Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

Analysis of Risk Factors of Epithelial Ovarian Cancer; Prevention & Diagnosis

Aiman Ashfaq[1], Tayyaba Shan[2], Nagina Zulfiqar[3], Syed Waqas Hassan[4], Bushra Gul[5*]

[1,2,4,5*]Department of Biosciences, Faculty of Basic Sciences, University of Wah.
[3]Department of Statistics, Faculty of Basic Sciences, University of Wah.
[2,5*]Department of Zoology, Faculty of Biological Sciences, Quaid e Azam University.
Corresponding Author Email: bushra.gul@uow.edu.pk

Abstract
To study the clinical heterogeneity of ovarian malignancy growth, what the job of*BRCA2*gene in human cell and how it is answerable to ovarian cancer. To study the hereditary qualities and subatomic and organic system include in the advancement of ovarian cancer, distinctive treatment and medical procedures that demonstrated advantageous in rewarding ovarian malignant growth and lessen its danger of reoccurrence. Data is collected from medical record of ovarian cancer patients fromPOF hospital between 1st Nov 2019 to 30th Jan 2020. Medical history of the patient was study in which her biopsy, hormonal, chemotherapy medication ultrasound of pelvic, CA125 blood test, TVUS, Transvaginal ultrasound, family history, imaging test, CT scan, laparoscopy report include. IBM SPSS statistic version 25 software is used to prepared result. Genetically, ovarian cancer is a heterogeneous and dynamic disease that presents several clinical and research challenges. The most common symptoms among ovarian cancer patients were GT tract symptoms in which pelvic mass, abdominal distension and ascites were most common. Most of the patient diagnosed at stage 3 and high level of CA125 is noticed in their blood test report. 40% of our patients under study suffer from serous ovarian cancer.60% of our patient treated with chemotherapy and 25% with medication. So, the purpose of our study is to provide relationship between lifestyle risk factors and epithelial cancer diagnosis.
Keywords: Ovarian cancer, risk factors, *BRCA2***,**lifestyle

Introduction

Our body is made up of cells which are the basics building blocks. Cancer is a disease of cell in which body cell divided uncontrolled and die in an unusual way due to which lymph called tumor formation took place (AIHW, Canberra, December 2017).Induction of proliferation of cells and mutations in DNA are the two broad terms for molecular trauma which causes cancer (Abbas *et al.,* 2021).Normally cell grow and divide but these cells cannot divide normally. There are two types of tumors. **Benign tumor** (If cell do not migrate to other areas of the body and confine in one area). **Malignant tumor** (Some cells migrate through blood stream or lymphatic system (lymph fluid) such cell is called cancerous cell(National Comprehensive Cancer Network US.,2017**).**Cancer is categorized into two types primary and secondary cancer. In **Primary cancer**, cancer advance within an organ and do not spread to adjacent tissues.**Secondary cancer or metastasis**, cancer grow and spread to surrounding areas and form tumors at new places. Both ovaries are present in the lower part of the abdomen and both side of the uterus. Ovaries are

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

composed of three types of tissue Epithelial, Germinal and Stromal cells. Cells form the outer layer of ovary is called epithelial cell. Germinal cells mature into egg and present inside the ovary. Stromal cells are supporting tissues. These cells produce two important hormone estrogen and progesterone (AIHW, Canberra, December 2017).The most lethal of all female reproductive cancers are ovarian cancer (Slatnik*et al*., 2015). It is also called silent killer; it is not identified even at advanced stages because indicationsare unclear and lack of definitive screening tools.(Jayson *et al.,* 2014). Even in70 % cases the symptoms are not clear even in stage 3 and 4. After 5-year survival rate for ovarian cancer is 47.4% (ChienIntJGynecolCancer.2018). Ovarian cancer does not begin in ovaries in most cases it starts from the fallopian tube (Mallen*et al*., 2018)**.** Under the age of 30 ovarian cancer risk are rare.Outcome of the disease is called prognosis (AIHW, Canberra, December 2017).Survival rate of women having ovarian cancer is directly related to the stage of disease at a time of diagnosis (Jayson *et al*., 2014). There are 90% chance of 5-year survival if women diagnosed at stage 1. Following were the three types of ovarian cancer. **Epithelial cancer** Outcome is influence by stage and grade of cancer. If the epithelial cancer is not spread outside of ovary (stage 1) it has good prognosis. Women with advanced cancer may respond very well but there are probabilities that cancer will return, and further treatment is required.**Germ cell and stromal cell tumors** treatment is successfully done.**Borderline tumors**have good prognosis (AIHW, Canberra, December 2017).Epithelial ovarian cancer is divided into 4 types serous, endometrioid, mucinous and clear cell.Epithelial ovarian cancer has 3 sites of origin ovarian, tubal and epithelial site in pelvis. There are 2 categories of epithelial ovarian cancer type 1 tumor and type 2 tumor. Type 1 tumor is less lethal than type 2 tumor. Main causes are continual ovarian cycles, inflammation, endometriosis. Endometriosis is a cause of 5% to 15 %of epithelial ovarian cancer.Type 2 tumor is more lethal than type 1 tumor (Slatnik& Duff, 2015). Unfortunately, it is not diagnosed early, and main causes of type 2 tumors are *BRCA* gene genetic mutation and p53 mutation and tumor suppressing gene.

Structure Of *BRCA* gene

On long arm of chromosome 13 (13q12.3) *BRCA* gene is located, and it composed of total 27 exon that encode a protein having 3,418 amino acid. PALB2 done interaction with the N-terminal domain of the *BRCA2*. 8 BRC repeats located in the central portion of the protein of *BRAC* gene it play an important role in binding to monomeric RAD51 (RAD51 binding domain: RAD51-B. BRCA2 binding to single-stranded DNA and poly (ADP-ribose) is promoted by the *BRCA2* DNA binding domain (DNA-BD). The TR2 domain interacts with RAD51 nucleo filaments on the C-terminal of *BRCA2* (Cannery*et al.,* 1984). RAD51-BD matches to the region that cover AA1003-2082 of *BRCA2* exon 11.

Mutations in *BRCA2* gene

BRCA2 is tumors suppressor gene involved in the maintenance of genome integrity by means of two main functions: DNA repair by homologous recombination and by Stabilization of replication forks under replication stress *BRCA2* interacts directly with RAD51 and promotes its specific recruitment to dbs. sites where recombination is initiated. The improved survival of ***BRCA1/ BRCA2*** germline mutation carriers, especially ***BRCA2*** carriers, compared with non-carriers. However, there is no clear explanation of why ***BRCA2***carriers fare better than *BRCA1* carriers. Genetic and functional studies of *BRCA2* revealed that mutations located in RAD51-BD impair the ability of ***BRCA2*** to recruit RAD51 (Cannery*et al.,* 1984).Mutations in the RAD51-

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

BD (exon 11) of the ***BRCA2*** gene impact progression-free survival (PFS), platinum-free interval (PFI), and overall survival (OS) in ovarian cancer patients. Ovarian cancer patients who were carriers of *BRCA**2*** germline mutation and were treated with DNA damage agent platinum showed prolonged survival. Not all ***BRCA2*** carriers are highly sensitive to DNA damage agents, and the response depends on the location of the mutation in the various functional domains of the protein. Estimates of the lifetime risk for ovarian cancer range from 16% to 60% for ***BRCA1/2*** mutation carriers. Among Ashkenazi Jewish women, in whom one of the three founder *BRCA* mutations has been found, lifetime ovarian cancer risks were 54% for ***BRCA1*** and 23% for ***BRCA2*** mutations. In support of this hypothesis, many (but not all) studies of the ovaries of ovarian cancer-prone individuals, i.e., women with a family history of ovarian cancer and/or a deleterious ***BRCA1*** *or* ***BRCA2*** mutation, have reported more changes in their surface epithelium than control ovaries. Additional hypotheses concerning steroid hormones and the retrograde transport of carcinogens through fallopian tubes may also contribute to ovarian cancer risk in certain circumstances and magnitude. However, gonadotropins may also stimulate an ovulation-like loss of the ovarian surface epithelial basement membrane. The loss of basement membrane may dramatically alter the biology of the epithelial cells in tissue organization and cell contact signaling.

Risk Factors

Due to nonspecific symptoms like abdominal bloating, abdominal pain and urinary frequency and changes in bowel habit women's do not seek medical care and ignore such symptoms. Ovarian cancer can occur in any women that have no notable risk factors(AmericanCancerSocietyCancerfactsandfigures2018).

Family history women risk of ovarian cancer increases if there is a history of breast and ovarian cancer is present within in family. If there is a mutation in a *BRCA 1* and *BRCA 2* and MMR gene risk of ovarian cancer increase to 1.6% to 40%,18% and 10 %(Tschernichovsky& Goodman 2017). If the women are a carrier of these mutation, there are 10% to 40% chances that she will get ovarian cancer by the age of 70. One of the autosomal dominant genetic disorders which is known as Lynch syndrome increases the risk of many types of cancer including colorectal and ovarian cancer. Ovulationalso increases risk of ovarian cancer. More ovulatory cycles more risks of ovarian cancer (Walker *et al*., 2015).Ovulations promote malignant ovarian tendencies because of pro inflammatory response of distal fallopian tubes **(**Mallen*et al*., 2018). There are many factors that decrease risks of ovarian cancer are pregnancy, breastfeeding, early menopause, early onset of menses and birth control use.Endometriosis is associated with epithelial ovarian cancer. Endometriosis that links to epithelial ovarian cancer develop in younger women and have better prognosis. There is no evidence that women chance of getting ovarian cancer decrease if we remove endometriosis lesions (SchenkenEndometriosis:pathogenesis). There are very few studies that shows what is the relationship between dietary fibers and ovarian cancer. Huang et al said ovarian cancer chances decreases if we increased intake of dietary fiber(Huang*et al.*, 2018). If women increase soy in her diet risk of epithelial ovarian cancer decrease.There will be high risk of developing ovarian cancer if there is a low level of Vitamin D in diet.There are certain ethnic group that have genetic risk of developing ovarian cancer is very high like Dutch, French Canadian, Jewish and Icelandic descent (Guo*et al.*, 2018).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

Prevention

To prevent ovarian cancer then educating women and health care providers about sign and symptoms, risk factors play a very important role. According to one of the study women in general population were unable to identify sign and symptoms of ovarian cancer and certain factors were associated wrongly with ovarian cancer. Only 40% women were slightly familiar with ovarian cancer sign and symptoms (Goldstein*et al*, 2015).

Teaching about ovarian cancer sign and symptoms and risk factors to general populations and to women's that may have a chance to develop cancer in near future increases health awareness this will also decrease the late diagnosis cases. **Interruption of ovulation**:40 %-50% ovarian cancer risk decreases due to oral contraceptive. Longer the use of oral contraceptive more the chances of getting ovarian cancer decreases. The women risk of getting ovarian cancer decreases by interruption ofovulation. Disruption of ovulation occur in many ways like removal of fallopian tube or ovaries, pregnancy, breastfeeding. If women become pregnant under the age of 25 risk of getting ovarian cancer also decreases.In one of the study it is mentioned that ovarian cancer chances decreases with use of aspirin (NCCN; ovarian cancer).While other studies reveal that there is no effect of aspirin and use of aspirin decreases the chances of ovarian cancer. Endometriosis produce inflammation that produce carcinogenesis, by using anti-inflammatory medication produce positive effect by decrease further tumor formation (Mallen*et al*., 2018).

Screening & Diagnosis

Ovarian cancer screening become very difficult because of nonspecific symptoms. Initially tumor marker CA125 (cancer antigen 125) used as a screening tool for ovarian cancer. But now CA125 marker is no more used as a screening tool because of lack of specificity and sensitivity. There is no effective screening tool for ovarian cancer, but combination of different tools is very effective. There are certain proteins produced by cancerous cell which is called tumor markers. The most common protein produced by cancerous cell is CA125.In patient suffering from cancer level of CA125 is very high but there are many reasons behind high level of CA125 like ovulation, menstruation, kidney disease and fibroid. It can be used: **At diagnosis;** If women are through menopause than CA125 test is more accurate for diagnosing ovarian cancer than in women's who have not. Initial ovarian cancer patient has normal ovarian CA125 level due to this combination of CA125 blood test and ultrasound is used. During treatment**,** If the cancerous cell produces CA125, the blood test is done to know how well the treatment is working. If the level of CA125 is decreasing means the treatment is working well but if the level is rising, then treatment is not working well (NCCN Guidelines, 2017). A **transvaginal sonography** is not specific for ovarian cancer if it is solely used but if it is combined with CA125 marker human epididymis protein 4 it became effective for ovarian cancer. **Core needle biopsy** play an important role in diagnosing ovarian cancer. In this treatment aspirated tissue is examined closer to discover malignancies.

Methodology

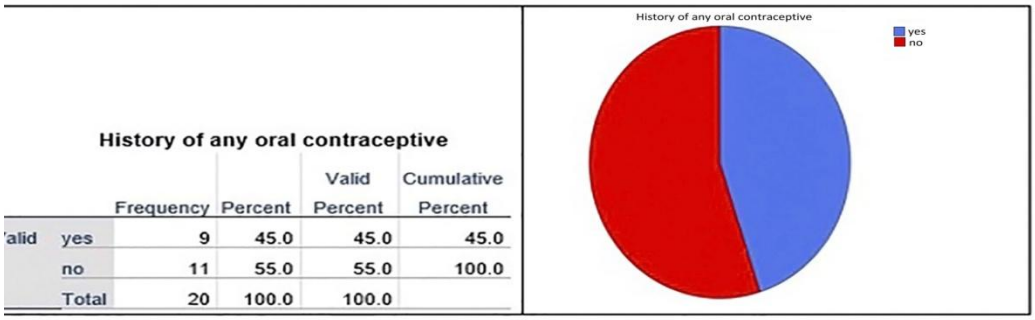
Data was collected from the patient who referred to medical oncology department of POF hospitalWahcantt, Pakistan. Information was collected between 1st Nov2019 to 30th Jan 2020. Eligibility criteria required for all the documentation related to ovarian cancer and ability of close relative and patient herself to provide information. In this analysis the patients that were suffering from any type of ovarian cancer whether initial or last stage and patients undergoing chemotherapy as well as the patient that were recovered from the ovarian cancer were included.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

Information was collected from the patient and their close relative during the interview.Medical history of the patient was studied in which her biopsy, hormonal, chemotherapy medication ultrasound of pelvic, CA125 blood test, Transvaginal ultrasound, family history, imaging test, CT scan, laparoscopy report included.

Results

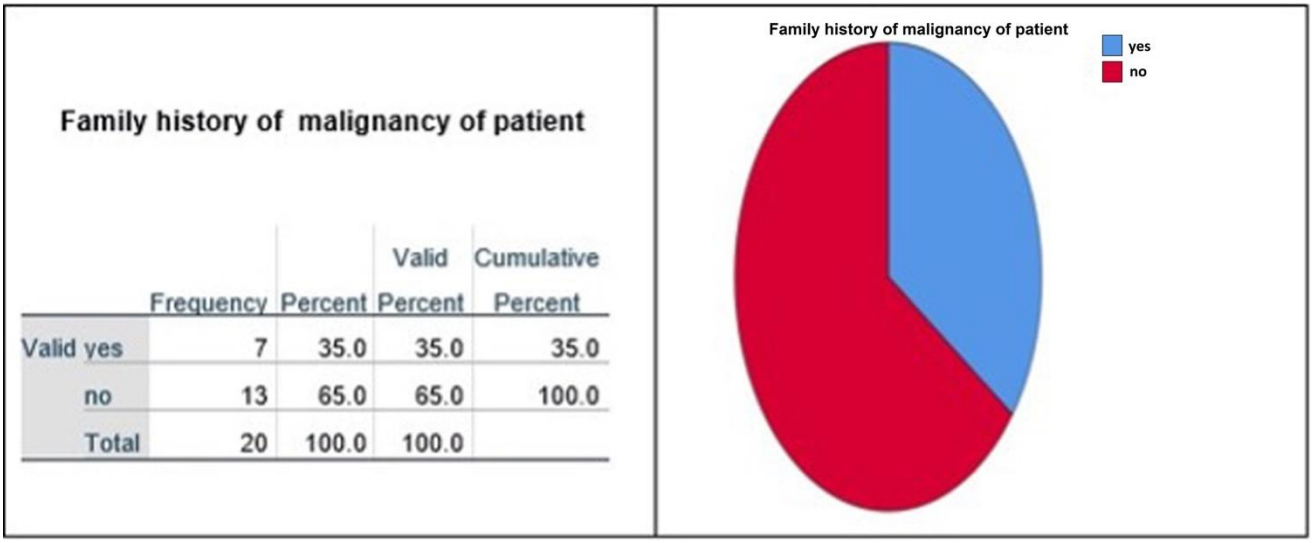
Mean ages of the women in our data is 60 and median was 59. Mean weight and height of the ovarian cancer patients in our data is 72.5 and 5.49. Mostly women belong to middle (40%) and low class (40%). 85% of women do not have any history of ovarian cancer.65 % of women have no family history of malignancy only 35 % of women have family history of any malignancy.80% of women do not have any personal history of any malignancy and only 20% person have personal malignancy history (Fig 2).10% of women said they have cyst in their uterus and 10 % said they have heavy vagina bleeding and 80 % said that there is no history of any gynecological problem (Figure 3).45% of patients were using oral contraceptives 50%(Fig 1). 15% of patients were using mineral water,while 45% said they use tap water and 40 % were using underground water.



History of any oral contraceptive

		Frequency	Percent	Valid Percent	Cumulative Percent
alid	yes	9	45.0	45.0	45.0
	no	11	55.0	55.0	100.0
	Total	20	100.0	100.0	

Figure 1. History Of Oral Contraceptives

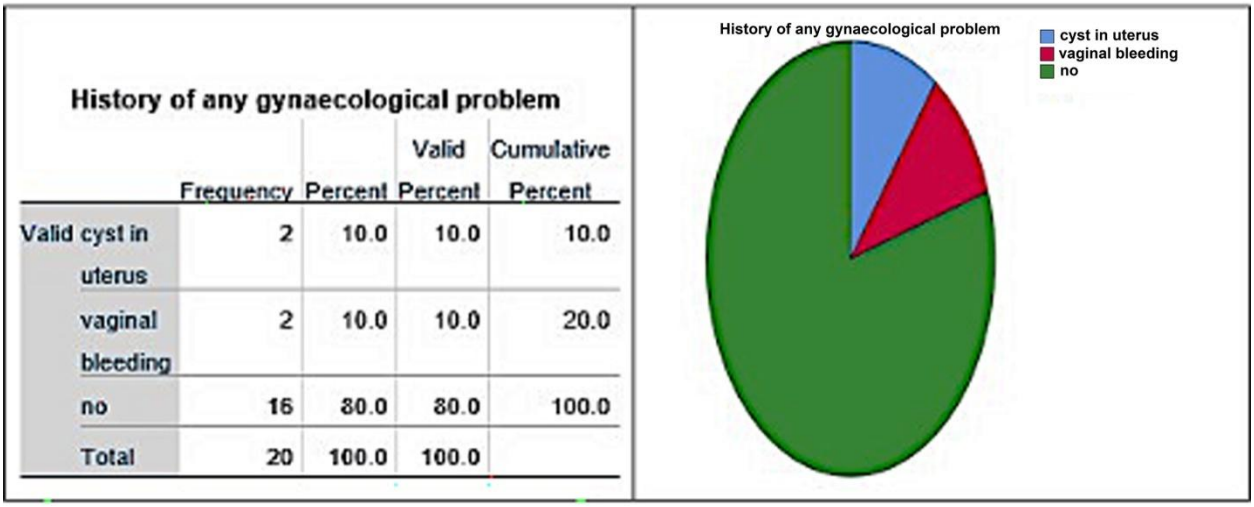


Family history of malignancy of patient

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	7	35.0	35.0	35.0
	no	13	65.0	65.0	100.0
	Total	20	100.0	100.0	

Figure 2: History of malignancy of patient

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

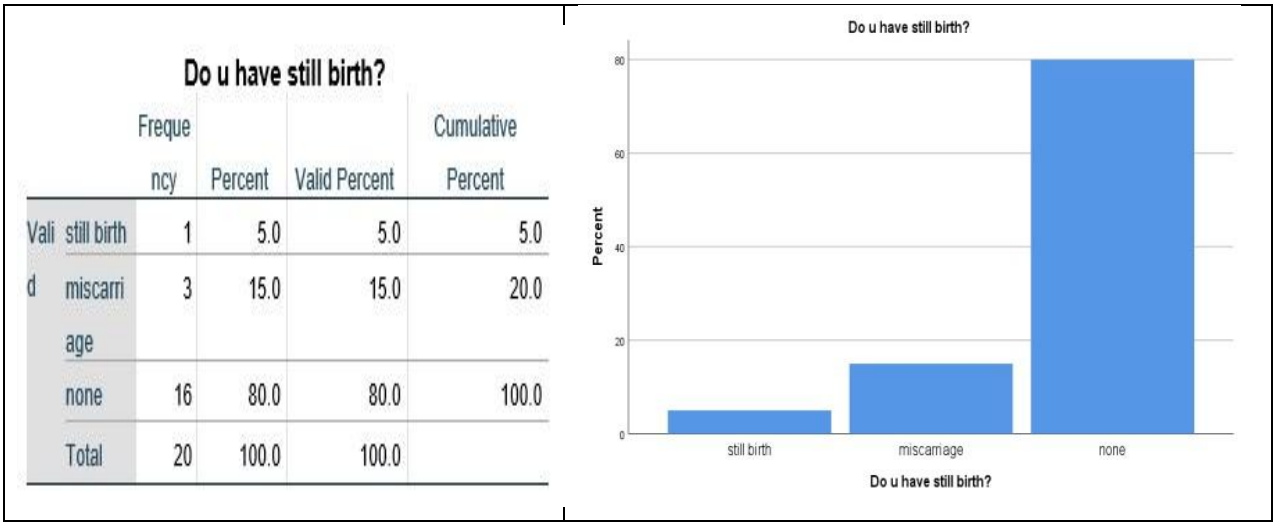


History of any gynaecological problem

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	cyst in uterus	2	10.0	10.0	10.0
	vaginal bleeding	2	10.0	10.0	20.0
	no	16	80.0	80.0	100.0
	Total	20	100.0	100.0	

Figure 3: History of Gynecological problem

5% of the women have still birth and 15% have miscarriage (Table 1).50% said their first menstrual cycle begin at 15-16 years and 25% said their menstrual cycle begins at 11-12 years. 40% women have their menopause at 48-50 year and 20% have their menopause at 57-60 (see table 3). 65% of the women have chemotherapy, 25% use medication and 10% use not any kind of treatment for ovarian cancer (see table 2). 35% of the women removed their uterus and 65% had not. 35 % of the women had their 1 child at 1923 years and 30% had their 1 child at 27-29. 60% of the women have stage 3 ovarian cancer, 25 % have stage 2 cancer,10% have stage 1 and 5% have stage 4 ovarian cancer.80% of the women have not noticed any kind of pain and 20% of the women have noticed a little bit pain. 55% of the women carry out lactation for 1 years,15% for 1.5 year and 10% for 2 years.



Do u have still birth?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	still birth	1	5.0	5.0	5.0
	miscarriage	3	15.0	15.0	20.0
	none	16	80.0	80.0	100.0
	Total	20	100.0	100.0	

Table 1: History of stillbirth or miscarriages

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

What king of treatment do u use for?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	chemotherapy	13	65.0	65.0	65.0
	medication	5	25.0	25.0	90.0
	none	2	10.0	10.0	100.0
	Total	20	100.0	100.0	

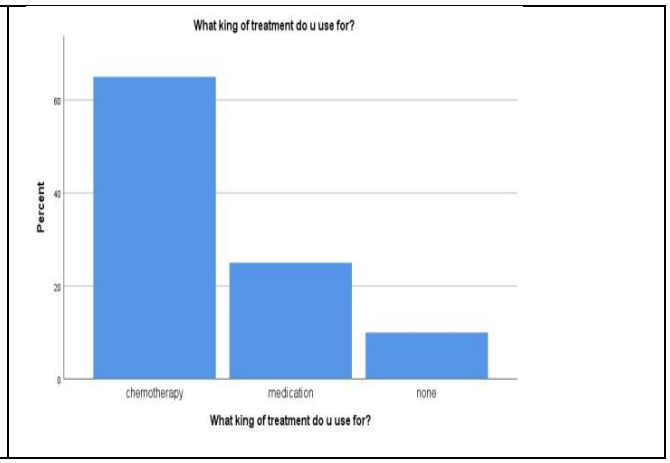


Table 2: Treatment used for ovarian cancer

At what age menopause occur?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	48-50	8	40.0	40.0	40.0
	51-53	4	20.0	20.0	60.0
	54-56	4	20.0	20.0	80.0
	57-60	4	20.0	20.0	100.0
	Total	20	100.0	100.0	

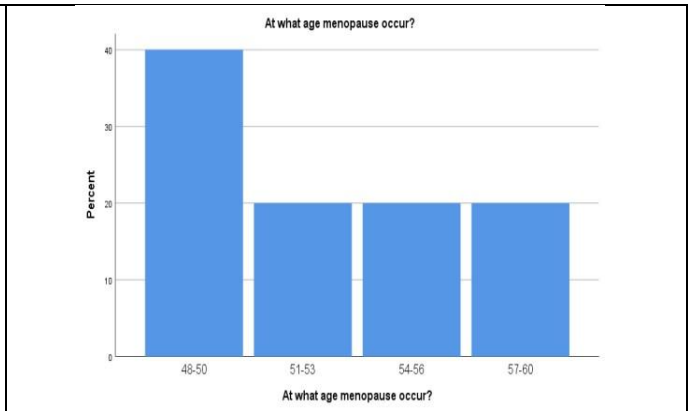


Table 3: Age at Menopause

Do u have any pelvic mass?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	small	3	15.0	15.0	15.0
	medium	4	20.0	20.0	35.0
	large	13	65.0	65.0	100.0
	Total	20	100.0	100.0	

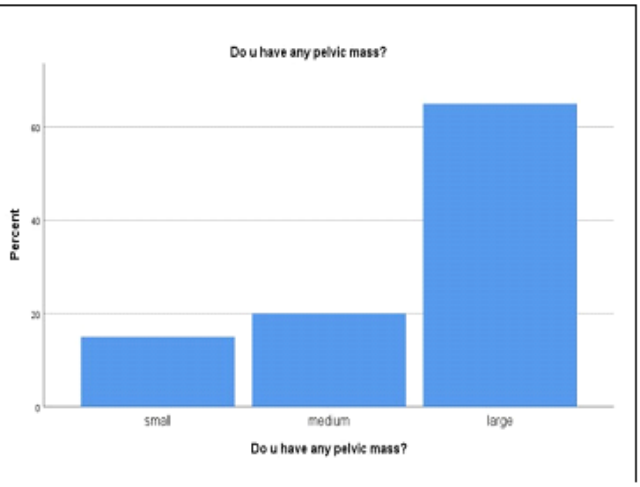


Table 4: Percentage of Pelvic mass in ovarian cancer patients

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

65% of the ovarian cancer women have large pelvic mass,20% have medium and only 15% have small pelvic mass (see table 4).85% of the women have bulky mass and 15% of the women had not. 85% of the women suffering from Ascites and 15% of the women were not.65 % of the women suffering from large amount of pleural effusion and 15% have small amount of pleural effusion.70% of the women have large amount of abdominal pap smear and 15% of the women have small amount of abdominal pap smear. 85% of the women have high amount CA125 level and 15% have low amount of CA125 level (see table 5). 55% of the women suffer from abnormal LFT'S and 45% of the women do not suffer from abnormal LFT's.

What is the level of CA125 in the blood?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	high	17	85.0	85.0	85.(
	low	3	15.0	15.0	100.(
	Total	20	100.0	100.0	

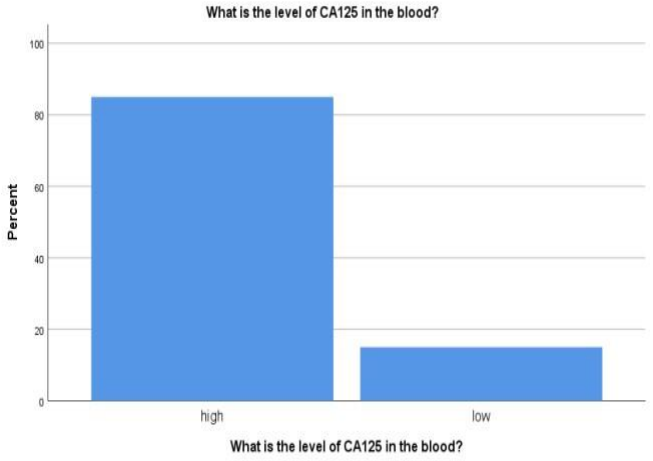


Table 5: Levels of CA125 in blood

What is the stage of ovarian cancer ?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	stage 1	2	10.0	10.0	10.0
	stage 2	5	25.0	25.0	35.0
	stage 3	12	60.0	60.0	95.0
	stage 4	1	5.0	5.0	100.0
	Total	20	100.0	100.0	

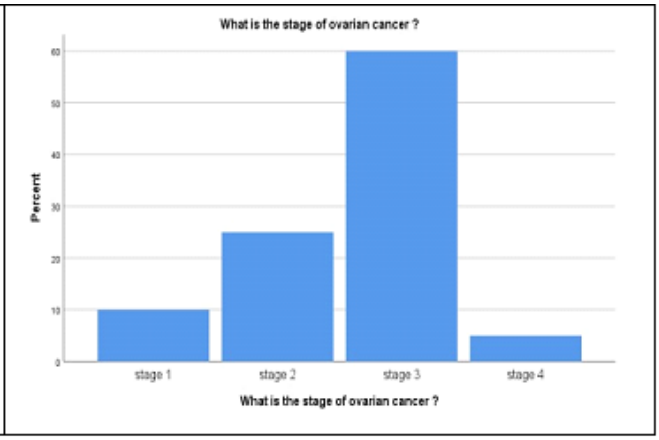


Table 6: Stage of ovarian cancer

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

Are u suffering from Ascites?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	17	85.0	85.0	85.0
	no	3	15.0	15.0	100.0
	Total	20	100.0	100.0	

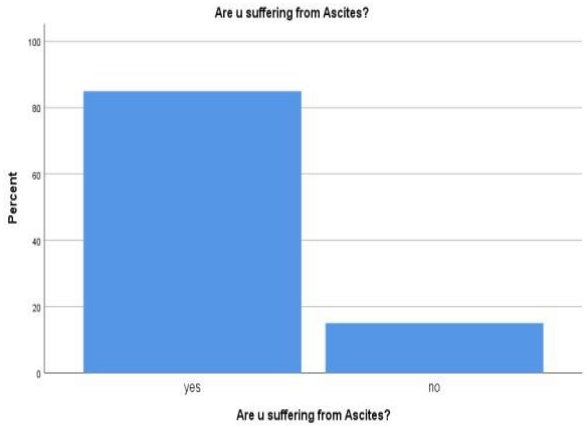


Table 7: Percentage of affecties with Ascites

60% of the women have stage 3, 25% have stage 2, 10 % have stage 2 and only 5 % have stage 4 of ovarian cancer (see table 7).60% of the women have grade 2 cancer, 30% have grades 3 and 10% have grade 1 ovarian cancer (table 8).40% have serous, 25% have mucinous,15 % have endometrioid and 10% have clear cell ovarian cancer (table 9).

What is the grade of ovaraian cancer?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	grade 1	2	10.0	10.0	10.0
	grade 2	12	60.0	60.0	70.0
	grade 3	6	30.0	30.0	100.0
	Total	20	100.0	100.0	

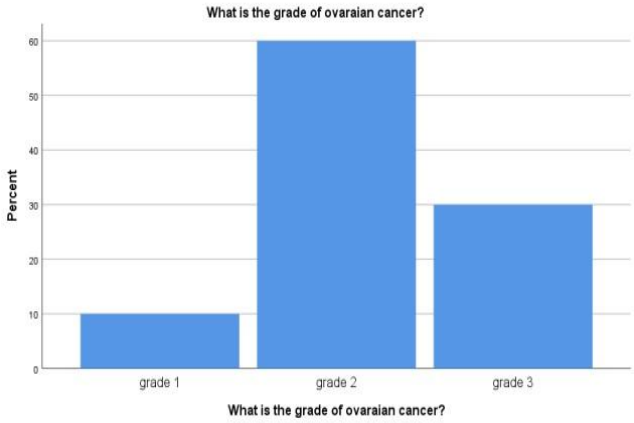


Table 8: Grade of ovarian cancer

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

Suffering from which kind of ovarain cancer?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	serous	8	40.0	40.0	40.0
	mucinous	5	25.0	25.0	65.0
	endometriod	3	15.0	15.0	80.0
	borderline	2	10.0	10.0	90.0
	clear cell	2	10.0	10.0	100.0
	Total	20	100.0	100.0	

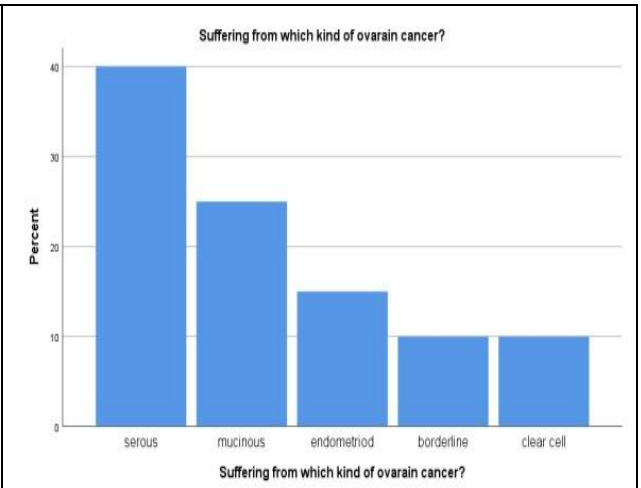


Table 9: Type of ovarian cancer

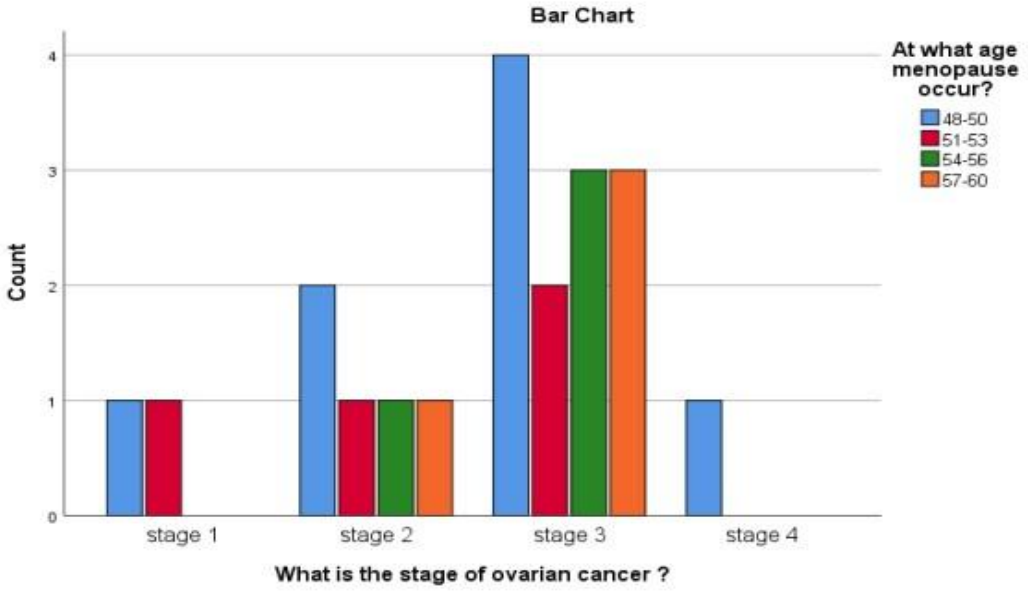


Figure 4

Women with the age 48-50, 10% of them have stage 1, 20 % of them stage 2 and 40 % have stage 3 ovarian cancer.Women with the age 54-56, 10% of them have stage 2 and 30 % of them have stage 3 ovarian cancer. Women with the age 57-60 ,10% of them have stage 2 cancer and 30 % of them have stage 3 cancer.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

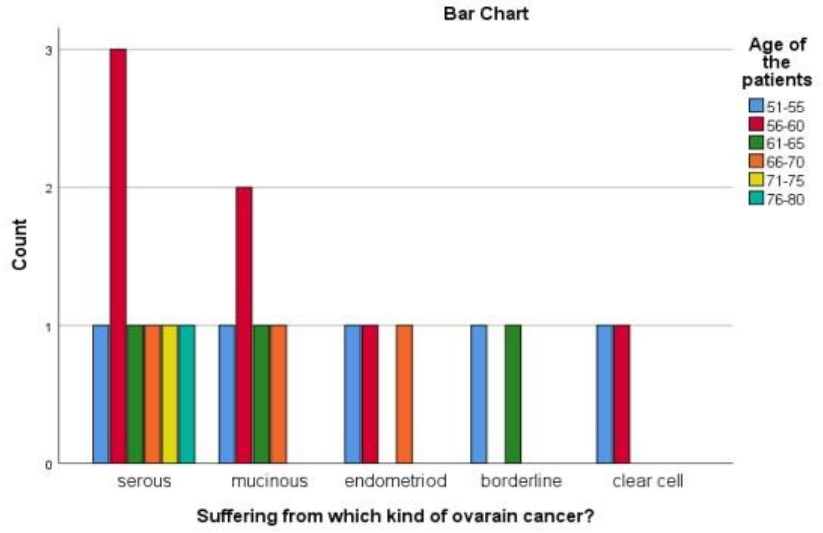


Figure 5

Ovarian cancer patients with the age 51-55, 10% of them have serous and 10 % of them have mucinous cancer. Patient with the age 56-60 ,30 % of them have serous cancer 20% of them have mucinous cancer and 10 % of them have endometroid cancer.

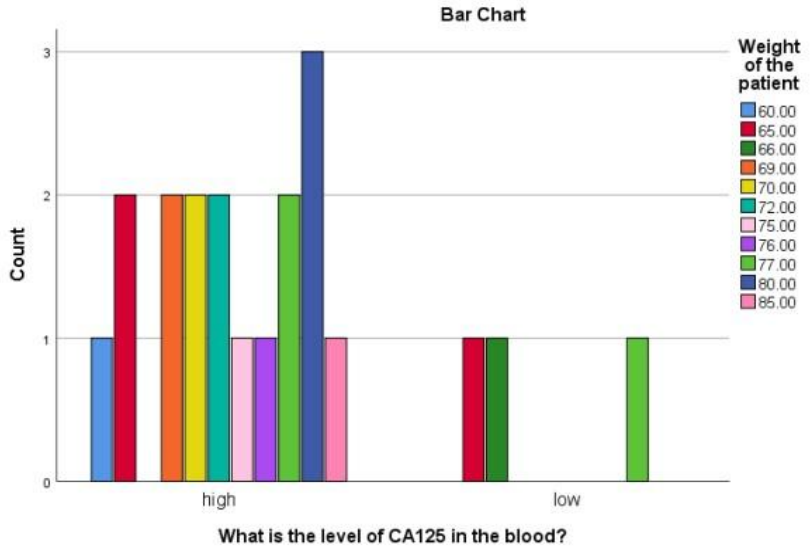


Figure 6

Women with the weight 80 have 30 % high level of CA125 in the blood as compared to the women having the weight of 60 with 10% of CA125 in the blood similarly women with weight

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

70 have high level of CA125 as compared women having the weight of 60 but less than the women with the weight of 80.

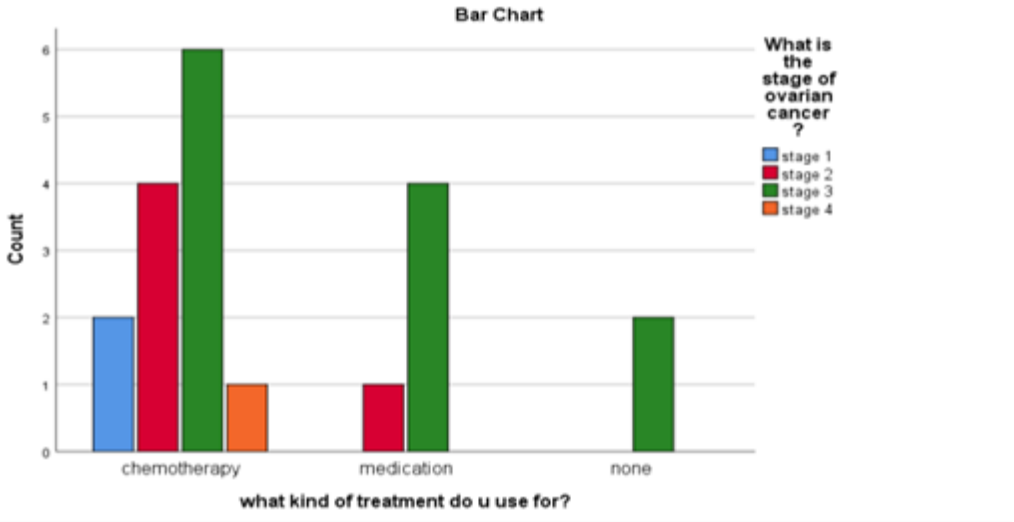


Figure 7

60 % of the women with the stage 3 receiving chemotherapy and 40 % of them receiving medication .40 % of the women with stage 2 cancer they are receiving chemotherapy and 10 % of them receiving medication**.**

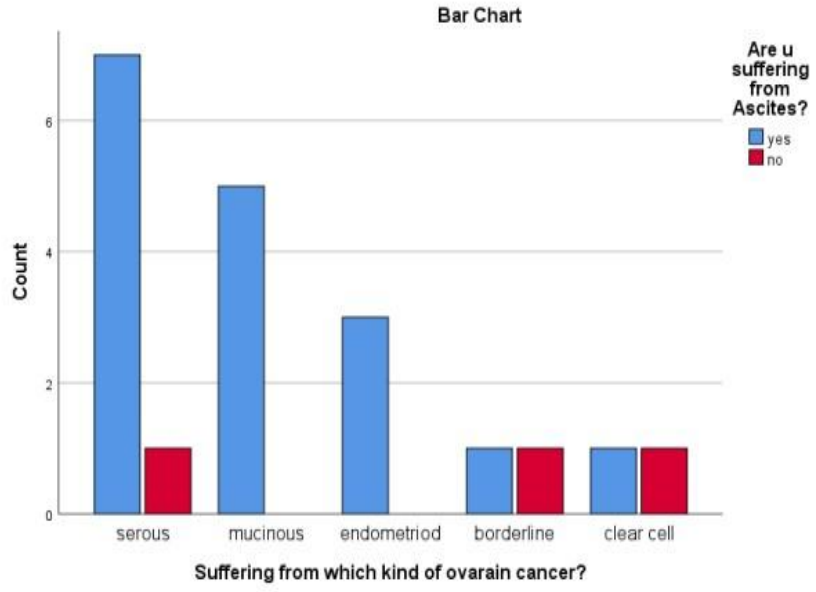


Figure 8

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

67% of the patient with serous cancer said they suffer from Ascites while 10% of them said they do not suffer from Ascites .30 % of the of the patient with endometrioid cancer said they suffer from Ascites .10% of the patient with borderline cancer said they suffer from Ascites while 105 said they do not.

Discussion

Ovarian malignant is the most widely recognized disease of gynecology in Pakistani women in contrast to few other nations of Asia. There has been an expansion in the examination enthusiasm for screening of ovarian malignant growth with greater part of research being centered around utilization of biomarkers and pelvic ultrasound with multimodal evaluations for early identification of ovarian disease (Menon*et al*., 2009). In the course of the most recent decade, research has been intensified on indication-based location of ovarian malignant growth with the potential preferred position of early recognition and auspicious treatment (Bankhead*et al.,* 2005). Like Japanese,Indian and Israeli women's the means age of ovarian cancer is 60 years in Pakistan women. However, Genetics as well as environment factors may involve but reason remain unknown still. National cancer institute in Pakistan is the organization in which the treatment of ovarian cancer done.55 % women do not take Oral contraceptive. It is interesting to note that there are very few cases of late childbirth and early menopause and null parity. Symptoms of ovarian cancer were vague and not clear. In the development of ovarian cancer family history is the important factor of ovarian cancer. Most of the respondent were either uncertain or not knowing the significance of family ancestry of ovarian disease. Only a minority are defined as hereditary ovarian cancers. 7 % of our patient have positive family history of ovarian cancer. Generally relative of these patients have first degree relationship with the patient and the greater part of them had either bosom or ovarian malignancy. This raises the probability of hereditary components playing a progressively significant job in ovarian malignancy. Consanguineous relationships are normal in Pakistan. Thirty five percent of all patients in our arrangement had consanguineous relationships. More research is expected to contemplate the impact of association in Pakistani patients with epithelial ovarian disease, especially in those with positive family ancestry. Clinical introduction and lab highlights of our patients are very attribute of the ailment. The information on manifestations and hazard components of ovarian malignancy among women in everyone is low, however, that women with ovarian cancer do suffer from symptoms (Lockwood*et al*., 2009). It is hard to recognize the manifestations of ovarian malignant growth from those of different conditions, for example, irritable bowel syndrome or other gastrointestinal infection. In this study 20% of women suffer from abdominal pain,85 % from abdominal distension and,80 % from nausea and dyspepsia, bulky uterus notices in 85% women's and 35% suffer from vaginal bleeding and 85% also suffer from Ascites. The present perception may propose that while analyzing the ovarian malignancy, equivalent importance should be given to stomach, gastrointestinal, and protected side effects. Ladies with ovarian malignant growth experience side effects all the more every now and again, harshly, and relentlessly than ladies without the malady. On chromosome 17q21 and 13q1213 *BRCA 1* and *BRCA 2* gene were present. *BRCA1* and *BRCA2* play an important part in the reaction to cellular stress, the localization to sites of damaged DNA, and the activation of DNA repair processes. Both genes through the conservative mechanism of homologous recombination repair DSB (Abbas *et al*., 2021). Large numbers of mutation could occur in both of these tumor suppressor gene which can cause protein inactivation. The concept of "BRCAness" illustrate the traits that some cancers may be occur due to ***BRCA1/2***mutation (Turner *et al*., 2004). Through a

number of epigenetic mechanisms such as promoter hyper methylation and loss of heterozygosity the inactivation of *BRCA1* occur which may become the cause of ovarian cancer (Bozzetti*et al.*, 2004). Ovarian cancer patients with the mutation of *BRCA1* carriers diagnosed at younger age (52-year average age) compared to women with *BRCA2* mutation carriers diagnosed at age of 62.

Level of CA125 in the blood is very important indication in clinical practice and in the preclinical asymptomatic phase of the disease its level increases. Level of CA125 is used to predict the level of malignancy of ovary. Sensitivity of CA125 in predicting ovarian cancer is 81 % to 91%.(Cannery*et al.*, 1984). In this study 85 % of the women with ovarian cancer have high CA125 blood level while only 15 % have low CA125 level (Zurawski*et al.*, 1988).It is suggested that lady with sign and symptoms of ovarian malignancy should have a cautious pelvic assessment. The National Institute for Health and Clinical Excellence (NICE, UK) Referral rules for suspected disease in 2005 suggested that any lady with a considerable stomach or pelvic mass on assessment that isn't clearly uterine fibroids or not of gastrointestinal or urological beginning ought to have a ultrasound examine.In the event that the sweep is reminiscent of malignant growth, or if ultrasound isn't accessible, a pressing referral ought to be made. It is critical to take note of that NICE, UK has refreshed the direction for acknowledgment and starting administration of ovarian malignant growth in 2011, which presently proposes that those patients identified by assessment to have ascites, or abdominal or pelvic mass should be referred urgently (NIH Clinicalguideline122).

References

1. AmericanCancerSociety.Cancerfactsandfigures2018.SpecialSection:OvarianCancer.Availableat:https://www.cancer.org/content/dam/cancerorg/research/cancerfactsandstatistics/annualcancerfactsandfigures/2018/cancerfactsandfiguresspecialsectionovariancancer2018.pdf.(Acce ssed30December2018).
2. Australian Institute of Health and Welfare (AIHW), Australian Cancer Incidence and Mortality (ACIM) books: ovarian cancer, AIHW, Canberra, December 2017.
3. Bankhead, C. R., Collins, C., Stokes-Lampard, H., Rose, P., Wilson, S., Clements, A., ... &Austoker, J. (2008). Identifying symptoms of ovarian cancer: a qualitative and quantitative study. BJOG: An International Journal of Obstetrics &Gynaecology, 115(8), 1008-1014.
4. Bankhead, C. R., Kehoe, S. T., &Austoker, J. (2005). Symptoms associated with diagnosis of ovarian cancer: a systematic review. BJOG: An International Journal of Obstetrics &Gynaecology, 112(7), 857-865.
5. Bergamini, A., Candiani, M., Taccagni, G., Rabaiotti, E., Viganò, R., De Marzi, P., ... &Mangili, G. (2016). Different patterns of disease spread between advanced-stage type I and II epithelial ovarian cancer. Gynecologic and obstetric investigation, 81(1), 10-14.
6. Boyd, J., Sonoda, Y., Federici, M. G., Bogomolniy, F., Rhei, E., Maresco, D. L., ... & Hoskins, W. J. (2000). Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. Jama, 283(17), 2260-2265.
7. Boyd, L. R., &Muggia, F. M. (2018). Carboplatin/paclitaxel induction in ovarian cancer: the finer points. Oncology (08909091), 32(8).
8. Bozzetti, C., Bortesi, B., &Merisio, C. (2004). Loss of heterozygosity (LOH) in ovarian cancer. International journal of gynaecology and obstetrics, 85(3), 294-295.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

9. Cannery PA, Moore M ,Wilkinson PM, James RD ,Ovarian cancer antigen CA125: a prospective clinical assessment of its role as a tumor marker.Br J Cancer 1984.
10. ChengYM,WangST,ChouCY.serumCA125inpreoperativepatientsathighriskforendometrioses.ObstetGynecol2002.
11. ChienJ,PooleE.Ovariancancerprevention,screeningandearlydetection:reportfromthe11tBiennialOvarianCancerResearchSymposium.IntJGynecolCancer.2018.https://www.uptodate.com/contents/screeningforovariancancer?search=Ovarian%20cancer%20statistics&sousearch_result&selectedTitle=1»150&usage_type=default&display_rank=1.(Accessed30December2018)
12. Farva Abbas, Tayyaba Shan, Syed Waqas Hassan, IrumFatima,Faiza Sattar, Kiran Jackson, Farhan Elahi Hashmi,Mariam Batool, Umar Sajid Kayani, Bushra Gul (2021) Status of BRCA1/2 in Breast Cancer Patients; where Pakistan stands?. Journal of Critical Reviews, 8 (3), 18-33. doi:10.31838/jcr.08.03.03
13. German Consortium for Hereditary Breast and Ovarian Cancer. (2002). Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. International Journal of Cancer, 97(4), 472-480.
14. GershensonD,BirrerM.Managementoflowgradecarcinomasoftheovary.Availableat:https://www.uptodate.com/contents/managementoflowgradeserouscarcinomasoftheovary?search=low%20grade%20serous%20carcinomas%20ovarian&source=search_result&selectedTitle=1»150 &usage_type=default&display_rank=1.(Accessed15November2018).
15. GershensonD.Ovariangermcelltumors:pathology,clinicalmanifestations,anddiagnosis.Availableat:https://www.uptodate.com/contents/ovariangermcelltumorspathologyclinicalmanifestationsanddiagnosis?search=germ%20cellovarian%20cancer&source=search_result&selectedTitle=1»38&usage_type=default&display_rank=1.(Accessed15November2018).
16. GershensonD.Overviewofsexcordstromaltumorsoftheovary.Availableat:https://www.uptodate.com/contents/overviewofsexcordstromaltumorsoftheovary?source=autocomplete&index=0»4&search=sex-cord.(Accessed15November2018).
17. GershensonD.Treatmentofmalignantgermcelltumorsoftheovary. Availableat: https://www.uptodate.com/contents/treatmentofmalignantgermcelltumorsoftheovary?search=germ%20cell%20ovarian%20cancer&source=search_result&selectedTitle=2»38&usage_type=default&display_rank=2#H1965172.(Accessed12November2018).
18. Goldstein, C. L., Susman, E. P., Lockwood, S., Medlin, E. E., &Behbakht, K. (2015). Awareness of symptoms and risk factors of ovarian cancer in a population of women and healthcare providers. Clinical journal of oncology nursing, 19(2).
19. GrayH.Canceroftheovary,fallopiantube,andperitoneum:stagingandsurgicalmanagement.Availableat:https://www.uptodate.com/contents/canceroftheovaryfallopiantubeandperitoneumstagingandinitialsurgicalmanagement?topicRef=86318&source=see_link.(Accessed15November2 018).
20. Guo, H., Guo, J., Xie, W., Yuan, L., & Sheng, X. (2018). The role of vitamin D in ovarian cancer: epidemiology, molecular mechanism and prevention. Journal of ovarian research, 11(1), 1-8.
21. Huang, X., Wang, X., Shang, J., Lin, Y., Yang, Y., Song, Y., & Yu, S. (2018). Association between dietary fiber intake and risk of ovarian cancer: a meta-analysis of observational studies. Journal of International Medical Research, 46(10), 3995-4005.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

22. JaysonGC,KohnEC,KitchenerHC,LedermannJA.Ovariancancer.Lancet.2014.https://www.uptodate.com/contents/screeningforovariancancer?search=Ovarian%20cancer%20statistics&sousearch_result&selectedTitle=1»150&usage_type=default&display_rank=1.(Accessed30December2018).
23. KimyonComertG,TurkmenO,KaralokA,etal.Managementofcatheterrelatedcomplicationsduringintraperitonealchemotherapyforovariancancer:twocasereportsandreviewoftheliterature.Mar maraMedJ.2018;31:88–93.
24. Lim, A. W. W., Mesher, D., Gentry-Maharaj, A., Balogun, N., Widschwendter, M., Jacobs, I., ... & Menon, U. (2016). Time to diagnosis of Type I or II invasive epithelial ovarian cancers: a multicentre observational study using patient questionnaire and primary care records. BJOG: An International Journal of Obstetrics &Gynaecology, 123(6), 1012-1020.
25. Lockwood-Rayermann, S., Donovan, H. S., Rambo, D., &Kuo, C. W. J. (2009). Women's awareness of ovarian cancer risks and symptoms: analysis of responses to an online survey shows that women ages 40 and older are not well informed. The American journal of nursing, 36-46.
26. Mallen, A., Soong, T. R., Townsend, M. K., Wenham, R. M., Crum, C. P., &Tworoger, S. S. (2018). Surgical prevention strategies in ovarian cancer. Gynecologic oncology, 151(1), 166-175.
27. Menon, U., Gentry-Maharaj, A., Hallett, R., Ryan, A., Burnell, M., Sharma, A., ... & Jacobs, I. (2009). Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The lancet oncology, 10(4), 327-340.
28. National Comprehensive Cancer Network (US), NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer, Version 4. 2017.
29. National Institute for Health and Clinical Excellence, Recognition and initial managementofovariancancer,(Clinicalguideline122),2011,https://www.google.com/search?q=VargasAN.Naturalhistoryoovariancancer.Ecancermedicalscience.2014&oq=VargasAN.Naturalhistoryofovariancancer.Ecancermedicalscience.2014&aqs=chrome..69i57.1759j0j8&sourceid=chrome&ie=UTF-8
30. National Institute for Health and ClinicalExcellence,CG27Referralguidelinesforsuspectedcancer,2005.https://www.google.com/search?q=VargasAN.Naturalhistoryofovariancancer.Ecancermedicalscience.2014&oq=VargasAN.Naturalhistoryofovariancancer.Ecancermedicalscience.2014&aqs=chrome..69i57.1759j0j8&sourceid=chrome&ie=UTF-8
31. NationalComprehensiveCancerNetwork.Ovariancancer:includingfallopiantubecancerandprimaryperitonealcancer.Availableat:https://www.nccn.org/professionals/physician_gls/pdf/ovaria n.pdf.(Accessed15November2018).
32. OvarianCancerResearchAlliance.Statistics.Availableat:https://ocrahope.org/patients/aboutova riancancer/statistics/.(Accessed30December2018).
33. Penson, R. (2018). Evolving Treatment Strategies in the Management of Ovarian Cancer: Expert Perspectives in PARP Inhibition. J Managed Care Med, 21, 20-23.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 7, 2021, Pages. 780 - 796
Received 05 May 2021; Accepted 01 June 2021.

34. SchenkenR.Endometriosis:pathogenesis,clinicalfeatures,anddiagnosis.Availableat:https://www.uptodate.com/endometriosispathogenesisclinicalfeaturesanddiagnosis?(AccessNov 2018).
35. Slatnik, C. L., & Duff, E. (2015). Ovarian cancer: Ensuring early diagnosis. The Nurse Practitioner, 40(9), 47-54.
36. Stewart, S. L., Rim, S. H., & Richards, T. B. (2011). Gynecologic oncologists and ovarian cancer treatment: avenues for improved survival. Journal of Women's Health, 20(9), 1257-1260.
37. Tschernichovsky, R., & Goodman, A. (2017). Risk-reducing strategies for ovarian cancer in BRCA mutation carriers: a balancing act. The oncologist, 22(4), 450.
38. Turner, N., Tutt, A., & Ashworth, A. (2004). Hallmarks of'BRCAness' in sporadic cancers. Nature reviews cancer, 4(10), 814-819.
39. Walker, J. L., Powell, C. B., Chen, L. M., Carter, J., Bae Jump, V. L., Parker, L. P., ... & Gibb, R. K. (2015). S ociety of G ynecologic O ncology recommendations for the prevention of ovarian cancer. Cancer, 121(13), 2108-2120.
40. Walker, J. L., Powell, C. B., Chen, L. M., Carter, J., Bae Jump, V. L., Parker, L. P., ... & Gibb, R. K. (2015). S ociety of G ynecologic O ncology recommendations for the prevention of ovarian cancer. Cancer, 121(13), 2108-2120.
41. Webb, P. M., Green, A. C., & Jordan, S. J. (2017). Trends in hormone use and ovarian cancer incidence in US white and Australian women: implications for the future. Cancer Causes & Control, 28(5), 365.
42. Yousefi, Z., Frazestanian, M., Davachi, B., Saeed, S., Azad, A., &Khorasani, S. T. (2018). Is transvaginal core needle biopsy a safe method in diagnosis of ovarian cancer?. International Journal of Cancer Management, 11(2).
43. Zurawski Jr, V. R., Orjaseter, H., Andersen, A., &Jellum, E. (1988). Elevated serum CA 125 levels prior to diagnosis of ovarian neoplasia: relevance for early detection of ovarian cancer. International journal of cancer, 42(5), 677-680.