was found of breast cancer with average months of breast feeding. In spite of the fact that this association was not statistically significant, the risk reduction of breast cancer by lactation and its duration in young premenopausal women has been observed in several studies with statistically significant level of this negative relationship [1,20].

This study has also included analysis of whether spontaneous or induced abortions, considered in combination, affects the risk for breast cancer. Results have shown elevated risk in women with breast cancer reporting abortions. Association also exists between number of abortion and breast cancer risk. There is suggestion that the incomplete differentiation of mammary gland cells during the first trimester could increase the subsequent susceptibility of breast tissue to carcinogenic agents [1,9].

Although most breast cancers are believed to be of a noninherited (sporadic) type, more than a quarter of all breast cancer patients have a family history of breast cancer in a first- or second-degree relatives. Women are especially at high risk if breast cancer developed in mother or sister or grandmother when they were premenopausal at that time [21]. In this study the risk arising from at least one family history of breast cancer among first- or second-degree relatives was elevated among cases. Moreover, the effect of not only breast, but also ovarian and uteri cancer among relatives was tested and significant association was found. This finding may indicate an existence of genetic factors leading to increased susceptibility to breast cancer. Furthermore, this study revealed that first- or second-degree relatives were diagnosed with cancer at ages under 45, supporting the hypothesis that the younger a patient is when she is diagnosed with cancer, the greater the elevation in lifetime risk of breast cancer is for her relatives.

It has been well demonstrated in this study that women with proliferative benign breast disease have an increased risk of breast cancer. Benign breast disease markers comprise changes in breast tissue which may progress through increasing premalignant phases and eventually evolve into cancer. To discuss the influence of benign breast diseases the possibility of information bias should be considered because women with breast cancer are more aware and more careful to recall any markers in breast tissue preceding the developing breast cancer.

In this study, active smoking elevated, but not much, the risk of young premenopausal breast cancer. MacMahon et al. demonstrated lower urinary estrogen levels in smokers than nonsmokers during the luteal phase of the menstrual cycle [22]; however the role of estrogen in the etiology of breast cancer is still unclear. Nevertheless smoking has already been shown by many studies to be carcinogenic and deleterious to health in many respects.

Despite several epidemiological studies that have shown the positive association between alcohol consumption and breast cancer risk [4,1,11], this study demonstrated a negative relationship between alcohol consumption and breast cancer. One of possible explanations of the reason that the drinking

habit did not account for an attributable risk of breast cancer women can be the supposition that the proportion of female drinkers in the younger generation is very small in Armenia compared to that in other countries.

The study revealed that only 35% of cases and approximately 55% of controls have knowledge about preventive measures by early detection of breast cancer through breast self-examination and mammography. This can explain the fact that 75% of cases were diagnosed with breast cancer at clinical stages of II and III. However, the possibility of recall bias should be considered in analysis of knowledge related questions, particularly for cases, because they were asked to recall the information before being diagnosed with breast cancer which can be inaccurate and confused with the information acquired after having breast cancer. On the other side, the beliefs held by cases and controls that “it is not necessary to have screening for breast cancer” and “we are too young to be screened” can be attributed to lack of appropriate knowledge about necessity of prevention strategies for young women, particularly breast self-examination, for early detection of breast cancer.

Conclusion and recommendations

Of all factors that were included in this investigation for their possible role in breast cancer etiology in younger women, only few of them stand out as being of particular importance in women under the age of 35 living in Yerevan. Positive family history, benign breast diseases have special significance as determinants of breast cancer risk in youngest women. Monthly income is a factor that is also associated with increased risk in women under the age of 35. Other factors that were investigated in this study also revealed important associations, but these associations were not statistically significant. One of elucidation of this fact is small number of cases and controls, because of nonspecific for breast cancer age group of study population. Furthermore, it can be suggested that because of very young study population the inevitable time interval between exposure to the factors and the occurrence of the disease was very small. The protective effect of factors occurring early in life such as an older

age at menarche, a younger age at first birth may be limited in time. Similarly, the protective effect of a high parity, corresponding to a decreasing number of undifferentiated cells with each parity, would be preferentially observed later in time.

Taking into consideration the epidemiological findings of this study the following recommendations related to prevention of developing breast cancer in young women can be made:

- to develop educational programs for relatively young women focused on prevention of breast cancer through breast self-examination as a form of physical examination for early detection not only breast cancer but also some of benign breast diseases which may progress and eventually evolve into cancer .
- to organize screening programs targeted towards women with family history of cancer (breast, ovarian, uteri) as a high risk population for developing breast cancer.
- to develop educational programs by providing the information about mammography for early detection of breast cancer in women.
- to conduct epidemiological studies for further investigation of breast cancer risk factors for women in Armenia.

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Annex I

Table V. Distribution of cases of breast cancer and controls according to knowledge related questions.

Questions	Cases		Controls		Total	
	No.	%	No.	%	No.	%
Have heard about breast self-examination	7	(35)	16	(52)	23	(45)
Sources of information						
• Magazines, newspaper, television	5	(71)	11	(69)	16	(70)
• Physician, nurse	0	(0)	4	(25)	4	(17)
• Friends, relatives, neighbors	3	(42)	5	(31)	8	(35)
• Other	0	(0)	3	(19)	3	(13)
Age to start self-examination						
- < 20 years of age	1	(14)	2	(12)	3	(13)
- 20-29	3	(43)	10	(63)	13	(57)
- 30-39	2	(29)	4	(25)	6	(26)
- ≥ 40	1	(14)	0	(0)	1	(4)
Frequency of breast self-examination						
- every month	1	(14)	2	(12)	3	(13)
- every 3 months	3	(43)	7	(44)	10	(44)
- every 6 months	2	(29)	4	(25)	6	(26)
- once a year	0	(0)	3	(19)	3	(13)
- every 2 year	0	(0)	0	(0)	0	(0)
- every 4 year	0	(0)	0	(0)	0	(0)
- other	1	(14)	0	(0)	1	(4)
Have heard about mammograms	7	(35)	18	(58)	25	(49)
Sources of information						
• Magazines, newspaper, television	4	(57)	11	(61)	15	(60)
• Physician, nurse	1	(14)	5	(28)	6	(24)
• Friends, relatives, neighbors	3	(43)	5	(28)	8	(32)
• Other	0	(0)	3	(17)	3	(12)
Age to start to have mammograms						
- < 20 years of age	0	(0)	1	(6)	1	(4)
- 20-39	5	(72)	7	(39)	12	(48)
- 40-59	1	(14)	8	(44)	9	(36)
- ≥ 60	1	(14)	2	(11)	3	(12)
Frequency of screening by mammography						
- every month	1	(14)	0	(0)	1	(4)
- every 3 months	1	(14)	0	(0)	1	(4)
- every 6 months	2	(30)	6	(34)	8	(32)
- once a year	1	(14)	8	(44)	9	(36)
- every 2 year	1	(14)	2	(11)	3	(12)
- every 4 year	0	(0)	0	(0)	0	(0)
- other	1	(14)	2	(11)	3	(12)

Table VI. Distribution of cases of breast cancer and controls according to access to health care facilities related questions.

Questions	Cases		Controls		Total	
	No.	%	No.	%	No.	%
Awareness of breast cancer screening services in Armenia	13	(65)	12	(39)	25	(49)
Accessibility to breast cancer screening services						
- Yes	7	(54)	8	(67)	15	(60)
- No	6	(46)	4	(33)	10	(40)
Reasons for inaccessibility						
• Transportation	1	(17)	0	(0)	1	(10)
• Hours	0	(0)	0	(0)	0	(0)
• Location	0	(0)	0	(0)	0	(0)
• Cost	5	(83)	4	(100)	9	(90)
• Other	0	(0)	0	(0)	0	(0)
Have been screened by physician						
- Yes	11	(55)	3	(10)	14	(27)
- No	9	(45)	27	(90)	36	(36)
Reasons for being screened						
• Recommended by doctor	5	(45)	2	(67)	7	(50)
• Self-motivated/own idea	4	(36)	1	(33)	5	(36)
• Had previous breast problem	1	(9)	1	(33)	2	(14)
• Other	2	(18)	0	(0)	2	(14)
Reasons for not being screened						
• Not recommended	1	(11)	2	(7)	3	(8)
• Cost	1	(11)	2	(7)	3	(8)
• Not necessary	4	(44)	22	(81)	26	(72)
• Too young	3	(33)	1	(5)	4	(11)
• No transportation	0	(0)	0	(0)	0	(0)
• Inconvenient hours	0	(0)	0	(0)	0	(0)
• Other	0	(0)	0	(0)	0	(0)
The place of performed breast examination						
- Polyclinic	0	(0)	1	(33)	1	(7)
- Hospital	4	(36)	1	(33)	5	(37)
- Oncology dispensary	5	(42)	1	(33)	6	(42)
- Other	2	(18)	0	(0)	2	(14)
Have ever done a mammogram						
- Yes	4	(20)	0	(0)	4	(8)
- No	16	(80)	31	(100)	47	(92)
Reasons for not getting a mammogram						
• Did not know about it	5	(31)	9	(29)	14	(31)
• Not recommended	4	(25)	5	(16)	9	(19)
• Cost	3	(18)	7	(23)	10	(21)
• Not necessary	2	(13)	9	(29)	11	(23)
• Too young	2	(13)	1	(3)	3	(6)
• No transportation	0	(0)	0	(0)	0	(0)
• Inconvenient hours	0	(0)	0	(0)	0	(0)
• Other	0	(0)	0	(0)	0	(0)

TABLE VII. Estimation of Average Percent Discordance of Risk Factors for Breast Cancer

Factors	Cases																				Controls Number and %	Average % discordance
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
Positive family history of breast cancer	-	-	-	-	-	+	-	-	-	+	-	-	-	+	+	-	-	+	-	-	5 (16%)	60
Benign breast diseases - Yes	-	+	+	+	+	+	+	-	-	-	+	-	+	+	-	-	+	+	+	+	7 (23%)	58
Monthly income ≤ 10.000 drams	+	+	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+	+	8 (26%)	52
No. of pregnancies ≤ 5	+	-	-	+	-	+	-	-	-	+	+	-	-	+	+	+	+	+	-	-	17 (71%)	50
No. of abortions ≥ 4	-	+	+	-	+	-	+	+	+	-	-	+	+	-	-	-	-	-	+	+	7 (23%)	50
Average months of breast feeding ≤ 4	-	-	-	-	-	+	+	+	-	-	-	-	+	-	-	-	+	+	+	+	10 (48%)	50
Parity ≤ 2	-	-	-	-	+	+	+	-	+	+	+	-	+	-	+	+	+	+	+	-	16 (52%)	46
Age at menarche ≤ 12	+	+	-	-	-	+	-	-	+	-	-	-	-	+	-	-	+	-	+	-	7 (23%)	42
Abortion - Yes	-	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	21 (68%)	41
Current smoker	-	-	-	+	-	+	-	+	+	-	-	-	-	+	-	+	-	-	-	-	8 (26%)	40
Nulliparity - Yes	+	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	8 (26%)	33
Positive Family history of any cancer	-	-	+	-	-	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	1 (3%)	27
Age at marriage ≥ 25	-	-	-	-	-	-	-	-	-	-	+	-	-	-	+	+	-	-	-	-	3 (12%)	23
Age at first full-term pregnancy ≥ 26	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	-	1 (3%)	17
Drinker ≥ 4 drinks/day	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 (6.5%)	11

Annex II

Questionnaire

Location _____

Questionnaire _____

Interviewer _____

Date of interview _____

I am a student of Public Health Department of the American University of Armenia. I am conducting a survey concerning risk factors of breast cancer in women aged less than 35 in Yerevan. And I am calling for your patience to help me answering the questions which I am going to ask you. Your personal experience and participation in this survey would make a valuable input in my investigation. The interview will take approximately 15 minutes.

Part A

Background information:

1. What is your date of birth?

____/____/____
month day year

2. What is your current address?

3. Have you ever lived outside of Yerevan more than 2 years?

___ Yes
___ No

[if yes]: specify what was your address outside of Yerevan

4. What is your level of education?

- ___ 1. school (8)
- ___ 2. school (10)
- ___ 3. college (2)
- ___ 4. institute/university (5-6)
- ___ 5. post. graduate
- ___ 6. other _____

Total years _____

5. Do you work now?

___ Yes
___ No [skip to 7.]

6. a. Please specify where? _____

b. What is your job title? _____

c. How many years did you work in this job? _____

7. Have you ever held job?

___ Yes
___ No [skip to 8.]

7a. Please specify your last job? _____

b. What was your job title? _____

c. How many years did you work in this job? _____

8. What is your marital status?

- 1. single [skip to 9.]
- 2. married
- 3. divorced
- 4. widowed

8a. When did you get married?

_____ year

8b. When your status changed?

_____ year

8c. What is the total number of years married?

_____ years

9. What is the total monthly income of your family?

- 1. below 10,000 dram
- 2. 10,000 to 40,000
- 3. more than 40,000

Part B

Reproductive and hormonal risk factors.

10. How old were you when you first started having menstrual periods?

_____ Years old

_____ Never had a menstrual period [skip to 15.]

11. Are you still having menstrual periods?

_____ Yes [skip to 14.]

_____ No

12. How old were you when you had your last menstrual period?

_____ years

13. For what reason did you stop having menstrual period?

_____ due to surgery

_____ other, explain: _____

_____ don't know

14. On average, about how many days were there from the first day of one menstrual period to the first day of your NEXT menstrual period?

_____ days

15. Have you EVER been pregnant?

_____ Yes

_____ No [skip to 23.]

16. In total, how many times have you been pregnant? Please include livebirths, stillbirths, abortions, miscarriages, and tubal pregnancies.

_____ Times pregnant.

17. How many of your pregnancies resulted in live births or stillbirths?

_____ pregnancies

_____ Zero

18. What was your age at first full-term pregnancy?
 _____ Years old.
19. Did you breast feed at least one of your child?
 _____ Yes
 _____ No [skip to 21.]
20. For how long did you breast feed your child?
 _____ Days
 _____ Months
21. Have you EVER had abortion? Please include spontaneous and induced abortion.
 _____ Yes
 _____ No [skip to 23.]
22. How many abortions have you had?
 _____ abortions.
23. Are you using oral contraceptives to delay or avoid getting pregnant?
 _____ Yes [skip to 25.]
 _____ No
24. Have you ever used oral contraceptives?
 _____ Yes
 _____ No [skip to 26.]
25. For how long did you use oral contraceptives?
 _____ < 5 years
 _____ ≥ 5 years

Part C

Family History

26. Was your MOTHER ever diagnosed with cancer?
 _____ Yes
 _____ No [skip to 27.]
 _____ Don't know
- 26a. How old was your MOTHER when diagnosed with cancer?
 _____ years old
 _____ don't know
- 26b. What kind of cancer(s) did your MOTHER have?

 _____ Don't know
27. Was your MATERNAL GRANDMOTHER ever diagnosed with cancer?
 _____ Yes
 _____ No [skip to 28.]
 _____ Don't know
- 27a. How old was your grandmother when diagnosed with cancer?
 _____ years old
 _____ don't know

27b. What kind of cancer(s) did your GRANDMOTHER have?

_____ Don't know

28. How many SISTERS do you have?

_____ sisters
_____ Zero [skip to 29.]

28a. Were any of your SISTERS ever diagnosed with cancer?

_____ sisters
_____ Zero [skip to 29.]
_____ Don't know

28b. For each of your SISTERS who was ever diagnosed with cancer, please list the type of cancer and how old your SISTER was when diagnosed with cancer for the first time.

SISTER #	Types of cancer	How old was your SISTER when the cancer was found?
1.		
2.		
3.		

_____ Don't know

PART D

Personal history

29. Have you EVER been told you had breast cancer?

___ No
 ↓

___ Yes
 ↓

29a. Have you ever had any problems with your breasts that were benign (not cancer), such as lumps, cysts, and/or fibrocystic disease?

___ Yes
___ No
___ Don't know

29b. Before you were told that you had breast cancer, did you ever have any problems with your breasts that were benign (not cancer) such as lumps, cysts, and/or fibrocystic disease?

___ Yes
___ No
___ Don't know

30. Are you a smoker?

___ Yes
___ No [skip to 31.]

30a. How old were you when started to smoke?

_____ years old

30b. How many cigarettes do you smoke per day?

___ < 20 cigarettes/day
___ 20-40 cigarettes/day

___ \geq 40 cigarettes/day

31. Have you EVER smoked?

- Yes
 No [skip to 32.]

31a. How old were you when you started to smoke?

___ years old

31b. How old were you when you stopped smoking?

___ years old

31c. How many cigarettes did you smoke per day?

- $<$ 20 cigarettes/day
 20-40 cigarettes/day
 \geq 40 cigarettes/day

32. What was your alcohol use during the previous 3 years?

- None
 $<$ 3 drinks/week
 4-9 drinks/week
 10-14 drinks/week
 \geq 15 drinks/week

Part E

Knowledge related questions.

[Note: If person diagnosed with breast cancer, preface some questions with "Before you were diagnosed with breast cancer..."]

33. (Before you were diagnosed with breast cancer) Have you EVER heard about breast self-examination?

- Yes
 No [skip to 37.]

34. Where did you get most of information about breast self-examination?

- Magazines, newspaper, television
 Physician, nurse
 Friends, relatives, neighbours
 Other, specify: _____

35. At what age do you think a woman should start self-examination?

- $<$ 20 years of age
 20-29
 30-39
 \geq 40
 Don't know

36. How often do you think a woman should have breast self-exam?

- Every month
 Every 3 month
 Every 6 month
 Once a year
 Every 2 year
 Every 4 year
 Other, specify _____

Don't know

37. (Before you were diagnosed with breast cancer) Have you EVER heard about mammograms?

Yes

No [skip to 41]

38. Where did you get most of your knowledge about mammograms?

Magazines, newspaper, television

Physician, nurse

Friends, relatives, neighbors

Other, specify: _____

39. At what age do you think a woman should start to have mammograms?

< 20 years of age

20-39

40-59

≥60

Don't know

40. How often do you think a woman should have mammograms?

Every month

Every 3 month

Every 6 month

Once a year

Every 2 year

Every 4 year

Other, specify _____

Don't know

Part F

Access of Medical Care Facilities

41. Are you aware of any breast cancer screening services offered by any health department in Armenia?

Yes

No [skip to 47.]

42. Having known about this services, were they accessible to you? For example, if you chose to go these services, would it have been easy for you to physically get there?

Yes

No [skip to 43.]

42a. What would be the reason of difficulty in getting there?

Transportation

Hours

Location

Other, please specify: _____

43. (Before you were told that you had breast cancer) Have you ever been screened by physician for breast cancer at a medical care facility?

Yes [skip to 44.]

No

43a. Why have you not been screened?

Not recommended

- Cost
- Not necessary
- Too young
- No transportation
- Inconvenient hours
- Other, specify: _____

44. When was your LAST breast examination?

- Less than 1 year ago
- 1-2 years ago
- More than 2 years ago

45. Why did you get this breast exam?

- Recommended by Doctor
- Self-motivated-own idea
- Had previous breast problem
- Other, specify: _____

46. Where did this examination take place?

- Polyclinic
- Hospital
- Oncology dispensary
- Other, specify: _____

47. If you know, new mammographic screening center has been opened in Yerevan.

A mammogram is an x-ray picture of the breast by a machine that flattens the breast while the picture is taken. Have you EVER done a mammogram?

- Yes [skip to 49.]
- No

47a. Why did you not get a mammogram?

- Did not know about it
- Not recommended
- Cost
- Not necessary
- Too young
- No transportation
- Inconvenient hours
- Other, specify: _____

