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Original Article

Histopathological patterns of primary malignant ovarian neoplasms in different age groups in Almadinah Almunawwarah region, KSA

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الملخص

أهداف البحث: النمط الوبائي لأورام المبيض في منطقة المدينة المنورة بالمملكة العربية السعودية لم يتم ذكره بشكل كامل في الأدبيات. لوحظ تشخيص متكرر على غير العادة لورم الخلايا الحّبيبية للبالغين في المدينة المنورة. تهدف هذه الدراسة إلى وصف نمط أورام المبيض في منطقة المدينة المنورة مع التركيز بشكل خاص على ورم الخلايا الحّبيبية للبالغين.

طرق البحث: تم جمع السجلات النسيجية لجميع عينات المبيض التي تم تشخيصها في الفترة من يناير ٢٠١١ إلى ديسمبر ٢٠١٦ من مستشفى النساء والولادة والأطفال بالمدينة المنورة. تم تحديد وفحص كل الشرائح النسيجية المصبوغة بصبغتى الهيماتوكسيلين والأيوسين من عينات الأورام المصلية، والموسينية الخبيثة، والمتوسطة، وكذلك أورام الحبل السدالي الجنسي، وأورام الأمشاج الخبيثة. كما تم صباغة شرائح نسيجية لورم الخلايا الحّبيبية للبالغين بصبغة خاصة بالجسم المناعى باستخدام تقنية الصباغة النسيجية الكيميائية المناعية.

النتائج: تم تحديد ٣٠١ عينة مبيض; ٢١٧ (٧٢٪) منها كانت لأورام في حين أن ٨٤ (٢٨٪) كانت عينات من غير الأورام. ١٣٥ (٦٣٪) من عينات الأورام كانت حميدة، في حين كانت ١٦ (٧٪) متوسطة و٦٦ (٣٠٪) أورام خبيثة. كانت ٤١ (٦٢٪) من الأورام الخبيثة سرطانات طلائية سطحية، و١٧ (٢٦٪) كانت أورام الحبل السدالي الجنسي، في حين شكلت أورام خلايا الأمشاج ٨ (١٢٪) حالات. وكان تواتر ورم الخلايا الحّبيبية للبالغين عاليا بشكل غير عادي ٦٦/١٦ (٢٦٪) من جميع الأورام الخبيثة للمبيض. ووُجدت الصبغة المناعية متغيرة في عينتين فقط من تواتر ورم الخلايا الحّبيبية للبالغين.

الاستنتاجات: في هذه الدراسة، مثّلت أورام المبيض الخبيثة ٣٠٪ من عينات أورام المبيض مع حدوث ورم الخلايا الحّبيبية للبالغين بشكل متكرر. لم تظهر هذه الأورام تعديلا كبيرا متغيرا لبروتين الصبغة المناعية. من الضروري إجراء المزيد من الدراسات لاستكشاف الأسباب الجزيئية الكامنة وراء الزيادة الملحوظة لهذه الأورام.

الكلمات المفتاحية: أورام المبيض؛ علم الأوبئة؛ ورم الخلايا الحّبيبية للبالغين؛ المدينة المنورة

Abstract

Objectives: In the literature, the epidemiological pattern of ovarian neoplasms in different age groups in the Almadinah Almunawwarah region in KSA has not been completely elucidated. Moreover, an unusually frequent diagnosis of adult granulosa cell tumour (AGCT) has been observed in patients in Almadinah Almunawwarah, KSA. This study aimed to describe the pattern of ovarian neoplasms in different age groups in the Almadinah Almunawwarah region with particular emphasis on AGCT.

Methods: Histopathological records of all ovarian specimens diagnosed from 2011 January to 2016 December were collected from the Maternity and Children Hospital in Almaadinah Almunawwarah, KSA. Hematoxylin and eosin (HE)-stained microscopic slides of serous and mucinous epithelial borderline neoplasms and of malignant epithelial, sex cord-stromal and germ line neoplasms were identified and examined. The tissue sections from the AGCT were stained immunohistochemically with *BRCA-1* antibody.

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Results: A total of 301 ovarian specimens were obtained. Of the specimens, 217 (72%) were neoplastic and 84 (28%) were non-neoplastic. In total, 135 (63%) of the neoplastic specimens were benign, 16 (7%) were borderline tumours, and 66 (30%) were malignant tumours. Moreover, 41 (62%) of the malignant tumours were surface epithelial carcinomas, 17 (26%) were sex cord-stromal tumours, and 8 (12%) were germ cell tumours. The incidence of AGCT was unusually high, which accounts for 26% (16/66) of all malignant ovarian neoplasms. Altered BRCA-1 expression was observed in only two specimens.

Conclusion: In this study, malignant ovarian neoplasms accounted for 30% of all neoplastic ovarian specimens, and the incidence of AGCT was remarkable. Such tumours did not show a significantly altered expression of *BRCA-1*. Further studies must be conducted to explore the underlying molecular causes of this condition.

Keywords: Adult-granulosa cell tumour (AGCT); Almadinah Almunawwarah region; Epidemiology; Ovarian neoplasms

Introduction

Ovarian neoplasm is the seventh most common malignant tumour in women, and it is the most fatal gynecologic malignancy. After surgery and chemotherapy, the 5-year survival rate of patients is 30%, which is extremely poor.[1] The most important factor in improving the outcome of ovarian malignancies is early diagnosis with a full understanding of the molecular mechanisms underlying the development and progression of the disease.[2] A positive family history of the disease, particularly among first-degree relatives, is one of the most significant risk factors of ovarian carcinoma.[3].

Several molecular abnormalities, such as alteration in the expression of tumour suppressor genes (*BRCA-1, BRCA-2*)[4] as well as dysfunction in the *P53* and *Kras* genes,[1] play an important role in the development and prognosis of ovarian cancer.

To the best of our knowledge, the prevalence of ovarian neoplasms and distribution in different age groups in Almadinah Almunawwarah region, KSA, have not been fully elucidated. Surface epithelial tumours are the most common type according to different regional studies.[5–8] During our practice in the histopathology laboratory of Maternity and Children Hospital (MCH) in Almadinah Almunawwarah, we observed an unusually frequent diagnosis of adult granulosa cell tumours (AGCT), which is a type of ovarian cancer that is considered rare worldwide.[9] A recent report has shown that the incidence rate of AGCT in KSA is 2.3%.[10] GCT belongs to the group of ovarian sex cord-stromal tumours, which differ from the common ovarian epithelial malignant tumours presenting in younger individuals and the indolent course of the disease.

The molecular basis underlying the development of GCT is less understood compared with that of the common surface epithelial tumours.[11] *BRCA* genes are tumour suppressor genes that normally maintain the integrity of the genome. *BRCA* mutation plays a significant role in the development of some ovarian tumours, such as ovarian serous carcinoma. However, their role in the development of GCT is not known.[12]

Thus, the present study aimed to

1. assess the frequency of the different histopathological types of primary malignant ovarian tumours in Almadinah Almunawwarah region.
2. describe the age distribution of each tumour category compared with the reported figures in other regions of KSA and other countries worldwide.
3. assess the frequency of AGCT compared with that of other ovarian neoplasms
4. analyse the pattern of *BRCA-1* expression in individuals with AGCT to identify if its expression is altered in an attempt to obtain a possible explanation for the high incidence of AGCT.

Materials and Methods

Settings

The histopathological reports of primary ovarian specimens obtained from January 2012 to December 2016 were collected from Maternity and Children Hospital (MCH), which is a tertiary hospital that provides services to patients from Almadinah Almunawwarah and other surrounding areas. It is the referral center for ovarian surgical specimens. H&E-stained tissue slides and formalin-fixed paraffin-embedded blocks of ovarian malignant tumours were identified and collected.

Specimens

The inclusion criteria included ovarian specimens obtained in the MCH histopathology and cytology department or received from other nearby hospitals on the condition that their data are found in the database of the department of pathology. For descriptive purposes, malignant tumours were classified into three groups according to the age of the patients (<20 years, 21−50 years, and >50 years). The incidence and percentage of each type in each age group were calculated. Tumours were classified into these age groups because ovarian tumours are heterogeneous in their age at presentation, and some tumours are most common during postmenopausal age. Moreover, tumours, such as juvenile granulosa cell tumour and yolk sac tumours, are most common at a young age. Meanwhile, others, such as adult sex cord-stromal tumours, are common during middle age. This stratification was used in similar previous studies for similar purposes.[8]

The representative sections from each specimen were collected for a detailed histopathological examination, and

tumours were classified into surface epithelial, germ cell, and sex cord-stromal tumours according to the recent WHO classification.[2] Each type was further classified into subtypes, which primarily depends on the following histological features: surface epithelial tumours classified into serous, mucinous, endometrioid, transitional, clear cell adenocarcinoma, and borderline. Sex cord-stromal tumours were subtyped into granulosa-stromal cell tumours and Sertoli-stromal cell tumours, and the former was further subtyped into the granulosa cell tumour group (adult and juvenile) and thecoma-fibroma group. The germ cell tumours were subdivided into dysgerminoma, choriocarcinoma, yolk sac tumour, embryonal carcinoma, and immature teratoma according to the recent WHO classification.[2]

An unusually high frequency of AGCT compared to the known average international frequency was observed. The diagnosis was made via H&E staining and was confirmed via inhibin alpha immunohistochemical staining.[13] Because of the known role in the genetic predisposition of some ovarian tumours and the high incidence of certain genetic disorders, such as inherited hemolytic anemias, in certain regions of KSA, we assessed the level of *BRCA-1* protein expression in these tumours to identify if the cause of the unusual increase in the incidence is the aberrant expression of *BRCA-1*.

Immunohistochemical staining

Sixteen formalin-fixed paraffin-embedded blocks of AGCT were identified. In total, 15 specimens with normal ovarian surface epithelium and 15 specimens with normal tubal epithelium were used as controls. Tissue sections from each specimen were stained using the Rabbit anti-*BRCA1* polyclonal antibody. Staining was performed using an immunoperoxidase technique with the autostainer Bench-Mark ULTRA instrument. In summary, paraffin sections were deparaffinized, rehydrated, treated in 3% H_2O_2 for 5 min, and washed. The sections were then incubated with the primary Ab (*BRCA-1*, Origene; TA310042, polyclonal; 1:100) for 45 min at room temperature. Antigen–antibody reaction was visualized using diaminobenzidine, counter-stained with hematoxylin, dehydrated, and mounted.

Assessment of *BRCA-1* expression was conducted using a semiquantitation approach. The intensity of nuclear staining was scored in a scale of 0–3: 0: negative; 1: weak; 2: moderate; and 3: strong. The same approach was used in several studies.[14]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 21 for Windows (SPSS Inc., Chicago, IL, the USA). Descriptive analysis using frequencies and percentages was carried out.

Results

Between 2012 January and 2016 December, data about 301 primary ovarian specimens were retrieved from the computerized database of the histopathology laboratory of MCH in Almadinah Almunawwarah region. Non-neoplastic lesions were identified in 84 (30%) of 301 specimens. A total of 217 specimens were diagnosed as ovarian neoplasms. Of the 217 neoplasms, 135 (63%), 16 (7%), and 66 (30%) were benign, borderline neoplasms, and malignant neoplasms, respectively.

Of the 66 malignant ovarian tumours, 41 (62%), 17 (25.7%), and 8 (12%) were classified as surface epithelial tumours, sex cord-stromal tumours, and germ cell tumour, respectively. Serous cystadenocarcinoma was the most common malignant tumour (n = 21, 32%; Tables 1 and 2).

Majority of sex cord-stromal tumours were granulosa cell tumours of adult type (16/66), followed by malignant Sertoli cell tumour.[2] All AGCT were unilateral, and of the 16 AGCT, 9 (56%) were found in the left ovary. Variable histological patterns were observed in individuals with AGCT. The tumours were composed of proliferating granulosa cells forming diffuse sheets, cords, trabeculae, characteristic Call-Exner bodies, and a combination of all previous patterns. Granulosa cells showed few cytoplasms and ovoid nucleus with longitudinal groove and prominent nucleoli, and mitosis varied from 1 to 5 HPF. Moreover, 1 (6%) of 16 tumours presented with pleomorphism and brisk mitoses. The diagnosis of all AGCT was confirmed via inhibin alpha staining.

The mean age of the participants was 41 years, and majority of cases (n = 48) were in the 20–49 age group, except

Table 1: Frequency of various ovarian neoplasms in different age groups in Almadinah Almunawwarah area.

Age, Years	Surface Epithelial Tumours	Sex Cord-stromal Tumours	Germ Cell Tumours	Total
<20	0	0	5	5
20–50	29	11	2	42
>50	12	6	1	19
Total %	(41) 59.7%	(17) 26.4%	(8) 13.8%	(66) 100%

Table 2: Frequency of borderline and malignant ovarian tumours in different age groups in Almadinah Almunawwarah area.

Diagnosis	Age Distribution			Total
	<20	21–50	>50	
Borderline tumours				
Serous	0	10	1	11
Mucinous	0	3	2	5
Total	0	13	3	16
Malignant tumours				
A- Surface epithelial				
Serous adenocarcinoma	0	15	6	21
Mucinous adenocarcinoma	0	9	3	12
Endometrioid carcinoma	0	1	1	2
Clear cell carcinoma	0	2	1	3
Malignant Brenner	0	2	1	3
B- Sex cord-stromal				
Adult granulosa cell tumour	0	10	6	16
Malignant Sertoli cell tumour	0	0	1	1
C- Germ cell tumours				
Immature teratoma	2	0	0	2
Dysgerminoma	1	2	0	3
Yolk sac tumour	2	0	0	2
Choriocarcinoma	0	0	1	1
Total	5	41	20	66

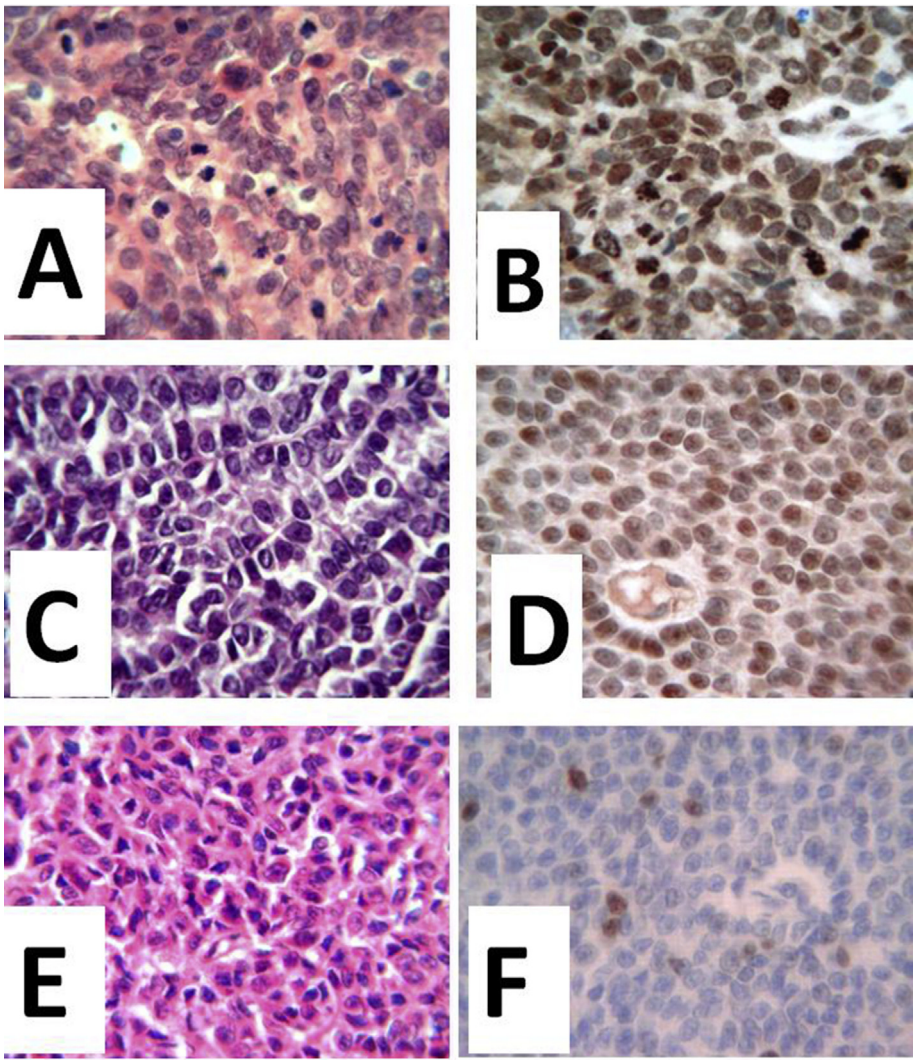

Figure 1: A–F show the three different GCT specimens stained with hematoxylin and eosin (A, C, and E) and immunohistochemically with antibodies for *BRCA-1* (B, D, and F). The upper and middle panels showed strong and moderate expressions, whereas the lower panel showed a weak expression.

for germ cell tumours in which more than half of the cases involved patients younger than 20 years. Women older than 50 years primarily presented with surface epithelial tumours (n = 12; 63%), followed by sex cord-stromal tumours (31.5%). The mean age of the patients with AGCT was 44.5 (age range: 30–75) years.

BRCA-1 expression in granulosa cell tumours

All normal ovarian surface and fallopian tube epithelium showed a uniform strong positive expression of *BRCA-1*. All granulose cell tumours were positive for *BRCA-1* expression, and of the 16 specimens, 14 presented with a strong positive expression with heterogenous intensity. A weak expression was detected in two specimens (Figure 1).

Discussion

This study described the pattern of ovarian neoplasms in different age groups in Almadinah Almunawwarah region and compared with the known pattern of these tumours worldwide.

In our cohort, 70% of the surgically resected ovarian specimens collected at MCH were ovarian neoplasms, and 30% of which were malignant tumours. Our finding is within the range reported in studies on different ethnic populations worldwide. The reported rates of malignant ovarian tumours in previous studies were as follows: 15% from Africa,[15] 40% from Asia,[16] 20–25% from the western population,[17] and 22% from other regions in KSA.[5]

The most common type of malignant neoplasms was the surface epithelial tumours with the serous cystadenocarcinoma, which is the most frequent type. They comprise 62% of malignant neoplasms in our cohort, which is similar to the data reported in KSA[5] and other countries worldwide.

Sex cord-stromal tumours were diagnosed in 26% of our specimens. Approximately 94% of such tumours were AGCT. Our rate (26%) was significantly higher than that reported from other areas in KSA (7.6%),[5] in studies of women from Asia (2–3%),[18,19] and in the western

population where sex cord-stromal tumours account for 5–10% of all ovarian malignancies.[17] This category of tumours originates from the stroma of the ovary, which originate from the sex cord cells of the embryonic gonad. The sex cord of the embryonic gonads is differentiated during development into granulosa and theca cells in women and to Sertoli and Leydig cells in men. Therefore, tumours arising from the ovarian stroma can be any of these four cell types; granulose cell tumours that are usually the mixture of granulosa and theca cells, Sertoli cell tumours, or Leydig cell tumours.[17]

The molecular carcinogenic mechanisms underlying sex cord-stromal tumours are not well understood. By reviewing the literature, we observed a variation in the incidence of AGCT among the ethnic populations. In a study in the USA, a higher incidence of sex cord-stromal tumour was observed in black women than in white woman, whereas a significantly higher frequency of surface epithelial tumours was observed in white woman than in black woman.[20]

These AGCTs were almost unilateral and have varying histological patterns with little pleomorphism and low mitotic activity. Our histopathological findings are in accordance with the known features of these tumours.[18] The histopathological morphological pattern of GCT is sometimes challenging for pathological diagnosis as it may mimic other carcinomas, particularly endometrioid carcinoma. We stained the GCT with inhibin for the confirmation of diagnosis. Inhibin is a protein secreted with granulosa cells and is a specific marker for the diagnosis and follow-up of GCT.[11,13]

We examined the reason behind the high incidence rate of GCT in our patients. Moreover, it may be a familial cause due to certain genetic abnormalities that can be inherited from one generation to another in Almadinah Almunawwarah region. Some diseases, such as hemolytic anemias, have significantly high rates in regions in KSA than in other regions worldwide.[21]

In individuals with ovarian carcinomas, the familial genetic abnormality in the *BRCA-1* gene is well documented in surface epithelial tumours. *BRCA-1* is a normal gene located in chromosome 17q21. The encoded protein functions as a tumour suppressor gene by repairing DNA damage.[22] The reported rate of *BRCA-1* mutation among patients with ovarian cancer varied among studies from 5% in some studies[23] to 60% in other studies.[24]

We examined GCT for the expression pattern of *BRCA-1* to validate if the aberrant expression of this protein has a role in the development of GCT. All our specimens showed a positive expression of the protein except in two cases in which the expression was low. Such finding indicates that BRCA-1 expression does not play a significant role in the carcinogenesis of these tumours.

Advances in molecular-based studies showed that genetic mutation through changes in the gene sequence itself is not the only mechanism associated with aberrant genetic function. Abnormal gene function may result from epigenetic changes in which the abnormal pattern of gene methylation has a direct impact on gene activity. In a study examining epigenetic changes in GCT, researchers have found that the hypermethylation of the promoters of certain genes, such as *CDH13*, *DKK3*, and *forkheadbox L2 (FOXL2)*, are significantly higher in GCT specimens compared to normal tissues.[25] Other studies have suggested that the main molecular event underlying GCT is an abnormal high proliferation of the granulose cells due to mutation in the *FOXL2* gene known as c.402C>G mutation. This mutation was found in majority of GCT both the primary and metastatic tissues. Due to its high prevalence in GCT, authors have recommended its use in the diagnosis of challenging GCT cases.[11] All these aforementioned changes in the activation of growth factors or methylation have been caused by exposure to environmental factors, such as pollutants and dietary components.[26] There may be certain undiscovered environmental factors in the Almadinah Almunawwarah region. These genetic changes have not been examined in the current study; however, it would be interesting to examine epigenetic changes in our tumour samples.

Germ cell tumours in our study were defined in 13% of cases, which is within the reported range in other studies[7] and is similar to other regions in KSA.[27]

The mean age of the patients in this study was 41 years. This age is younger than that described in other regional studies with a comparable range from 7 to 91 years in both studies, and most cases were observed in the 20–50 age group, which was obviously younger than that of other findings in different regional studies.[5,27] These findings indicated the need of investigating the genetic predisposition of different ovarian malignant neoplasms in the Almadinah Almunawwarah region.

In conclusion, malignant ovarian neoplasms in individuals in Almadinah Almunawwarah region accounted for 30% of neoplastic ovarian specimens. Despite the overall low frequency of malignant ovarian tumours in Almadinah Almunawwarah region, a remarkably frequent AGCT was observed. These tumours did not show a significantly altered expression of *BRCA-1*, which increases the risk of surface ovarian tumours. However, this conclusion should be taken with caution due to the limited number of samples that were assessed in the study. Further studies must be conducted to explore the underlying molecular causes behind the observed high incidence of GCT.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The research ethics committee of Taibah University (CM-REC) and the histopathology laboratory of Maternity and Children hospital approved this study.

Authors' contributions

HMAY: Conceived and designed the study, conducted the research, provided research materials, collected data, organized data, and obtained results. **RAAM:** Conceived and designed the study, conducted the research, analyzed and interpreted data, and wrote the initial and final draft of the article. **HM:** Participated in data collection and histopathological analysis of specimens. **ZS:** Analyzed and interpreted

data and participated in writing the draft of the manuscript. **AB**: Provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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References

1. Chene G, Penault-Llorca F, Raoelfils I, Bignon YJ, Ray-Coquard I, Seffert P, et al. Ovarian carcinogenesis: recent and past hypotheses. **Gynecol Obstet Fertil 2011**; 39(4): 216–223. Epub 2011/03/25. La cancerogenese : theories actuelles et passees.
2. Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. **Arch Gynecol Obstet 2016**; 293(4): 695–700. Epub 2016/02/20.
3. Alsuhaibani A, Elashwah A, Mahmood R, Abduljabbar A, Alhomoud S, Ashari L, et al. Dose escalation with Simultaneous Integrated Boost (SIB) using Volumetric Modulated Arc Therapy (VMAT) in rectal cancer. **J Gastrointest Canc 2018**. https://doi.org/10.1007/s12029-018-0133-0.
4. Alshamrani AM, Sairafi RA, Alzahrani AM, Abdel-Raheem M. Appendicular schwannoma presenting as vague abdominal pain. **J Surg Case Rep 2018**; 2018(7): rjy149. Epub 2018/07/12.
5. Abdullah LS, Bondagji NS. Histopathological pattern of ovarian neoplasms and their age distribution in the western region of Saudi Arabia. **Saudi Med J 2012**; 33(1): 61–65. Epub 2012/01/26.
6. Alzahrani AF, Hassan B, Alzahrani F, Almoria AA, Assiri ME, AY F. Histopathological pattern of ovarian neoplasms and their age distribution in Asir region of Saudia Arabia. **Int Sci Res Organ J 2018**; 3(1): 2455–8818.
7. Alzahrani AS, Alqahtani A, Alhazmi M, Gaafar R, Bajabir D, Alharbi IM, et al. Attitudes of cancer patients and their families toward disclosure of cancer diagnosis in Saudi Arabia: a Middle Eastern population example. **Patient Prefer Adherence 2018**; 12: 1659–1666. Epub 2018/09/15.
8. Abdullah Layla S, Bondagji NS. Histopathological pattern of ovarian neoplasms and their age distribution in the western region of Saudi Arabia. **Saudi Med J 2012**; 33(1): 61–65.
9. Geetha P, Nair MK. Granulosa cell tumours of the ovary. **Aust N Z J Obstet Gynaecol 2010**; 50(3): 216–220. Epub 2010/07/14.
10. Zeyad Saeed A-S, Ahmed Saleh H, Ali Saeed A-Z, Hind Mohammed A-M, et al. *Cancer incidence report Saudi Arabia*. Kingdom of Saudi Arabia: Saudi Health Council, Saudi Cancer Registry; 2016.
11. Kottarathil VD, Antony MA, Nair IR, Pavithran K. Recent advances in granulosa cell tumor ovary: a review. **Indian J Surg Oncol 2013**; 4(1): 37–47. Epub 2014/01/16.
12. Kalfa N, Veitia RA, Benayoun BA, Boizet-Bonhoure B, Sultan C. The new molecular biology of granulosa cell tumors of the ovary. **Genome Med 2009**; 1(8): 81. Epub 2009/09/04.
13. Suresh PS, Rajan T, Tsutsumi R. New targets for old hormones: inhibins clinical role revisited. **Endocr J 2011**; 58(4): 223–235. Epub 2011/04/12.
14. Sundararajan S, Ahmed A, Goodman Jr OB. The relevance of BRCA genetics to prostate cancer pathogenesis and treatment. **Clin Adv Hematol Oncol H&O 2011**; 9(10): 748–755. Epub 2012/01/19.
15. Forae GD, Aligbe JU. Ovarian tumors among Nigerian females: a private practice experience in Benin-City, Nigeria. **Adv Biomed Res 2016**; 5: 61–66.
16. Ahmad Z, Kayani N, Hasan SH, Muzaffar S, Gill MS. Histological pattern of ovarian neoplasma. **JPMA J Pakistan Med Assoc 2000**; 50(12): 416–419. Epub 2001/02/24.
17. Lora Hedrick E, Edyta P. The female tract. In: Cotran RS KV, Collins T, editors. *Robins pathologic basis of diseases*. 6th ed. Philadelphia: W,B Saunders Company; 1999. p. 1068.
18. Gilks CB. *Diagnostic pathology of ovarian tumors*. New York, NY: Springer; 2011.
19. Abu-Zaid A, Nazer A, Alomar O, Azzam A, Al-Eid HS, Elhassan TA, et al. Incidence of malignant ovarian germ cell tumors (MOGCTs) in Saudi Arabia. **Hematol/Oncol Stem Cell Ther 2014**; 7(1): 41–43. Epub 2014/01/15.
20. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. **CA Cancer J Clin 2018**; 68(4): 284–296. Epub 2018/05/29.
21. Ganeshaguru K, Acquaye J, Samuel AP, Sejeny SA, Omer A. Intertribal variation in the prevalence of alpha-thalassemia in Saudi Arabia. **Birth Defects Orig Artic Ser 1988**; 23(5B): 365–370. Epub 1988/01/01.
22. Moschetta M, George A, Kaye SB, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. **Ann Oncol Off J Eur Soc Med Oncol 2016**; 27(8): 1449–1455. Epub 2016/04/03.
23. Hughes C, Gomez-Caminero A, Benkendorf J, Kerner J, Isaacs C, Barter J, et al. Ethnic differences in knowledge and attitudes about BRCA1 testing in women at increased risk. **Patient Educ Counsel 1997**; 32(1–2): 51–62. Epub 1997/11/14.
24. Wendt C, Lindblom A, Arver B, von Wachenfeldt A, Margolin S. Tumour spectrum in non-BRCA hereditary breast cancer families in Sweden. **Hered Cancer Clin Pract 2015**; 13(1): 15. Epub 2015/06/18.
25. Xu Y, Li X, Wang H, Xie P, Yan X, Bai Y, et al. Hypermethylation of CDH13, DKK3 and FOXL2 promoters and the expression of EZH2 in ovary granulosa cell tumors. **Mol Med Rep 2016**; 14(3): 2739–2745. Epub 2016/07/20.
26. Alzahrani AS, Murugan AK, Qasem E, Alswailem MM, AlGhamdi B, Moria Y, et al. Absence of EIF1AX, PPM1D, and CHEK2 mutations reported in Thyroid Cancer Genome Atlas (TCGA) in a large series of thyroid cancer. **Endocrine 2018**. https://doi.org/10.107/s12020-018-11762-6.
27. Alghamdi IG, Hussain II, Alghamdi MS, Alghamdi MM, Dohal AA, El-Sheemy MA. Incidence rate of ovarian cancer cases in Saudi Arabia: an observational descriptive epidemiological analysis of data from Saudi Cancer Registry 2001–2008. **Int J Women's Health 2014**; 6: 639–645. Epub 2014/07/17.

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