Original Article

Global epidemiology, risk factors, and histological types of ovarian cancers in Trinidad

Srikanth Umakanthan[1], Vijay K. Chattu[2], Sherene Kalloo[3]

[1]Department of Paraclinical Sciences, Anatomical Pathology Unit, Faculty of Medical Sciences, [2]Department of Paraclinical Sciences, Public Health and Primary Care Unit, Faculty of Medical Sciences, [3]Department of Obstetrics and Gynaecology, MTS Plaza, San Juan, Trinidad and Tobago

Abstract

Background: Ovarian cancer is the seventh most common cancer in women in the world and Trinidad and Tobago is ranked 18th in the world with respect to the rate of occurrence. About 68% cases are diagnosed at a late stage, resulting in low survival rates. Since there is very scanty literature available on the epidemiology of ovarian cancer in the Caribbean region, this study was undertaken to assess the most common risk factors, presenting symptoms and common histological varieties in Trinidad. **Methods:** A hospital-based, cross-sectional study was designed, and all the 23 diagnosed ovarian cancer cases registered during 2015–2017 were considered. Information on sociodemographics, presenting symptoms, and histological type of cancers were collected after getting the ethical approval. Of the total 23 cases, 17 cases were included in this study after ensuring completeness of data as detailed analysis of patient data was done using Microsoft Excel. **Results:** The common risk factors identified were previous pregnancies, previous surgeries, and irregularities in the menstrual cycle. The commonest histological variety was granulosa tumors and the most common associated symptoms were irregular menses and abdominal pain in premenstrual women, and abdominal distention in postmenopausal women. **Conclusions:** It would greatly enhance the detection rate if screening and testing for the CA-125 gene were a mandatory practice, for any patient found with more than three risk factors. The public health authorities should identify the modifiable risk factors and implement cancer reduction and health promotion activities to reduce the mortality related to ovarian cancers.

Keywords: Cross-sectional design histology hormone replacement therapy, ovarian cancer, risk factors, serous carcinoma

Introduction

Ovarian cancer is the fifth leading cause of cancer death in women and the leading cause of gynecologic cancer death.[1] About 68% are diagnosed at a late stage; thus, survival rates of those patients are lower than those diagnosed at an earlier stage. Ovarian cancer has a far lower survival rate than other cancers as people are unaware that its risk factors and symptoms are easily disguised as normal menstrual problems or other abdominal ailments/diseases. As such, ovarian cancer is mostly detected at a late stage that may be untreatable resulting in unfavorable prognosis. According to statistics gathered by the World Cancer Research Fund International, Trinidad and Tobago is ranked 18th in the world with respect to the rate of occurrence of this disease.[2] Its onset is asymptomatic in the early stages so is already in the latter stages of development.[3,4] Patients diagnosed with this cancer have approximately 50% of their survival time for the next 5 years. The reason for ovarian cancer being such a dilemma is the fact that its detection at early stages is highly difficult. The appalling statistic is that only about 19% of such cases are diagnosed before the cancer manifests itself to surrounding areas from within the ovaries, that is, when the treatment is actually most receptive. Statistics suggest that a remarkable 77% of cases could have only been diagnosed after escalating to advanced stages in the cancer's progression, the reason being that symptoms in early stages are often subtle, inconsistent, or

Address for correspondence: Dr. Vijay K. Chattu, Lecturer- Public Health and Research Coordinator, Public Health Research Coordinator, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad and Tobago.
E-mail: Vijay.chattu@sta.uwi.edu

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_384_18

How to cite this article: Umakanthan S, Chattu VK, Kalloo S. Global epidemiology, risk factors, and histological types of ovarian cancers in Trinidad. J Family Med Prim Care 2019;8:1058-64.

misinterpreted. The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 estimates the incidence of ovarian cancer in 2017 around 2861,000[5] and the percentage change in disability-adjusted life years (DALYs) during 2007–2017 rose to 29%.[6] According to the American Cancer Society, approximately 90% of ovarian cancers are epithelial ovarian carcinomas which are subdivided based on their microscopic features into serous, mucinous, endometrioid, clear cell, and undifferentiated.[7] Less than 2% of ovarian cancers are germ-cell tumors. The subtypes are, namely, teratomas, dysgerminomas, endodermal sinus tumors, and choriocarcinomas, which also have different appearances under the microscope. Lastly, ovarian stromal cell tumors make about 1% of ovarian cancers.[8] These can produce hormones (e.g., estrogen) and include granulosa cell and granulosa-theca tumors. Since there is very scanty literature and data available on the epidemiology of ovarian cancer in the Caribbean region and in Trinidad and Tobago, this study was undertaken to assess the most common risk factors, presenting symptoms and common histological varieties of ovarian cancers in Trinidad.

Methods

Setting

This study is conducted at Eric Williams Medical Sciences Complex (EWMSC), a hospital of the North Central Regional Health Authority of Trinidad and Tobago. This hospital includes a Women's Hospital, as well as a histopathology department, making it ideal for this study. EWMSC is also a teaching facility for medical students.

Ethical approval

The ethical approval was sought from the Campus Ethics Committee of The University of the West Indies, St. Augustine, Trinidad and Tobago.

Study design

A hospital-based, cross-sectional study was designed, and all the diagnosed ovarian cancer cases registered during 2015–2017 were included. Of the 23 cases registered, complete information available for all the 17 cases of ovarian carcinomas were collected and the remaining cases had to be omitted due to incomplete data in the case files.

Sample collection

The records of the identified cases were obtained with permission from the histopathology unit and information on medical, physical, social, and genetic factors were noted and tabulated to observe trends and common prominent risk factors among the sample population.

Study population

All the women aged 18 years and above with diagnosed ovarian carcinomas, who had complete medical records and who sought treatment at Mt. Hope Women's Hospital, were included in the study. Exclusion criteria included women whose records were not present and women who were diagnosed prior to the time frame of the study (before 2015).

Data collection, protection, and confidentiality

Patient information, relevant to our research, was obtained via the hospital records at Mt. Hope as there is no primary need for face-to-face interaction. Potential subjects were selected from preexisting databases. Anonymous, coded questionnaires were used to ensure privacy and data were stored securely to ensure confidentiality.

Results

Risk factors

The risk factors included a variety of factors ranging from previous pregnancies, previous surgeries, cancer diagnosis, irregular menstrual cycles, smoking, use of contraceptive pills, hormone replacement therapy (HRT), recreational drug use, and family history of cancer.

Figure 1 shows many factors for ovarian cancer that were recorded from the patient records. Factors such as previous pregnancies, surgeries, and irregular menstrual cycle were recorded most frequently as 13, 12, and 9 patients, respectively. Factors seen slightly less frequently were previous cancer diagnosis, smoking, contraceptive use, and alcohol use, with 7, 6, 5, and 4, respectively. Those rarely seen were family history of cancer, infertility, recreational drug use, and HRT, with 1, 2, 0, and 0 patients, respectively.

Presenting symptoms

The most common presenting symptoms were studied separately for postmenopausal and non-menopausal women. The prevalence of common presenting symptoms among the participants diagnosed with ovarian cancers is shown in Figure 2.

The non-menopausal patients seem to, more frequently, experience irregular menses (7), abdominal/back pain (7), ovarian

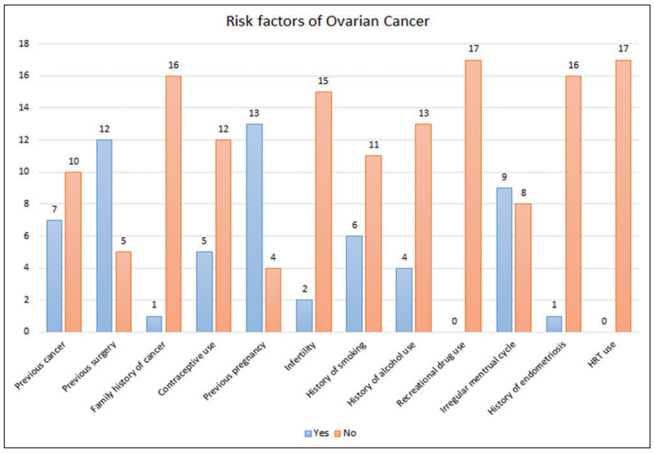

Figure 1: Distribution of risk factors among the study participants

cysts (5), PV bleeding/discharge (4), and uterine fibroids (2); whereas the postmenopausal patients exhibited mostly abdominal distension (4 patients), PV bleeding/discharge, (3) and other symptoms such as nausea, headaches, dizziness, etc., (6). There was also one postmenopausal patient with abdominal pain, ovarian cysts, and uterine fibroids.

Figure 3 illustrates the most common histological varieties/types recorded in the patient files. Most of the records (58%) showed no data on histological types though 16% of patients had granulosa cell tumors and 6% had leiomyomas. Meanwhile, the remaining recorded types, papillary serous cystadenofibroma, serous cystadenoma, cystic teratoma, and insular ovarian carcinoma, each accounted for 5% of patients.

Discussion

Risk factors

Of the total study participants assessed for the prevalence of various risk factors, 41% (7) of the patients were reported to have had previous cancers and 5.9% (only one person) was reported to have had a family history of cancer. There is a strong genetic link to cancer and recent studies have pointed out mutations, such as BRCA1 and BRCA2, as somewhat a "carrier gene" for cancer, increasing the risk of particularly breast, fallopian tube, peritoneal, and ovarian cancer.[9] Among the 17 study participants, 11.8% (2 persons) tested positive for the CA-125 gene, based on their lab reports. This gene has been termed as "clinically reliable diagnostic marker for ovarian cancer."[10] A majority (12, 70.5%) of the patients were reported to have undergone previous surgeries. Most prevalent among these surgeries were Total abdominal hysterectomy/bilateral salphingo-oophorectomy (TAH/BSO), cystectomies, and the removal of products of conception. Traditionally, these surgeries reduce the risk of ovarian cancer and research published by *BJOG* (Sharma *et al.*) suggests that the occurrences of benign ovarian cysts do not increase the risk of ovarian cancer later on in life.[11] In this study, 5 out of the 17 (29.4%) patients used birth control or other such contraceptives and most contraceptives, especially those which utilize both progestin and estrogens, drastically reduce the risk of ovarian cancer.[12,13] A majority of 76.5% (13) of the patients had previous pregnancies. Women who have had their first full-term pregnancy after the age of 35 or who have never conceived or carried a baby to full term are at an increased risk of ovarian cancer.[14] This was consistent with the findings in this study. Among the 17 patients, there were 4 documented counts of spontaneous abortions. Two (11.8%) of the total participants had problems with infertility. There is a connection between women with infertility and increased cancer risk.[15] Recent studies have also found a link between the ovulation – inducing fertility treatments and a large incidence of ovarian cancer.[16] In regards to smoking habits, 35.2% (6) of the patients with ovarian cancer admitted to having a history of smoking and 23.5% (4) of the patients had a history of alcohol use. While studies suggest that smoking and alcohol consumption do not directly affect the risk of ovarian cancer, smoking increases the chance of mucinous cancers, which includes a rare type of ovarian cancer.[17] According to research, like many other conditions, the risk of ovarian cancer can be greatly reduced by maintaining a balanced diet. Alcohol intake, specifically from wine, was shown by a study entitled "Wine and other alcohol consumption and risk of ovarian cancer in the California Teachers Study cohort" to significantly raise the risk of ovarian cancer.[18] The global estimation of occupational exposure to asbestos as a contributor to cervical cancer burden[19] is shown in Table 1.

Around 53% (9) of the patients reported irregular menstrual periods. Researchers say there is a strong association between irregular periods and a slightly increased risk of ovarian cancer, although it is uncertain as to why the relationship occurs.[20,21] Only one patient (5.9%) was reported to have endometriosis.

Hippisley-Cox *et al.*[22] conducted research to "derive and validate an algorithm to estimate the absolute risk of having ovarian cancer in women with and without symptoms." They surveyed women aged 30–84, who had no previous diagnosis of ovarian cancer and no symptoms consistent with the disease. Their risk factors were then assessed, and projections of their likelihood

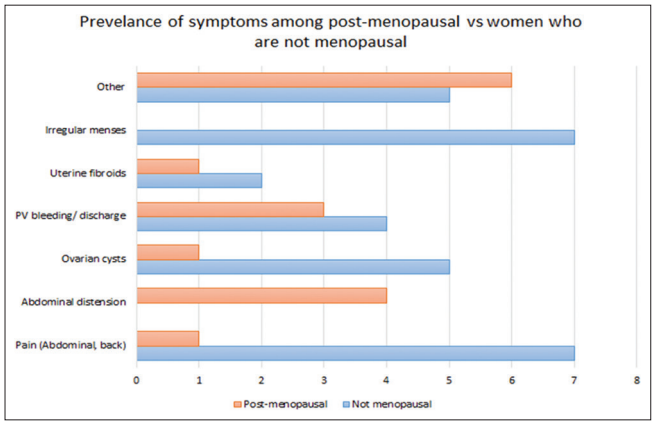

Figure 2: Distribution of presenting symptoms among study participants

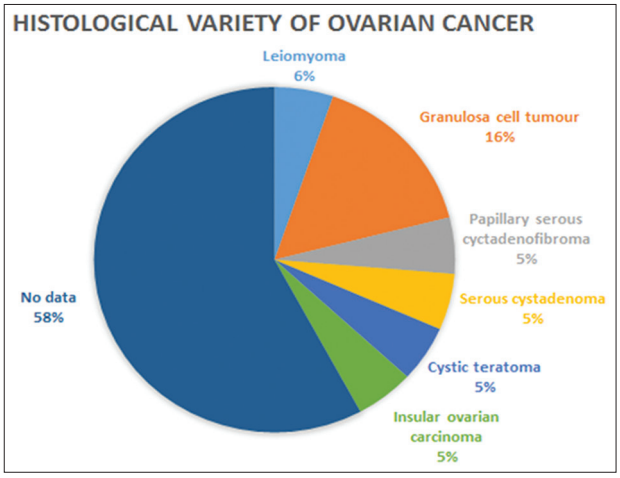

Figure 3: Distribution of various histological varieties of ovarian cancer (2015–2017)

of developing any type of ovarian cancer in the future, based on these factors, were evaluated. Risk factors assessed included "age, family history of ovarian cancer, previous cancers other than ovarian, body mass index (BMI), smoking, alcohol, deprivation, loss of appetite, weight loss, abdominal pain, abdominal distension," etc. These women were observed for the next 2 years and observed that the top risk factors were abdominal distention, age, family history of ovarian cancer, and abdominal pain. Around 10% of patients with the highest predicted risk factors had one form of ovarian cancer after the 2-year period. The results obtained were accurate and gave a reliable indication of the most common risk factors associated with ovarian cancer, in the United Kingdom. Obesity also plays a role in the predisposition to ovarian cancer. Research conducted by the Continuous Update Project[23] concluded that increased height and weight (measured by BMI) are contributing factors to ovarian cancer, and furthermore, maintaining an appropriate weight, in accordance with BMI projections, has shown to prevent up to 5% of cases. Further statistics revealed that the more developed countries (United States and United Kingdom) have a higher incidence (risk of occurrence) than less developed countries (Africa and Asia); however, the rate of occurrence is highest in Fiji, followed by several eastern European countries.

Many studies make a clear correlation between endometriosis and ovarian cancer. It is thought that hyperestrogenism, which is a huge risk factor in both endometriosis and cancers in women, plays a role. The two are similar in nature as they are both wildly proliferative and invaginate into other tissues. It is estimated that a woman with endometriosis may be three times likely to get ovarian cancer.[24,25]

Epidemiology

Trinidad and Tobago is ranked 18th with respect to the incidence of ovarian cancer among the population.[2] According to Dr. Cory Couillard's article entitled "World Ovarian Cancer Day builds awareness" in May 2013, ovarian cancer has a far lower survival rate than other cancers, notably breast cancer, and most of the women are unaware of its metabolic, genetic, environmental, and behavioral risk factors.[26] Postmenopausal women, usually over 50 years of age (especially those with a family history of breast, ovarian, or colorectal cancers), and women who undergo estrogen-only hormone replace therapy are at higher risk of developing ovarian cancer. As such, ovarian cancer is mostly detected at a late stage that may be untreatable, explaining its low survival rate when compared to other cancers. The global incidence, prevalence, years lived with disability, and DALYs due to ovarian cancers are shown in Table 2. If ovarian cancer can be accurately diagnosed quickly in its progression, the chances of surviving it will be remarkably higher. Hence, it is of utmost importance for a woman to be aware of the symptoms and possible risk factors.

Histopathology

Regarding the histological varieties of ovarian cancer, 16% of patients demonstrated granulosa cell tumors which is a type of sex cord stromal tumor, which usually occurs in women over 15 years of age and is, in many cases (75%), associated with hyperestrogenism and can cause endometrial hyperplasia.[27] There is a 5–25% risk of malignancy, though this cannot be determined via histology. About 6% of the cases showed leiomyoma. This is a rare benign smooth muscle (purportedly) tumor that is usually/mostly unilateral in adults. Though benign, it causes abdominal pain similar to appendicitis.[28] Papillary serous cystadenofibroma and serous cystadenoma account for 5% each of the cases seen. They are both a type of benign serous tumor, named based on the proportion of fibrous stroma that the tumor encompasses.[29] Of the total, only 5% of the cases were cystic teratoma. Teratomas are germ-cell tumors which can either be benign (cystic/mature) or malignant (solid/immature). However, malignant mature teratoma is rarely seen. Only 5% of the cases were insular ovarian carcinoma, usually a unilateral carcinoid tumor, although there are cases where the contralateral tumor are mucinous in nature (more aggressive).[30] The symptoms of ovarian cancer are varied and certain symptoms seem to affect the premenopausal women more frequently as opposed to the postmenopausal and vice-versa. This includes irregular menses and abdominal pain for the premenopausal women, which are the usual symptoms for ovarian cancer, while the postmenopausal patients exhibit abdominal distension and other symptoms like nausea, dysuria, headache, dizziness, etc.[13] Then, there are those symptoms like uterine fibroids, PV bleeding/discharge, and ovarian cysts which are also seen in fairly expectant frequencies. Overall, these symptoms can be

Table 1: Global estimation of occupational exposure to asbestos as a contributor to ovarian cancer burden

Occupational exposure	2007 Deaths (thousands)	2017 Deaths (thousands)	Percentage change in deaths, 2007-2017	2007 DALYs	2017 DALYs	Percentage change in DALYs, 2007-2017
Asbestos	4 (0-10)	6 (0-13)	34.5% (22.4-39.8)*	111 (0-251)	149 (0-334)	35.1 (22.6-41.2)*

*Statistically significant increase. DALY=Disability-adjusted life years

Table 2: Global burden, years lived with disability (YLDs), and disability-adjusted life years (DALYs) of ovarian cancer

Prevalence (thousands) 2017 counts	Incidence (thousands) 2017 counts	YLDs (thousands) 2017 counts	Percentage change in YLDs counts, 1990-2007	Percentage change in YLDs counts, 2007-2017	All age-DALYs (thousands) 2017	Percentage change in DALYs 2007-2017
1353 (1313.7-1401.1)	286.1 (278.1-295.3)	176.1 (127.9-224.2)	48.9% (42.2-56.6)*	27.7% (22.9-32.9)*	4670 (4530-4830)	29% (24.7-33.1)*

*Statistically significant increase. YLD=Years lived with disability; DALY=disability-adjusted life years

misunderstood for those of a less serious/noncancerous disease. The presence of these symptoms was not used as a diagnostic tool for ovarian cancer; a biopsy was always done to confirm the diagnosis in all the patients sampled.

However, there are some limitations in this study as the records obtained at the hospital only consisted of cases up to 3 years old, resulting in a limited sample size, and several cases had to be omitted due to incomplete information in the case files.

Role of primary care physicians in case detection and management

Around a quarter of those in the developed world die of cancer and this figure is rising.[31] Most of these cancers present with symptoms and most of them are reported initially to primary-care physicians.[32] Though it is well know that ovarian cancer is a silent killer, few studies have highlighted it as a "noisy killer" with nonspecific symptoms like fatigue, abdominal pain, and increased urinary frequency initially. The other symptoms like abdominal distension has a relatively high risk of cancer with a 2.5% positive predictive value and numerous studies on primary care show that the patients report first to their general practitioners (GPs) or primary-care physicians.[33-38] The most common problem seems to be GPs as they either don't think of ovarian cancer with such symptoms or consider it so unlikely as not to warrant examination or investigation, thereby making ovarian cancer a frequent miss.[39] In this context, the GPs are no worse or better in diagnosing ovarian cancer than any internal cancer.[40] Therefore in primary-care settings, measuring serum CA-125 is possible, but it has reasonable specificity and sensitivity is not known because of its debatable value.[41,42] However, numerous screening studies indicate that intra-vaginal ultrasound is a better method with good performance characteristics.[43] Hence, there is a great role of GPs in doing risk assessments, screening the ovarian cancers at an early stage, and providing proper referral services, thereby improving the survival rate and quality of life of patients. There is a great need of standard screening guidelines, capacity building programs for the GPs, and at the same time, there must be good infrastructure and essential diagnostics made available at the primary-care settings in order to improve the early case detection.

Conclusions

The most common risk factors associated with ovarian cancer are previous pregnancies, previous surgeries, and irregularities in the menstrual cycle. The most common histological variety was granulosa tumors, and the most common associated symptoms were irregular menses and abdominal pain in premenstrual women and abdominal distention in postmenopausal women. It would greatly enhance the detection rate if screening and testing for the CA-125 gene were a mandatory practice, for any patient found with more than three risk factors. It is of great importance to public health authorities to identify modifiable risk factors and use this to implement cancer reduction and health promotion activities, thus reducing the mortality related to ovarian cancer. This information can be used to encourage a more thorough history taking by the physician to identify family history of ovarian cancer, previous history of cancer, use of contraceptives, etc., as these risk factors are crucial in early diagnosis of ovarian cancer and thus help in initiating an early target treatment. Health facilities should also be encouraged to keep proper record keeping and ensure completeness and functioning by using good-quality instruments, for example, ultrasound equipment operated by specialists as this can also affect the time and accuracy of diagnosis. Lastly, education of the public on risk factors is also important as they can identify if they are at risk for ovarian cancer and take relevant precautions to prevent it.

Acknowledgments

The authors would like to acknowledge all the authors and researchers of the articles that were reviewed in preparing this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. American Cancer Society, Key Statistics for Ovarian Cancer. Available from: https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. [Last accessed on 2018 Oct 11].
2. Llanos AAM, Warner WA, Luciani S, Lee TY, Bajracharya S, Slovacek S, *et al.* Gynecologic cancer mortality in Trinidad and Tobago and comparisons of mortality-to-incidence rate ratios across global regions. Cancer Causes Control 2017;28:1251-63.
3. World Cancer Research Fund International. Ovarian cancer statistics. World Cancer Research Fund International [Internet]. [cited 2016 Nov 5]; Available from: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/ovarian-cancer-statistics.
4. Warner WA, Lee TY, Badal K, Williams TM, Bajracharya S, Sundaram V, *et al.* Cancer incidence and mortality rates and trends in Trinidad and Tobago. BMC Cancer 2018;18:712.
5. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858.
6. Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al.* Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1859-922.
7. Feeley KM, Wells M. Precursor lesions of ovarian epithelial malignancy. Histopathology 2001;38:87-95.

8. Antovska VS, Trajanova M, Krstevska I, Gosheva I, Chelebieva J, Prodanova I. Ovarian strumal carcinoid tumour: Case report. Open Access Maced J Med Sci 2018;6:540-3.
9. Ramus SJ, Antoniou AC, Kuchenbaecker KB, Soucy P, Beesley J, Chen X, *et al.* Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Hum Mutat 2012;33:690-702.
10. Felder M, Kapur A, Gonzalez-Bosquet J, Horibata S, Heintz J, Albrecht R, *et al.* MUC16 (CA125): Tumor biomarker to cancer therapy, a work in progress. Molecular Cancer 2014;13:129.
11. Sharma A, Gentry-Maharaj A, Burnell M, Fourkala EO, Campbell S, Amso N, *et al.* Assessing the malignant potential of ovarian inclusion cysts in postmenopausal women within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A prospective cohort study. BJOG 2012;119:207-219. Retrieved from BJOG: An International Journal of Obstetrics and Gynaecology. Published online 2011 Jul 15.
12. Treviño LS, Buckles EL, Johnson PA. Oral contraceptives decrease the prevalence of ovarian cancer in the hen. Cancer Prev Res (Phila) 2011;5:343-9.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC Monogr Eval Carcinog Risks Hum 2007;91:74-84.
14. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, *et al.* Ovarian cancer risk factors by histologic subtype: An analysis from the ovarian cancer cohort consortium. J Clin Oncol 2016;34:2888-98.
15. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: A review. J Assist Reprod Genet 2016;34:167-77.
16. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: A review. J Assist Reprod Genet 2016;34:167-77.
17. Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, *et al.* Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Br J Cancer 2015;113:809-16.
18. Chang ET, Canchola AJ, Lee VS, Clarke CA, Purdie DM, Reynolds P, *et al.* Wine and other alcohol consumption and risk of ovarian cancer in the California Teachers Study cohort. Cancer Causes Control 2007;18:91-103.
19. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, *et al.* Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1923-94.
20. Harris HR, Titus LJ, Cramer DW, Terry KL. Long and irregular menstrual cycles, polycystic ovary syndrome, and ovarian cancer risk in a population-based case-control study. Int J Cancer 2016;140:285-91.
21. Merritt MA, De Pari M, Vitonis AF, Titus LJ, Cramer DW, Terry KL. Reproductive characteristics in relation to ovarian cancer risk by histologic pathways. Hum Reprod 2013;28:1406-17.
22. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithms to estimate future risk of common cancers in men and women: Prospective cohort study. BMJ Open 2015;5:e007825.
23. World cancer research Fund International. The Continuous Update Project. Available from https://www.wcrf.org/int/continuous-update-project. [Last accessed on 2018 Oct 04].
24. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: A meta-analysis. Br J Cancer 2014;110:1878-90.
25. Wendel JRH, Wang X, Hawkins SM. The endometriotic tumor microenvironment in ovarian cancer. Cancers (Basel) 2018;10:261.
26. Couillard C. World Ovarian Cancer Day builds awareness. Trinidad Express Newspapers [Internet]. 2013 May 13 [cited 2016 Nov 5]. Available from: http://www.trinidadexpress.com/featured-news/World-Ovarian-Cancer-Day-builds-awareness-207149451.html.
27. Haroon S, Zia A, Idrees R, Memon A, Fatima S, Kayani N. Clinicopathological spectrum of ovarian sex cord-stromal tumors; 20 years' retrospective study in a developing country. J Ovarian Res 2013;6:87.
28. Primary ovarian leiomyoma associated with endometriotic cyst presenting with symptoms of acute appendicitis: A case report. DiagnosticPathology.Biomedcentral.com website. Available from: https://diagnosticpathology.biomedcentral.com/articles/10.1186/1746-1596-4-25. [Last accessed on 2017 Jul 08].
29. Hashmi AA, Hussain ZF, Bhagwani AR, Edhi MM, Faridi N, Hussain SD, *et al.* Clinicopathologic features of ovarian neoplasms with emphasis on borderline ovarian tumors: An institutional perspective. BMC Res Notes 2016;9:205.
30. Hakim MM, Abraham SM. Bilateral dermoid ovarian cyst in an adolescent girl. BMJ Case Rep 2014;2014:1-4.
31. Hamilton W. Cancer diagnosis in primary care. Br J Gen Pract 2010;60:121-8.
32. Hamilton W. Five misconceptions in cancer diagnosis. Br J Gen Pract 2009;59:441-7.
33. Bankhead C, Collins C, Stokes-Lampard H, Rose P, Wilson S, Clements A, *et al.* Identifying symptoms of ovarian cancer: A qualitative and quantitative study. BJOG 2008;115:1008-14.
34. Tate A, Martin A, Murray-Thomas T, Anderson SR, Cassell JA. Determining the date of diagnosis-is it a simple matter? The impact of different approaches to dating diagnosis on estimates of delayed care for ovarian cancer in UK primary care. BMC Med Res Methodol 2009;9:42.
35. Bankhead C, Kehoe S, Austoker J. Symptoms associated with diagnosis of ovarian cancer: A systematic review. BJOG 2005;112:857-65.
36. Friedman GD, Skilling JS, Udaltsova NV, Smith LH. Early symptoms of ovarian cancer: A case-control study without recall bias. Fam Pract 2005;22:548-53.
37. Goff B, Mandel L, Melancon C, Muntz H. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA 2004;291:2705-12.
38. Hamilton W, Peters TJ, Bankhead C, Sharp D. Risk of ovarian cancer in women with symptoms in primary care: Population based case-control study. BMJ 2009;339:b2719.
39. Reeve G, Mackay-Thomas S. The invisible worm: Ovarian cancer. BMJ 2009;338:b2072.
40. Hamilton W, Round A, Sharp D. Ovarian cancer. Not a silent killer. BMJ 2009;339:b2719.

41. Rufford BD, Jacobs IJ, Menon U. Feasibility of screening for ovarian cancer using symptoms as selection criteria. BJOG 2007;114:59-64.
42. Sturgeon CM, Lai LC, Duffy MJ. Serum tumour markers: How to order and interpret them. BMJ 2009;339:b3527.
43. Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, *et al.* 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). Lancet Oncol 2009;10:327-40.