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RISK FACTORS AMONG PATIENTS WITH OVARIAN CANCER ATTENDING ONCOLOGY - HEMATOLOGY CENTER IN BASRAH CITY

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Abstract

Worldwide, approximately 225,500 ovarian cancers are diagnosed annually. The leading cause of gynecological cancer death (140,200 worldwide annually) is the ovarian cancer, which accounts for more deaths than all the other gynecological cancers combined. The ovarian cancer is the fourteenth commonest cancer among population in Basrah city in Iraq.

This is a case control study carried out in the Basrah oncology – hematology center and primary health care centers in Basrah city. The study include 103 cases of ovarian cancer and 206 control.

We found that more than half of case of ovarian cancer aged 50 years and above. History of insulin treatment is a risk factor for ovarian cancer (OR more than one) with significant statistical association. Hysterectomy and tubal ligation are protective against ovarian cancer .

There are many risk factors of ovarian cancer some of these are modifiable while the others are not modifiable. Hysterectomy and tubal ligation considered as protective factors.

Keywords: Patient,cancer,oncology,basrah.

Introduction

The ovarian cancer is a malignant proliferation of ovarian cells of one or both ovaries, 80% of ovarian malignancies are epithelial. Endometrioid and serous cancers are the commonest forms of epithelial type, mucinous or clear cell are about 5% of it. Worldwide, approximately 225,500 ovarian cancers are diagnosed annually. The leading cause of gynecological cancer death (140,200 worldwide annually) is the ovarian cancer, which accounts for more deaths than all the other gynecological cancers combined [1]. Ovarian cancer is also common in western countries. For example it is the fifth commonest cancer in women, with about 6000 cases diagnosed and over 4000 women dying of the disease each year in the UK. Incidence slowly rising. The majority of cases occur over the age of 55 years, with the peak in the 65–75years age group [2].

The ovarian cancer is the sixth commonest cancer among female in Basrah, and it is the fourteenth commonest cancer among population in Basrah city in Iraq [3].

Regarding the risk factors of ovarian cancer, a number of factors are implicated including advancing age particularly beyond the age of 50 years [1,4], Greater adult attained height [5,6] high body mass index (BMI) [5,7], infertility [4,8] , hormonal factors [9], family history [10,11], chronic co-morbidity like diabetes mellitus [12,13], tobacco smoking [7] and Nulliparity [10]. Factors which might have protective effect against ovarian cancer include the use of oral combined contraceptives [1,14], higher parity [10] and tubal ligation [15].

Aim of study

The present study was planned to identify the risk factors among patients with ovarian cancer attending Basrah oncology- hematology center and comparing them with the risk factors among patients in other population.

Patients & Methods

The present study is a case control study designed to study the association between ovarian cancer and selected risk factors. The study was carried out in Basrah Governorate over a period of six months, started from the 1st of February 2016 to the 30th of July 2016.

Cases were women with a histologically diagnosed ovarian cancer who were attending The On-

cology Center In Basrah during the studied period. The study included 103 cases identified during the study period. The study was approved by the Health Research Committee in Basrah Directorate General.

Data on both cases and controls were collected through the use of a special questionnaire form designed for the purpose of the study. The questionnaire covered socio-demographic characters, medical and surgical history ,reproductive history , family history of ovarian cancer or other types of cancer, use oral combined pills or progesterone only pills, history of infertility and it's treatment, and history of smoking. .

Statistical analysis of the data was conducted by computer, using SPSS (Statistical Package of Social Sciences), version 19, using Chi squared test. P values of less than 0.05 were considered significant association. The confidence intervals (CI) of the odds ratio(OR) calculated by using Woolf's method (OR=adlbc) [16].

Results

Age: Both groups have similar age distribution as shown in Table 1.This reflects the achievement of the matching process of cases to controls. Just under two thirds of the cases (64.1%) and the controls (64.6%) were from Basrah city. Most of the cases and controls were aged 50 years and above (53.4%). The majority were housewives (79.6% and 69.9% respectively) and of low level of education being illiterate or have less than primary level education in (33%) of the cases and 1(7.5%) of the controls .

Table 1: Distribution of cases and controls according to age

Age in years	Cases		Control	
	No.	%	No.	%
<20	1	1.0	0	0
20-29	4	3.9	10	4.9
30-39	18	17.5	37	18
40-49	25	24.3	49	23.8
50-59	24	23.3	51	24.8
60 and above	31	30.1	59	28.6
Total	103	100.0	206	100.0

Medical/surgical risk factors: Only the use of insulin as treatment for diabetes mellitus was significantly associated with the risk of being a case of ovarian tumour. Diabetes itself had an association but its statistically not significant, history of tubal ligation , hysterectomy and appendectomy had a protective effect and also the association was statistically not significant.

Reproductive history risk factors; more than half of cases were menstruated at the age 11 years and more and there was a relationship between age at menarche and ovarian cancer but it was statistically not significant. The risk of ovarian cancer was higher among those who were reached menopause at age 50 and above than those who reached it before and the association was statistically not significant. Most of cases and control had at least one child and most of them delivered the first child before the age of 35.

Other risk factors; family history of cancer whether ovarian ,breast or any other cancer in the first degree relative was considered a risk factor for ovarian cancer with OR more than one. Regarding hormonal therapy we had (46.6 %) and (56.5%) of cases and control were used combined oral pills but the use of pills was irregular and mostly for a period less than five years. we had only (3.9 %) of cases who used progesterone only pills and also the use of pills was not regular and for a period not exceed one year. No any cases in this study used androgen. There was a positive association between infertility and treatment with ovarian cancer and the association was statistically not significant. A significant association was found between history of smoking and ovarian cancer.

Table 2: Comparison of selected medical/surgical risk factors

Risk factor		Cases reported exposure		Controls reported exposure		OR	P Value
		No.	%	No.	%		
History of diabetes mellitus		28	27.2	41	19.9	1.5	> 0.05
Use of insulin as treatment for diabetes mellitus		18	64.3	14	34.1	3.47	< 0.05
History of gynecological surgery: History of tubal ligation		3	2.9	15	7.3	0.38	> 0.05
History of hysterectomy		1	0.9	10	4.9	0.192	> 0.05
History of other surgery	None	78	75.7	173	84	1	> 0.05
	Appendectomy	4	3.9	5	2.4	1.77	
	Others	21	20.4	28	13.6	1.66	
Total		103	100	206	100		

Table 2: Comparison of selected reproductive risk factors

Variable		Cases		Controls		OR	P Value
		No.	%	No.	%		
Age at menarche	< 11	28	27.2	48	23.3	1.84	NS P > 0.05
	11 and more	75	72.5	158	76.7	1	
Age at menopause	Not	54	52.4	100	48.5		NS P > 0.05
	< 40	1	1	1	0.5	0.5	
	40 - 44	2	1.9	1	0.5	0.25	
	45 - 49	13	12.6	26	12.6	1	
	50 and more	33	32	78	37.9	1.18	
Parity	Nulliparous	19	18.4	21	10.2	2.28	NS P > 0.05
	Any parity	84	81.6	185	89.8	1	
Age at first child birth	Nulliparous	19	18.4	21	10.2	1.8	NS P > 0.05
	< 35	80	77.7	171	83	1	
	≥ 35	4	3.9	14	6.8	1.6	
Total		103		206			

Table 4: Other risk factors

Risk factor		Cases with the risk factor		Controls with the risk factor		OR	Confidence Interval (CI)
		No.	%	No.	%		
Family history *	Ovarian cancer in first degree relative	6	5.8	11	5.3	1.3	0.119-14.07
	Breast cancer in first degree relative	21	20.4	30	14.6	1.7	0.399-7.23
	Other cancers in first degree relative	15	14.6	15	7.3	2.5	0.416-14.4
	Negative history in first degree relative	61	59.2	150	72.8	1	----
Use of oral contraceptive drugs **		48	46.6	116	56.3	1.47	0.92-2.37
Use of progesterone only pills +		4	3.9	11	5.3	1.396	0.43-4.49
Use of androgens ++		0	0	8	3.9		
History of infertility and treatment #		16	15.5	24	11.7	1.4	0.29-6.6
History of cigarette smoking ##	Active	12	11.7	8	3.9	6.2	0.61-62.68
	Passive	69	67	107	51.9	1.7	0.5-6.26

* $\chi 2=7.049$	d.f=3	p>0.05	** $\chi 2=0.315$	d.f=1	p>0.05
+ $\chi 2=0.315$	d.f=1	p>0.05	++ $\chi 2=4.1$	d.f=1	p>0.05
# X2=2.98	d.f=2	p>0.05	## $\chi 2$ 9.96	d.f=1	p<0.05

Discussion

Worldwide, ovarian cancers are the 8th most common cancers among women, with 224,747 incident cases [17,18]. Of all female cancers cases ,ovarian cancer accounts for 4% [19].

Regarding the age of participants , more than half of cases aged 50 years and above. This result was comparable to other study carried out in Iran [20]. The important aspects in the past medical history which was related to the risk of ovarian cancer include history of diabetes mellitus and the type of its treatment. This study was found that women with history of diabetes mellitus were more likely to develop ovarian cancer than those without such history, as well as those on insulin were more likely to develop ovarian cancer than those on oral hypoglycemic agents .These results agreed with other studies in many countries such as Taiwan and UK in 2012, 2013 and 2015 [21, 22, 23] these studies showed that the ovarian cancer risk was higher in diabetics compared to non-diabetics and the risk among diabetics on insulin higher than those on hypoglycemic agents.

In the present study, it was found that history of tubal ligation and history of hysterectomy were a protective factors of ovarian cancer.

In respect to history of tubal ligation, many studies were carried out in USA and UK in 2012 and 2013 [24,25] showed that tubal ligation lowering the risk with variation according to ovarian cancer subtypes.

Regarding history of hysterectomy, recently hysterectomy without oophorectomy to decrease uses of hormonal replacement therapy, two studies were carried out in Australia and UK in 2012, and 2013 [25,26] showed that hysterectomy lowering the risk may be due to changes in average age at hysterectomy, surgical technique or uses of hormonal replacement therapy post hysterectomy.

In this study we had only four cases with history of appendectomy. One study which was carried out in Turkey in 2014 [27], found that the epithelial ovarian cancer, stage, grade, presence of ascitis, right-sided location and large tumor size had importance for estimation the risk of appendicular

metastasis ,on the other hand another study in UK in 2014 [28] showed that prior appendectomy was not protective against development of malignant or borderline ovarian cancer. In our study more than half of cases were menstruated at age of 11 years and above. Studies were carried out in Korea and Australia in 2005 and 2016 [29,30] showed that pubertal levels of reproductive hormones influence ovarian cancer risk in younger women, another study which was carried out in US in 2016 [31], found that age at menarche may be independently associated with risk of gynecological cancers beyond the contribution of the individual risk factors. A study which was carried out in Poland in 2012, found that females who began menstruating by the age of 11 years, the risk of ovarian cancer was higher than among those in whom the first period occurred at the age of over 13 years [32]. This study, showed that menopause at the age of 50 and above was considered a risk factor of ovarian cancer. Studies carried out in Korea and USA in 2016 [29,31] showed that longer reproductive spans were associated with an increased risk of breast and ovarian cancer [32]. Our study found that most of the cases were delivered the first child at the age less than 35 years and we had only four cases who delivered the first child at age more than 35 years. A study carried out in Taiwan found an increasing risk of ovarian cancer was seen with increasing age at first birth [33]. Regarding the parity, in the present study most of cases were multipara. Nulliparous considered a risk factors of ovarian cancer. Another study in Egypt showed that the of ovarian cancer was increase with increase the number of ovarian cycle and similarly high risk was also reported for increase number of pregnancy [34].

The risk increase in women with a first-degree relative with ovarian cancer and the risk increase when two first-degree relatives are affected. About 5–10% of all epithelial ovarian cancer results from hereditary predisposition. Women under 40 years of age with a history of breast cancer had sevenfold increase in risk of future ovarian cancer if they had a first-degree relative with a history of breast, ovarian or both cancers [8]. Higher risk in women whose sibling had other types of cancer [11]. Our study found that a positive family history of cancer in first degree relatives had a positive association with ovarian cancer but the association was statistically not significant. Another study which was carried out in UK in 2011 [11], also showed that family history of cancer increase the risk of ovarian cancer. The uses of oral combined contraceptives decrease the risk by approximately 50% after 5 years of use. The protection increases with duration of use to 10 years and appears to last for approximately 15 years after discontinuation of use [4]. In this study, more than half of cases had never used of oral contraceptive pills, and those who used the pills used them irregularly. One study which was done in UK 2010 [35], showed that oral contraceptive pills considered as a protective against ovarian cancer. This study was found that the percentage of female patients with history of never use of progesterone was high and also those who used progesterone used by irregular manner ,other studies which were done in 2016 [36, 37] showed that progesterone was a protective factor for ovarian cancer. Also in our study there was no any female patient who had a history of using androgen. A study which was done in 2016 showed that androgen signaling contributes to the development of ovarian cancer [38]. In present study, it was found an association between infertility and its treatment with the risk of ovarian cancer, comparable to a study carried out in Egypt in 2013 [39], which showed that infertility and its treatment associated with gynecological cancer but it's difficult to differentiate between the effect of each one. Regarding smoking both active and passive smoking were associated with increased risk of ovarian cancer and the association was statistically significant. This result is comparable to other studies which were carried out in Australia and Denmark in 2006 and 2013 [40, 41].

Conclusion

In conclusion we found that there are many factors which are associated with increased risk of ovarian cancer such as diabetes mellitus and its treatment, early menarche and late menopause, null parity, positive family history of cancers in first degree relatives , infertility and its treatment ,active and passive smooking,while tubal ligation and hysterectomy have protective effect against ovarian cancer . Some of these are modifiable and other non-modifiable, so that public health education regarding risk factor of ovarian cancer should be discussed.

References

1. Richard P, Shujuan L, Bolin L, Sebastien G, Sigurd L, Eric L, et al. Gynecological cancers.In: David J, Kerr Daniel G , Haller Cornelis J, Michael B. Oxford Textbook of Oncology .3rd ed .Bell & Bain Ltd, Glasgow;2016:576-602.

2. Jim C, Donald B, Roy A, Miranda P, Gareth MS, Gynaecological cancer in Oxford Handbook of Oncology. Fourth edition. C&C Offset Printing Co. Ltd;2014:446-50.

3. Habib Os, Al-Diab JMA, Mohsin A, Elwe WM, Hassan JG, Al-Haroun SS ,et al. Experience and outcome of population - based cancer registration in Basrah- Southern Iraq in four years (2005 -2008). Asian Pacific Journal of Cancer prevention; 2010;11: 51-54.

4. Robert L , Pedro T , and David M .Neoplastic Diseases of the Ovary .In : Gretchen M. , Roger A. , David M. ,and Vern L. Comprehensive Gynecology .6th ed. Philadelphia, PA ; 2012 :731-770.

5. Aune D, Nvarro Rosenblatt DR, Chan DS, et al. Anthropometric Factors of Ovarian Cancer risk :A systematic review and non linear dose -responses meta- analysis of prospective studies . Int . J cancer 2015 Apr 15; 136(8):1888-98.

6. Ma X1, Beeghly-Fadiel A, Shu XO, Li H, Yang G, Gao YT, Zheng W. Anthropometric measures and epithelial ovarian cancer risk among Chinese women: results from the Shanghai Women's Health Study. Br J Cancer. 2013 Aug 6;109(3):751-5.

7. Beral V ,Hermon C, Peto R ,et al. Ovarian Cancer and Body size :individual participant met -analysis including 25 ,157 women with ovarian cancer from 47 epidemiological studies .PLOS Med 2012 ;9:(4).

8. Rushdan N, Eng Hseon T, and Jeffrey L. Cancer of Ovary . In : Rushdan N., Eng Hseon T., Jeffrey L.Gynecologic Cancer A Handbook for Students and Practitioner. Taylor & Francis Group ;2014:350-430.

9. Beral V, Million Women Study Collaborators. Bull D, et al. Ovarian Cancer and Hormone Replacement Therapy in Million Women Study .Lancet 2007;369(9574):1703-10.

10. Robert L , Pedro T , and David M .Neoplastic Diseases of the Ovary .In : Gretchen M. , Roger A. , David M. ,and Vern L. Comprehensive Gynecology .6th ed. Philadelphia, PA ; 2012 :731-770.

11. Sundquist J, Hemminki K, Branlt A, Incidence and Mortality in Epithelial Ovarian Cancer by Family history of any cancer .Cancer 2011;117(17):3972-80.

12. Lee JY, Joen I, Kim JW, et al. Diabetes mellitus and Ovarian Cancer risk :systematic review and meta-analysis of observational studies . Int J Gynecol Cancer 2013;23(3): 402-12.

13. Starup -Linde J, Karlstad O, Eriksen SA, et al. CARING (Cancer Risk and Insulin Analogues):The Association of Cancer Risk and Diabetes Mellitus with focus on Possible Determinants. A systematic Review and meta-analysis .Cur Drug Saf 2013 ;8(5): 296-332.

14. Robert C, Jr. Bast ,M. D. Kufe , M.D. Pollock, Raphael E,Donald W. Holland -Frei Cancer Medicine .6th ed. Hamilton (ON) : BC Decker :2011 .8.Robert L , Pedro T , and David M .Neoplastic Diseases of the Ovary .In : Gretchen M. , Roger A. , David M. ,and Vern L. Comprehensive Gynecology .6th ed. Philadelphia, PA ; 2012 :731-770.

15. Hawilesky LJ, Gierish JM, Moorman PG, et al. Oral Contraceptive use for the primary prevention of ovarian cancer. Evid Rep Technol Assss (Full Rep) ,2013;(212): 1-514.

16. Niazi AD. Data analysis ,Confidence Interval of Odds ratio .Statistical Analysis in medical researches ,2nd ed. 2004;86-88.

17. Ferlay J ,Pakin Dm, Curado MP, Bray F, Edwards B, Shin HR, et al. Cancer incidence and mortality worldwide . GLOBOCAN 2008;(1.2).IARC Cancer Base

18 . Merritt MA, Cramer DW. Molecular pathogenesis of endometrial and ovarian cancer .Cancer Biomark 2010;9:287-305.

19. Parkin DM, Bray F, Ferlay J, Pisani p. Global cancer statistic ,2002.CA:Cancer J Clin 2005;55:74-108.

20. Momtahen S1, Kadivar M, Kazzazi AS, Gholipour F. Assessment of gynecologic malignancies: a multi-center study in Tehran (1995-2005). Indian J Cancer. 2009 Jul-Sep;46(3):226-30.

21. Gapstur SM, Patel AV, Diver WR, et al. Type II Diabetes mellitus and the Incidence of epithelial Ovarian Cancer in cancer prevention study-II nutrition cohort .Cancer Epidemiol Biomarkers Prev 2012; 21(11):2000-5.

22. Dilokthornsakul P, Chiayakuanapruk N, Termrungruanglert W, et al. The Effect of Metformin on Ovarian Cancer : A systematic Review .Int J Gynecol Cancer, 2013 Nov;23(9):1544-51.

23. Hsu PC1, Lin WH, Kuo TH, Lee HM, Kuo C, Li CY. A Population-Based Cohort Study of All-Cause and Site-Specific Cancer Incidence Among Patients With Type 1 Diabetes Mellitus in Taiwan. J Epidemiol. 2015;25(9):567-73.

24. Sieh W1, Salvador S, McGuire V, Weber RP, Terry KL, Rossing MA, et al .Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group, Goodman MT, Lurie G, Chang-Claude J. Tubal ligation and risk of ovarian cancer

subtypes: a pooled analysis of case-control studies. . Int J Epidemiol. 2013 Apr;42(2):579-89.
25. Rice MS, Murphy MA,Tweroger SS .Tubal ligation ,Hysterectomy and ovarian cancer: Ameta-analysis. JOvarian Res .2012;5(1):13.
26. Jordan SJ1, Nagle CM, Coory MD, Maresco D, Protani MM, Pandeya NA, Balasubramaniam KD, Webb PM. Has the association between hysterectomy and ovarian cancer changed over time? A systematic review and meta-analysis. Eur J Cancer. 2013 Nov;49(17):3638-47
27. Kokanali MK1, Guzel AI, Erkilinc S, Tokmak A, Topcu HO, Gungor T. Risk factors for appendiceal metastasis with epithelial ovarian cancer. . Asian Pac J Cancer Prev. 2014;15(6):2689-92.
28. Elias KM, Labidi-Galy SI, Vitonis AF, Hornick JL, Doyle LA, Hirsch MS, et al. Prior appendectomy does not protect against subsequent development of malignant or borderline mucinous ovarian neoplasms. Gynecol Oncol. 2014 Feb;132(2):328-33.
29. Jung KJ, Park C, Yun YD, Jee SH. Duration of ovarian hormone exposure and gynecological cancer risk in Korean women: the Korean Heart Study. Cancer Epidemiol. 2016 Apr;41:1-7.
30. Jordan SJ1, Webb PM, Green AC. Height, age at menarche, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):2045-8.
31. Yang HP, Murphy KR, Pfeiffer RM, George N, Garcia-Closas M, Lissowska J,et al. Lifetime Number of Ovulatory Cycles and Risks of Ovarian and Endometrial Cancer Among Postmenopausal Women. 2016 May 1;183(9):800-14.
32. Yang HP, Murphy KR, Pfeiffer RM, George N, Garcia-Closas M, Lissowska J,et al. Lifetime Number of Ovulatory Cycles and Risks of Ovarian and Endometrial Cancer Among Postmenopausal Women. 2016 May 1;183(9):800-14.
33. Yang CY1, Kuo HW, Chiu HF. Age at first birth, parity, and risk of death from ovarian cancer in Taiwan: a country of low incidence of ovarian cancer. Int J Gynecol Cancer. 2007 Jan-Feb;17(1):32-6.
34. El-Khwsky FS1, Maghraby HK, Rostom YA, Abd El-Rahman AH.Multivariate analysis of reproductive risk factors for ovarian cancer in Alexandria, Egypt. J Egypt Natl Canc Inst. 2006 Mar;18(1):30-4.
35 65. Parkin DM,. Cancer attribute to exposure to hormones in the UK in 2010.Br J Cancer. Dec.2011;105(s2):s42-s48.
36. Jeon SY, Hwang KA, Choi KC. Effect of steroid hormones, estrogen and progesterone, on epithelial mesenchymal transition in ovarian cancer development. J Steroid Biochem Mol Biol. 2016 Apr;158:1-8.
37. Lima MA, da Silva SV, Freitas VM . Progesterone acts via the progesterone receptor to induce adamts proteases in ovarian cancer cells. J Ovarian Res. 2016 Feb 25;9:9.
38. Zhu T, Yuan J, Xie Y, Li H, Wang Y. Association of androgen receptor CAG repeat polymorphism and risk of epithelial ovarian cancer. Gene. 2016 Jan 10;575(2 Pt 3): 743-6.
39. Sallam HN, Abdel-Bak M, Sallam NH. Does ovulation induction increase the risk of gynecological cancer. Facts Views Vis Obgyn. 2013;5(4):265-73.
40. Jordan SJ1, Whiteman DC, Purdie DM, Green AC, Webb PM. Does smoking increase risk of ovarian cancer? A systematic review. Gynecol Oncol. 2006 Dec;103(3):1122-9.
41. Faber MT1, Kjær SK, Dehlendorff C, Chang-Claude J, Andersen KK, Høgdall E, et al. Cigarette smoking and risk of ovarian cancer: a pooled analysis of 21 case-control studies Cancer Causes Control. 2013 May;24(5):989-1004.