Original Article

RISK FACTORS OF OVARIAN CANCER AMONG THE POSTMENOPAUSAL WOMEN

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ABSTRACT

Background: Ovarian cancer ranks 5thin cancer deaths among women. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 75. Cancer mainly develops in older women.

***Methods*:** The case control study was carried out among 154 respondents in medical oncology department, NIRCH, Dhaka from July 2016 to June 2017. Among the participants, 77 were cases who had ovarian cancer and another 77 were controls who had no ovarian cancer. Convenient sampling technique was used and data were collected by face-to-face interview using a pretested semi-structured questionnaire. Data were entered on to the template of SPSS and analysis was done.

***Results*:** The mean age of case and control group were 60.06±7.00 and 59.89±6.96 years respectively. Highest number of respondents were illiterate. Majority came from rural area and had no personal monthly income. Most of them were taken high fiber diet, 83.1% in case and 77.9% in control group. About 80.5% in case and 66.2% in control group had BMI ≥25 kg/m^2. Sedentary workers 40.3% in case and 13.0% in control group; moderate workers were 31.2% in case and 20.8% in control group and hard workers were 28.5% and 66.2% in case and control group respectively. The mean age of menarche 12.02±1.19 years and 12.87±1.30 years in case and control group respectively and mean age of menopause in case and in control groups respectively 51.54±2.39 and 49.61±1.29 years. In case group 49.3% had early term pregnancy whereas in control group 9.5% had early term pregnancy; in case group 82.1% and in control group 86.5% had breast feeding history. Around 16.9% in case group and 27.3% in control group used to take OCP. Significantly more respondents 6.5% in case group had personal H/O breast cancer than control group. Positive family history of breast and ovarian cancer was found 16.9% in case group and 2.6% in control group. In binary logistic regression analysis for risk factors of OC was found that sedentary activity was associated with increased risk, increased BMI (≥25 kg/m^2), early age of menarche (≤12 years), late age of menopause (>51 years), nullipara and early term pregnancy. Family H/O breast or ovarian cancer significantly associated with development of ovarian cancer.

Conclusion: Ovarian cancer observed more in older age group (≥60 years) among sedentary worker with high body mass index (≥25 kg/m^2). Early age of menarche (≤12 years), late menopause (>50 years), never having given birth to a child in life time, early term of pregnancy and family history of breast and ovarian cancer were significantly associated with ovarian cancer among post-menopausal women.

Key Words: Ovarian Cancer (OC), post-menopausal women, risk factors.

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INTRODUCTION

Cancer is the rapid creation of abnormal cells which grows beyond their usual boundaries and which can invade adjoining parts of the body and spread to other organs, the process is called metastasis. Metastases are the major cause of death from cancer. Cancer intrudes one and all in the rich and poor, the men, women and children, the young and old and represents a huge burden on patients' families and societies. Cancer is one of the top causes of death in the world, particularly in developing countries. Ovarian cancer (OC) remains primarily a cancer in women account for an estimated 239,000 new cases and 152000 deaths worldwide annually [1]. OC is the 10th most common cancer and the 5th leading causes of cancer death. OC causes more deaths than any other cancer in female reproductive system but it accounts of 3% of all cancers in women [2]. Nearly, all benign and malignant ovarian tumors originate from one of three cell types: epithelial cells, stromal cells, and germ cells. In developed countries, more than 90% of malignant ovarian tumors are epithelial in origin [3].

Risk factors are anything that changes the chance of getting a disease like cancer. A woman's risk of getting OC during her life time is about 1 in 75. Her life time chance of dying from OC is about 1 in 100 [6]. The risk of developing OC gets higher with increasing age and most ovarian cancer developed after menopause. Half of all OCs are found in women 63 years of age or older. One of the most significant risk factors for OC is a family history of disease [7]. First-degree relatives of probands have a 3-7-fold increased risk, especially if multiple relatives are affected, and at an early age of onset [8]. Another risk factor, pregnancy causes anovulation and suppresses secretion of pituitary gonadotropins and is thus consistent with both the 'incessant ovulation' and the 'gonadotropin' hypotheses. Indeed, parous women have a 30-60% lower risk than nulliparous women [9,10]and each additional full-term pregnancy lowers risk by approximately 15% [11]. Lactation suppresses secretion of pituitary gonadotropins and leads to anovulation, particularly in the initial months after delivery [12] and reduces the risk of OC. Several gynecologic conditions have been examined as risk factors for OC, including PCOS, endometriosis, and pelvic inflammatory disease (PID) [13]. It is well established that among high-risk women bilateral prophylactic oophorectomy decreases risk by at least 90% [14].

Use of oral contraceptive is inversely associated with the risk factor of OC. The protective effect increases with longer duration of use [15,13]. Post-menopausal HRT may enhance estrogen induced proliferation of ovarian cells and therefore increase risk [16]. Elevated BMI appear to increase risk of OC. Physical activity and exercise estimated a nearly 20% lower risk for the most active women compared with the least active [17]. Smoking, alcohol consumption, exposure to the asbestos and talcum powder increase the risk of OC where as several studies have observed an inverse association between aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) and OC incidence [18-19].

Bangladesh is a low-income country with Gross National Income (GNI) is less than US $2020 per capital (World Bank 2018). Approximately 40% of the population is unemployed, 60% of women are illiterate [20]. Cancer is predicted to be increasingly important cause of morbidity and mortality in few decades. The estimated incidence of 12.7 million new cases will rises to 21.4 million by 2030. In a survey of 117 cancer patients in Dhaka, 81% had ovarian cancer. The annual mortality rate per 100000 people from ovarian cancer in Bangladesh has increased by 40.3% since 1990, an average of 1.8% a year [21]. OC is a killer of women in high-income countries also. For instance, in 2015 in the United States, a 66% death rate is predicted with an estimated 21,290 new cases of OC and an anticipated 14,080 deaths [22]. Conversely, in low-income countries, breast and cervical cancer are the leading causes of cancer-related deaths of women [1]. The aim of the study was to find the risk factors for ovarian cancer among the postmenopausal women in Bangladesh perspective so that effective preventive measures can be undertaken.

METHODS

The case-control study was carried out in NIRCH, Mohakhali, Dhaka, Bangladesh from July 2016 to June 2017 to find out the risk factors of OC among the postmenopausal women. A total 154 respondents, out of them 77 patients were included as case and another 77 healthy persons were

included as controls were selected conveniently as sample in the study. Cases were the postmenopausal female patients with histologically confirmed ovarian cancer attending department of medical oncology, NICRH, Dhaka. Controls were the postmenopausal healthy female attendants of concerned patients or other patients without OC present during the time of data collection. Relevant data were collected by face-to-face interview using pre tested semi-structured questionnaire. Before starting data collection, institutional permission from concerned authority of NICRH was taken. A written informed consent was taken from each of the respondents, in maintaining full autonomy of the participants. After collection, data were checked, verified, coded and edited. Data processing and analysis ware done using SPSS.

RESULTS

The study showed the mean age of case and control group were 60.06(±7.00) and 59.89(±6.96) years respectively. The highest number of the respondents were illiterate. Majority came from rural area and had no personal monthly income. No significant difference($p>0.05$) was found between two groups (Table-1).

Table-1: Distribution of respondents by Socio-demographic characteristics of respondents

Characteristics	**Case (n-77)**		**Control (n-77)**		**P value**
	Frequency	**Percentage**	**Frequency**	**Percentage**	
Age group in years	**n**	**%**	**n**	**%**	
50-59	31	40.3		42.9	
60-69	41	53.2	37	48.0	
≥70	5	6.5	7	9.1	
Mean ± SD	**60.06±7.00 years**		**59.89±6.96 years**		**0.88**
Education					
Illiterate	66	85.7	59	76.6	
Primary	7	9.1	13	16.9	0.495
Secondary	2	2.6	3	3.9	
> Secondary	2	2.6	2	2.6	
Resident					
Rural	61	79.2	67	87.0	
Urban	16	20.8	10	13.0	
Income – Monthly in Taka					
No income	51	66.2	59	76.6	
5000-10000	22	28.6	12	15.6	0.140
>10000	4	5.2	6	7.8	
5000-10000	10	13.0	19	24.7	
10001-15000	48	62.3	37	48.1	0.115
>15000	19	24.7	21	27.3	

The study showed that the difference was not statistically significant ($p>0.05$) between two groups in dietary habit. It was statistically significant ($p<0.05$) between two groups in BMI. The difference was statistically significant ($p<0.05$) between two group on basis of physical activity (Table-2).

Table-2: Distribution of respondents by dietary habit, body mass index and physical activity

Characteristics	**Case (n-77)**		**Control (n-77)**		**X^2**	**P value**
	n	**%**	**n**	**%**		
Dietary habit						
High fiber diet	64	83.1	60	77.9	0.662	0.415^{ns}
Low fiber diet	13	16.9	17	22.1		

Body Mass Index (kg/m^2)						
<25	15	19.5	26	33.8	4.022	**0.044^s**
≥25	62	80.5	51	66.2		
Physical activity						
Sedentary	31	40.3	10	13.0	7.166	**0.001^s**
Moderate	24	31.2	16	20.8		
Hard worker	22	28.5	51	66.2		

The mean age of menarche between two groups was statistically significant (p<0.05). Mean age of menopause in case and in control groups respectively 51.54±2.39 and 49.61±1.29 years. The difference was statistically significant (p<0.05) between two groups (Table-3).

Table-3: Distribution of respondents by age of menarche and menopause (n=154, Case-77 & Control-77)

Characteristics	Case (n-77)		Control (n-77)		X^2	P value
	n	%	n	%		
Age of menarche						
10-12	48	62.3	32	41.6	10.81	0.001^s
13-15	29	37.7	45	58.4		
Mean (±SD)	**12.02±1.19 years**		**12.87±1.30 years**			
Age of menopause						
45-50	33	42.9	59	76.6	38.75	0.001^s
51-55	44	57.1	18	23.4		
Mean (±SD)	**51.54±2.39 years**		**49.61±1.29 years**			

The difference between two groups was statistically significant (p<0.05) on basis of gestational age. The difference was not statistically significant (p>0.05) between two groups in breast feeding (Table-4).

Table 4: Distribution of respondents by gestational age, breast feeding history of child

Characteristics	Case (n-67)		Control (n-74)		X^2	P value
	n	%	n	%		
Gestational age						
Early term	33	49.3	7	9.5	27.402	0.001^s
Full term	34	50.7	67	90.5		
Breast feeding history						
Yes	55	82.1	64	86.5	0.516	0.472^{ns}
No	12	17.9	10	13.5		

The difference was not statistically significant (p>0.05) between two groups of taking OCP. No significant (p<0.05) difference was noted regarding post-menopausal HRT between two groups. Significantly more respondents 6.5% in case group had personal H/O breast cancer than control group (0.0%). Significant difference was noted regarding positive family history of breast and ovarian cancer in these two groups (Table-5).

Table-5: Distribution of respondents by use of OCP, personal and family history of breast and ovarian cancer

Characteristics	Case (n-77)		Control (n-77)		X^2	P value
	n	%	n	%		
Use of OCP						
Yes	13	16.9	21	27.3	2.416	0.120^{ns}
No	64	83.1	56	72.7		
Personal history						
H/O post-menopausal HRT						

Yes	3	3.9	0	0.0	3.060	0.080[ns]
No	74	96.1	77	100		
Personal H/O breast cancer						
Yes	5	6.5	0	0.0	5.168	0.023[s]
No	72	93.5	77	100		
Family history of breast and ovarian cancer						
Positive	13	16.9	2	2.6	8.937	0.002[s]
Negative	64	83.1	75	97.4		
Relation with the respondents if family history positive						
Mother	11	84.6	2	100.0		
Sister	2	15.4	0	0.0		

Sedentary activity was associated with increased risk of ovarian cancer. This was also true for increased BMI (≥25 kg/m^2), early age of menarche (≤12 years), late age of menopause (>51 years), nulli para and early term pregnancy. Family H/O breast or ovarian cancer also significantly associated with development of ovarian cancer (Table-6).

Table-6: Binary logistic regression analysis of risk for ovarian cancer

Risk factors of ovarian cancer	Odds ratio (OR)	95% CI		P value
		Lower	Upper	
Dietary habit (Low fiber diet)	1.436	0.526	3.917	0.480[ns]
Sedentary worker	1.507	2.018	10.105	0.001[s]
High body mass index (≥25 kg/m^2)	2.107	1.010	4.397	0.047[s]
Early age of menarche (≤12 years)	2.328	1.219	4.443	0.010[s]
Late age of menopause (>51 years)	2.497	1.205	5.174	0.014[s]
Nullipara	1.303	1.009	13.946	0.048[s]
Early term pregnancy	9.290	3.724	23.173	0.001[s]
No child breast feeding	1.342	0.489	3.684	0.568[ns]
Non user of OCP	2.001	0.751	5.329	0.165[ns]
History of tubal ligation	0.563	0.237	1.337	0.193[ns]
History of hysterectomy	0.617	0.236	1.615	0.326[ns]
Family H/O breast or ovarian cancer	7.516	1.634	34.564	0.010[s]

DISCUSSION

The mean age of case was 60.06±7.00 years and control were 59.89±6.96) years. A study conducted in 2016 observed that mean age of the case was 48.31±2.28) years and control was 48.03±2.38) years. There was no age difference between the cases and the controls (t=0.84, p=0.934) reflecting a successful age frequency matching [23]. In present study, majority respondents were illiterate in both groups, which was 85.7% in case group and 76.6% in control group.

In the study, in both groups' majority respondents taken high fiber diet, 83.1% in case and 77.9% in control group. In similar study by Shanmughapriya *et. al*., in 2016 vegetarians were found 2.7% in case group and 14.9% in control group. No vegetarians were 97.3% in case and 85.1% in control group [23]. In current study, sedentary worker was found 40.3% in case and 13.0% in control group. Moderate worker was 31.2% in case and 20.8% in control group. Hard worker was 28.5% and 66.2% in case and control group respectively. Similar results were observed in the Iowa women's health study with highest category of physical activity had a two-fold increase in risk [25]. Recent studies conducted to understand the moderate to vigorous physical activity and leisure time sitting in relation to ovarian cancer risk, revealed no association between physical activity and ovarian cancer, whereas prolonged sitting was associated with higher risk [26-27].

Majority respondents had BMI ≥25 kg/m^2 in both groups, which was 80.5% in case and 66.2% in control group. In another study showed that body mass index <25 kg/m^2 was found 39.0% in case and 37.0% in control group. BMI 25-29.9 kg/m^2 was 29.0% and 33.0% in case and control group respectively. BMI ≥ 30 kg/m^2 was 32.0% in case and 29.0% in control group [24]. Regarding age of

menarche, mean age of menarche 12.02±1.19 years and 12.87±1.30 years in case and control group respectively. Study conducted by Shanmughapriya *et. al.,* in 2016 reported that age of menarche ≤12 years was found 43.2% in case and 5.4% in control group. Age of menarche 13-15 years was 45.9% in case and 62.2% in control group. Age of menarche 15-17 years was 10.8% and 29.7% in case and control group respectively. The difference was statistically significant ($p<0.05$) between the groups[23]. Similar observation was found in another study, they showed that the majority patients age of 12-13 years in both groups, 53.0% in case group and 56.0% in control group [24]. In the study, mean age of menopause in case and in control groups respectively 51.54±2.39 and 49.61±1.29. Similar study was done in 2016 showed the age of menopause 45-50 was found 30.4% in case and 69.6% in control group. Age of menopause 51-55 was 69.6% and 30.4% in case and control group respectively [23]. Another study that the majority patients age of menopause were 50-54 years in both groups, 45.0% in case group and 43.0% in control group [24].

Nullipara was found 13.0% in case and 3.9% in control group. Primipara was 18.2% and 5.2% in case and control group respectively. Multipara was 68.8% in case and 90.9% in control group. Shanmughapriya *et. al.,* (2016) study found that nullipara was found 9.1% in case group and 2.9% in control group [23]. Parity 1-2 was 15.2% in case and 42.9% in control group. The difference was not statistically significant ($p>0.05$) between two groups. In both groups majority of the respondents had first child birth during 21-25 years, which was 49.3% in case and 55.4% in control group. Case-control studies with hospital controls have reported elevated risk with late age at first birth (>30 years of age) [28-29]. Use of oral contraceptive pill (OCP) was found 16.9% in case and 27.3% in control. Shanmughapriya *et. al.,* (2016) observed that use of contraceptive was found 12.1% in case group and 17.1% in control group [23]. The difference was not statistically significant ($p>0.05$) between the groups. Moorman et al. (2008) study showed that the use of OCP was found 60.0% in case and 61.0% in control group [24]. The difference was not statistically significant ($p>0.05$) between two groups. In present study, post-menopausal HRT was found 3.9% in case group and personal history of breast cancer was found 6.5% in case group. Personal history of breast cancer was statistically significant ($p<0.05$) between two groups. HRT reduces the secretion of gonadotropins and should therefore decrease risk, but the reduced levels are still higher than pre-menopausal women [30]. Conversely, postmenopausal HRT may enhance estrogen-induced proliferation of ovarian cells and therefore increase risk. In current study, positive family history of breast and ovarian cancer was found 16.9% in case and 2.6% in control group. Moorman et al. (2008) study revealed that family history of breast or ovarian cancer was found 15.0% in case and 10.0% in control group [24].

In binary logistic regression analysis, sedentary activity ($p=0.001$), high (≥25 kg/m^2) body mass index ($p=0.047$), early age (≤12 years) of menarche ($p=0.010$), late age (>51 years) of menopause ($p=0.014$), nulli para ($p=0.048$), early term pregnancy ($p=0.001$) and family history breast or ovarian cancer ($p=0.010$) were significantly associated with the development of ovarian cancer. A meta-analysis estimated a nearly 20% lower risk for the most active women compared to the least active (pooled relative risk=0.81, 95% CI: 0.72–0.92) [17]. A meta-analysis of 28 population studies reported an increased risk of OC for overweight women (BMI of 25–29.9 kg/m^2) and obese women (BMI ≥ 30 kg/m^2) compared with normal weight (BMI of 18.5–24.9 kg/m^2), pooled RR=1.2 and 1.3, respectively [31]. Although a meta-analysis yielded an overall inverse association with age at menarche (RR=0.85, 95% CI: 0.75–0.97) [32]. Data on age at natural menopause and OC risk are also inconsistent. Case-control studies have reported odds ratios ranging from 1.4 to 4.6 in the highest category of age at menopause [33,34]. Indeed, parous women have a 30%-60% lower risk than nulliparous women [9,35] and each additional full-term pregnancy lowers risk by approximately 15% [28-29]. Studies in African American (Moorman et al. 2016) and Asian (Gay et al. 2015) populations have yielded similar results [24,36]. A recent meta-analysis indicates a significant protective effect (summary RR=0.68, 95% CI: 0.61–0.76) for breastfeeding that increased with longer duration (summary RR=0.85, 0.73, and 0.64 for <6 months, 6–12 months, and >12 months of total breastfeeding duration [37].

CONCLUSION

Ovarian cancer observed more in older age group (≥60 years) among sedentary worker with high body mass index (≥25 kg/m^2). Early age of menarche (≤12 years), late menopause (>50 years), never having given birth to a child in life time, early term of pregnancy and family history of breast and ovarian cancer were significantly associated with ovarian cancer. For identification of risk factors and

to enhance prevention, knowledge and awareness on risk factors regarding ovarian cancer must be raised at the community level.

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