Incidence, Risk Factors, and Natural History of Ovarian Cysts in Postmenopausal Chinese Women: a Retrospective Cohort Study

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Objective: To evaluate the incidence of and risk factors for ovarian cysts in postmenopausal Chinese women, and the resolution rate of various morphological cysts and their association with ovarian cancer with use of serum CA-125 level and risk of malignancy index (RMI).
Methods: This was a retrospective cohort study conducted at a regional hospital in Hong Kong. All women who were first assessed in our clinic from May 2014 to January 2016 were included. We reviewed the ultrasound reports of their 6- to 9-monthly interval rescan, as well as the demographics, clinical history, and ultrasound findings of women who presented with postmenopausal bleeding. For women with any ovarian cysts on rescans or in surgery, ultrasonographic findings on interval scans and pathological reports from surgery up to 1 year were reviewed.
Results: A total of 1158 Chinese women were included. The overall incidence of ovarian cysts on a single ultrasound scan was 6.6%. The age-related incidence increased after 50 years of age and peaked at 60 to 64 years, then dropped until a second peak occurred at 75 to 79 years of age. No other potential risk factors for an increased incidence of ovarian cysts were identified. Chance of resolution of simple cysts was 26% in a single rescan. The resolution rate for a non-simple cyst was low (6%). All ovarian cysts with RMI score of <200 were benign. A RMI score of ≥200 was associated with a higher risk of ovarian cancer.
Conclusion: The resolution rate of ovarian cysts was comparable with that of overseas studies. Current management guidelines from overseas are appropriate for the Chinese population. The age-related incidence of postmenopausal cysts among Chinese women may support focusing on a target age-group in the population if a screening programme were to be implemented. Further prospective studies are warranted.
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Keywords: Incidence; Natural history; Ovarian cysts; Postmenopause; Risk factors

Introduction

Ovarian cysts are common in postmenopausal women. Although the majority of these cysts are benign, it is important to identify those that are potentially malignant because ovarian cancer is associated with high mortality[1]. Ovarian cancer is now the most common cause of death in Hong Kong due to cancer of the female genital tract although it has a lower overall prevalence[2]. Early disease is often asymptomatic and many women present late with advanced disease.

Although early diagnosis is associated with improved prognosis, there remains a lack of established screening programmes worldwide for ovarian cancer, due to the limited specificity of non-invasive screening tests[3-5] and the increase in unnecessary morbidities from invasive procedures. A recent breakthrough from a national randomised controlled trial in the UK[6] showed that annual screening for ovarian cysts with ultrasonography (USG) and serum CA-125 in low-risk postmenopausal women was associated with a significant reduction in mortality after 7 to 14 years of screening. Therefore, the efficacy and cost-effectiveness of an ovarian cancer screening programme is now being further evaluated in national studies in the UK.

With increasing evidence that screening for postmenopausal ovarian cysts may reduce mortality from ovarian cancer, data on the incidence of and risk factors for postmenopausal ovarian cysts will be helpful in clinical counselling, recommendations, and policy planning. Previous overseas studies have estimated the incidence of postmenopausal ovarian cysts to be 5% to 17%[7-10], but no

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data have been published for the Chinese population. The primary aim of this study was to evaluate the incidence of and risk factors for ovarian cysts detected on a single USG scan in postmenopausal Chinese women. We also explored the natural history of postmenopausal cysts in a low-risk population and the risk of ovarian cancer associated with a morphological complex ovarian cyst, elevated CA-125 level, and high risk of malignancy index (RMI). This study therefore also attempted to determine the value of applying international guidelines for the management of postmenopausal cysts to our predominantly Chinese population.

Methods

This was a retrospective cohort study conducted at the postmenopausal bleeding assessment (PMBA) clinic of a regional hospital in Hong Kong. All women who were first assessed in the PMBA clinic from May 2014 to January 2016 were included, and the ultrasound reports of their 6- to 9-monthly interval rescan were reviewed. Ethics approval was obtained from the local institutional research ethics committee with patient consent waived due to its retrospective nature (Ref: HKEC-2016-098).

All patients who presented to the PMBA clinic during the study period were managed according to the latest departmental operational guidelines, in which their clinical history, physical examination, and pelvic USG findings were documented on a standardised electronic template.

Clinical history of postmenopausal bleeding and presence of associated symptoms including lower abdominal pain and abdominal distension were documented. Further details including the patient's obstetric history, medical history, medication history (e.g. hormone contraception or hormone replacement therapy), social history (e.g. ethnicity and smoking history), and family history of gynaecological, breast, or colorectal cancers were also recorded.

Pelvic USG was performed in every patient by medical officers who had completed and passed the accredited examination of the Obstetrics and Gynaecology Ultrasound Training Programme of the Hospital Authority of Hong Kong. Transvaginal scans were routinely performed except in patients who had never been sexually active, in which case a transabdominal or transrectal approach was adopted. Endometrial thickness was routinely screened as well as bilateral ovaries and adnexa. A 5-7.5 MHz transvaginal probe was used to measure each ovary and describe any observed abnormalities. The examiner spent at least 5 minutes searching for both ovaries, but the scan was halted if the iliac vessels were visualised and the ovaries were not visible.

Presence of ovarian or adnexal cysts were documented with the following details: (1) size measured along the major and minor axes of both transverse and longitudinal planes; (2) laterality; (3) non-simple features including presence of loculations, any mixed (solid / cystic) component, any solid area or papillary projection that extended into the cyst cavity; and (4) presence of ascites.

Serum CA-125 was measured in any woman with ovarian cyst(s) and the RMI calculated (RMI I score was used[11]). For patients with simple ovarian cysts and Ca-125 level of <35 U/ml — defined in this study by cyst size of <5 cm; unilateral; and absence of non-simple features as mentioned above or ascites — a repeat pelvic USG assessment was arranged in 6 to 9 months' time. If the cysts persisted on two consecutive scans or had altered features, bilateral oophorectomy was offered.

Women with non-simple ovarian cysts or elevated CA-125 level and RMI I score were counselled about surgical intervention. In patients who opted for surgery, an USG assessment was arranged as part of their preoperative assessment. In those who declined surgery, pelvic USG assessment was repeated after a further 6 months.

In this study, clinical data of women who attended the PMBA clinic were extracted from medical records of the electronic patient record database of the Hospital Authority, Hong Kong. The overall incidence of ovarian cysts and possible risk factors for developing ovarian cysts were studied. The natural history of either simple or complex cysts of these patients was also reviewed to determine the chance of resolution on follow-up scans. For patients who underwent surgery, operative findings and clinical pathological reports of the ovaries were reviewed.

Statistical analysis was performed using Stata Windows version 14.0. To measure the relative risk of potential risk factors, comparison between the outcome groups was made by Fisher's exact test for binary and categorical variables. A p value of <0.05 was considered statistically significant.

Inclusion and Exclusion Criteria

All women who were assessed in the PMBA clinic from May 2014 to January 2016 were included. Since the target group in this study was the low-risk Chinese

population, patients were excluded if they fulfilled any of the following criteria: non-Chinese; not postmenopausal according to clinical history (in our study, postmenopausal was defined as a woman who had no menstruation for 12 consecutive months in the absence of any identified secondary causes); history of gynaecological malignancy; history of salpingo-oophorectomy or oophorectomy; history of hysterectomy as it reduces sensitivity in detecting an adnexal cyst; or known carrier of *BRCA1*, *BRCA2*, or Lynch syndrome.

Results

A total of 1243 patients attended the PMBA clinic during the study period, of which 85 were excluded based on our exclusion criteria. In patients who were referred with confirmed *BRCA1*, *BRCA2* gene mutation or Lynch syndrome, follow-up with regular ultrasound surveillance was arranged in the gynaecology clinic, not the PMBA clinic. As a result, data of 1158 (93%) women were reviewed (Figure 1). Table 1 summarises their demographics and characteristics.

Incidence of Ovarian Cysts

Among the 1158 women enrolled in this study, 76 (6.6%) had ovarian or adnexal cysts identified during a single episodic pelvic USG, of whom 29 had either non-simple ovarian cysts and / or elevated CA-125 level. In our study, the incidence of ovarian cysts increased with age after 50 years and peaked in the 60-64 years. The incidence then dropped until a second smaller peak at 75-79 years (Table 2).

When samples were allocated to various 2x2 contingency tables according to the bisecting ages, the odds ratio (OR) of having an ovarian cyst was significantly higher at the age of ≥65 years (OR=1.725, p=0.027) compared with the age of <65 years (Table 3).

Risk Factors for Ovarian Cyst

Multivariate analysis was performed to assess the association of traditional risk factors or protective factors for ovarian cancer with development of postmenopausal ovarian cyst. There was no significant increase in risk for having a first-degree family history of colorectal, breast or ovarian cancer; or a history of metabolic disease (diabetes, hypertension, obesity, hyperlipidaemia). There was also no associated risk for parity or history of hormone replacement therapy (Table 4).

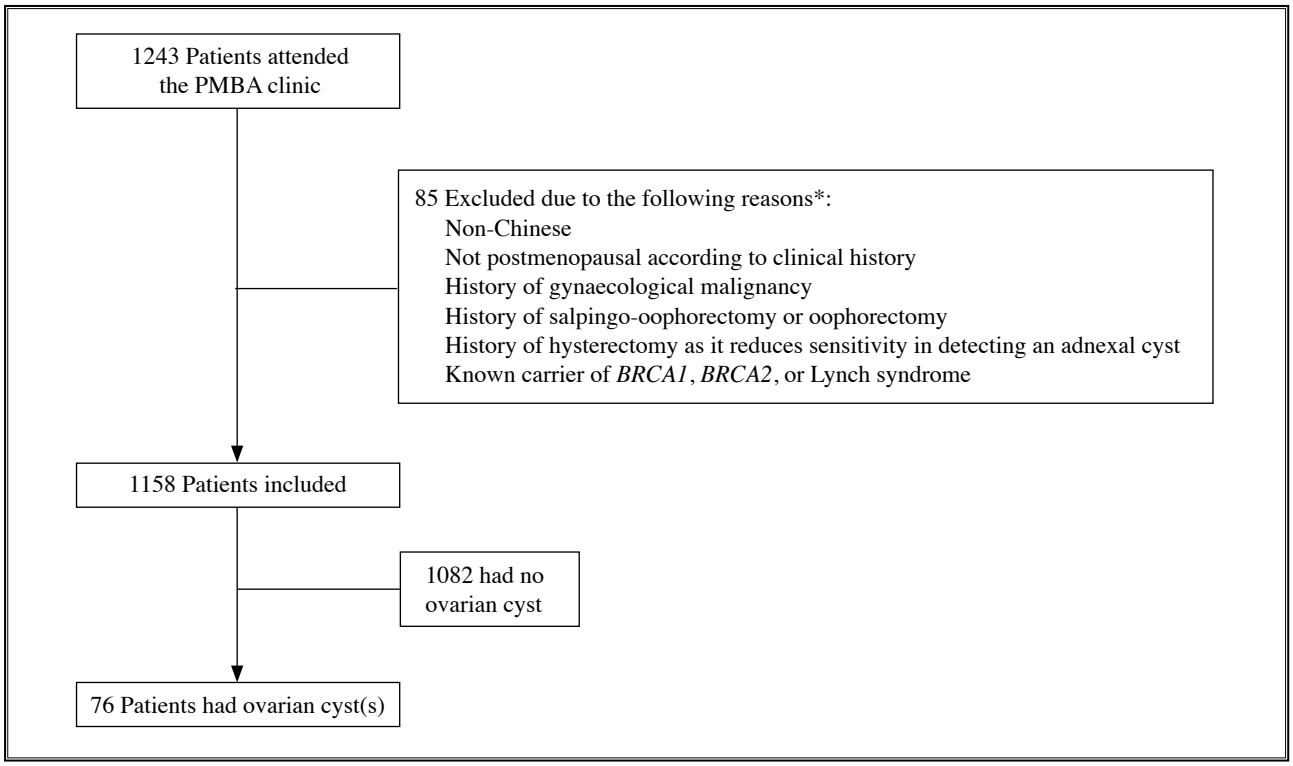

Figure 1. Study flow diagram of ovarian cyst study cohort

Abbreviation: PMBA = post-menopausal bleeding assessment

* Some patients might meet more than one exclusion criterion

Table 1. Demographics and characteristics of the ovarian cyst study cohort (population of effective data = 1158)

Demographics / characteristic	No. (%) of patients
Age-group (years)	
40-44	6 (0.52)
45-49	35 (3.02)
50-54	207 (17.88)
55-59	322 (27.81)
60-64	174 (15.03)
65-69	156 (13.47)
70-74	62 (5.35)
75-79	69 (5.96)
80-84	59 (5.09)
85-90	46 (3.97)
90-94	15 (1.30)
95-99	7 (0.60)
Parity	
Nulliparous	156 (13.47)
Primiparous / multiparous	1002 (86.53)
Sexual history	
Never sexually active	70 (6.04)
Ever sexually active	1084 (93.61)
Missing data	4 (0.35)
First-degree family history of colorectal, breast or ovarian cancer	
Yes	199 (17.18)
No	954 (82.38)
Missing data	5 (0.43)
History of hormone replacement therapy	
Yes	33 (2.85)
No	1121 (96.8)
Missing data	4 (0.35)
History of metabolic diseases (diabetes / hypertension / obesity / hyperlipidaemia)	
Yes	507 (43.78)
No	648 (55.96)
Missing data	3 (0.26)

Natural History of Ovarian Cyst

The serial re-imaging of ovarian cysts at standard intervals in this study provided information about the natural history of various ovarian cysts. Of 76 patients who had ovarian or adnexal cysts identified during a single episodic pelvic USG, 47 (62%) had simple ovarian cysts with normal CA-125 level and RMI I score of <200. Among these, 38 were re-imaged and 10 were cyst-free on one USG performed after 6 to 9 months, yielding a resolution rate of 26%. In women with persistent ovarian cysts, there was no change to cyst morphology (Figure 2).

Table 2. Age-related incidence of postmenopausal ovarian cyst

Age-group (years)	Absence of cyst	Presence of cyst	Incidence (%)
50-54	196	11	5.31
55-59	298	24	7.45
60-64	159	15	8.62
65-69	149	7	4.49
70-74	60	2	3.23
75-79	65	4	5.80
80-84	56	3	5.08
≥85	65	3	4.41

Table 3. Risk of postmenopausal ovarian cyst in various bisecting ages

Age-group (years)	Odds ratio	p Value (1-sided Fisher's exact test)
<55 vs. ≥55	1.150	0.354
<60 vs. ≥60	1.230	0.166
<65 vs. ≥65	1.725	0.027
<70 vs. ≥70	1.569	0.100

Of the remaining 29 patients who were diagnosed with non-simple cyst, 17 (94%) of 18 women with an RMI-I score of <200 who underwent interval USG re-imaging had persistent ovarian cysts. Seven opted for surgery and cysts were benign in all cases. Among four women with RMI I score of ≥200, one was not medically fit for surgery and died before workup, and another defaulted follow-up. Of the two patients who were further evaluated, one had a benign ovarian tumour and underwent subsequent laparotomy; the other was diagnosed with metastatic ovarian cancer. This last patient aged 63 years and attended for postmenopausal bleeding; she was otherwise asymptomatic except for a non-specific bloating sensation. USG revealed a 10-cm complex adnexal cyst and CA-125 level was 30096 U/ml. Computed tomographic scan of thorax, abdomen, and pelvis showed a left adnexal mass with ascites suspicious of omental cakes, enlarged lymph nodes in the para-aortic and common iliac regions, as well as unilateral pleural effusion with soft tissue nodules over the left chest wall.

Table 4. Risk factors for ovarian cyst

Risk factor	Prevalence of ovarian cyst		Adjusted association	
	No. of women	Rate of ovarian cyst (%)	Odds ratio	p Value (1-sided Fisher's exact test)
Parity	1158			
Nulliparous	156	5.77		
Primiparous / multiparous	1002	6.67	1.170	0.413
Sexual history	1154			
Never sexually active	70	7.14		
Ever sexually active	1084	6.55	0.911	0.496
Family history of colorectal, breast, or ovarian cancer (first-degree relative)	1153			
No	954	6.50		
Yes	199	7.04	1.089	0.441
History of hormonal replacement therapy	1154			
No	1121	6.51		
Yes	33	9.10	1.436	0.372
History of metabolic diseases	1155			
No	648	5.86		
Yes	507	7.50	1.301	0.161

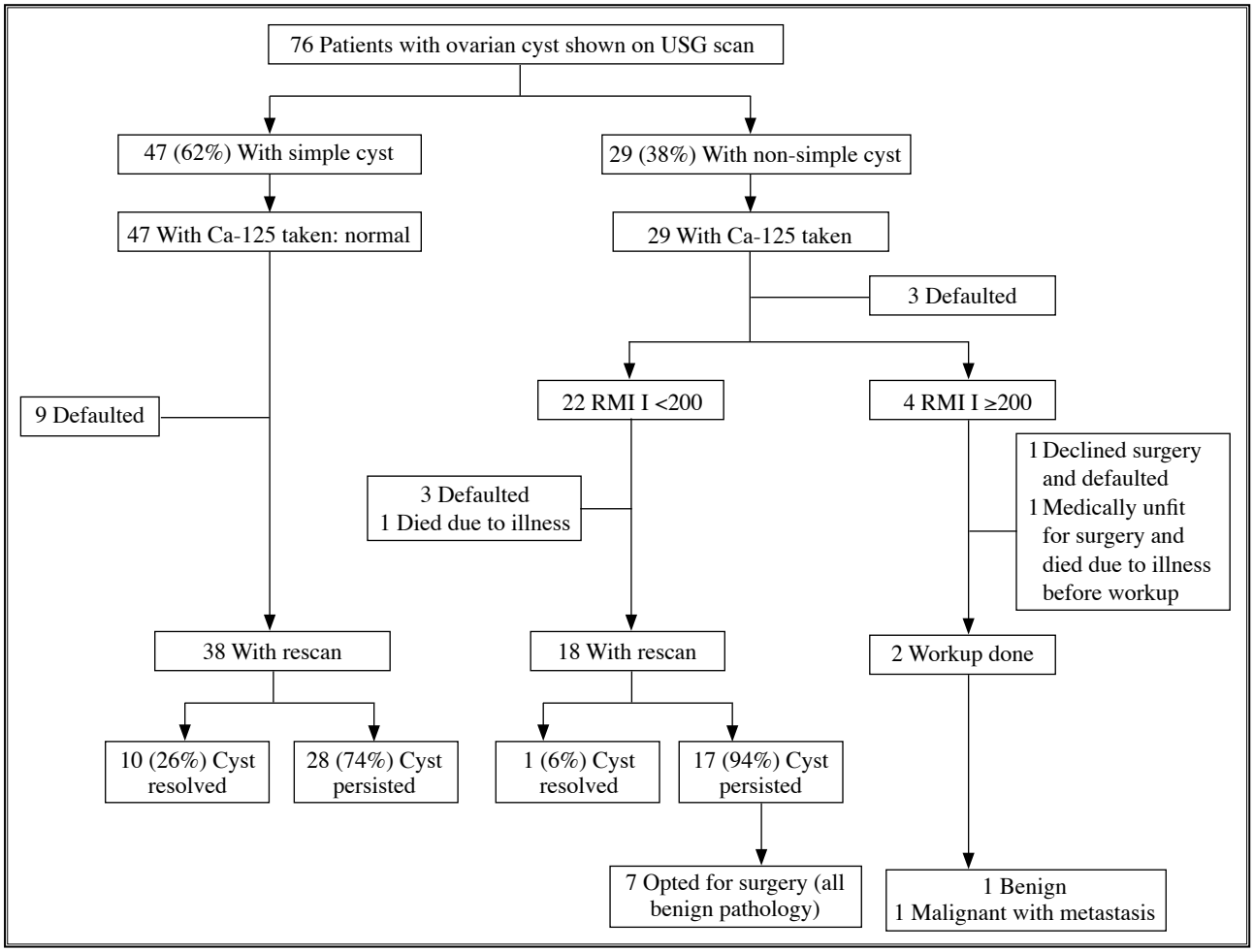

Figure 2. Study flow diagram of patients with ovarian cysts shown on ultrasonographic scan

Abbreviations: RMI = risk of malignancy index; USG = ultrasonography

Biopsy was taken and histopathology confirmed high-grade serous adenocarcinoma. USG-guided aspirated pleural fluid cytology and chest wall nodule biopsy confirmed metastasis from the female genital tract. The patient was referred to a clinical oncologist and underwent chemotherapy.

In summary, cysts were benign in all patients with simple cysts, and those with non-simple cysts and RMI I score of <200. Patients with RMI I score of ≥200 had a 50% risk of having ovarian cancer (Figure 2).

Discussion

Ovarian cysts are common findings on ultrasonography in postmenopausal women. The incidence of postmenopausal ovarian cysts on a single USG in our study was 6.6%, which is comparable with previous overseas cancer screening trials[1].

The incidence of postmenopausal ovarian cyst correlated with age in our study. A double peak pattern was observed, with the incidence increasing by the age after 50 years, peaking at the 60-64 years' age-group, then dropping until a second smaller peak at the age of 75-79 years. When the bisecting age reached 65 years, the OR of having ovarian cysts was maximised and there was a statistically significantly higher risk of having ovarian cysts between menopause and the age of 65 years. Whether this group of patients is at a higher risk of ovarian cancer requires further larger-scale prospective study.

Multivariate analysis revealed that traditional ovarian cancer risk factors (metabolic disease, family history of breast or colorectal or ovarian cancer, nulliparity) were not associated with a significant increase in ovarian cysts, probably due to the small sample size. The occurrence of postmenopausal cysts does not directly reflect risk of ovarian cancer. Nonetheless, we still advise health care providers and patients to be conscious about these health risks.

The overall findings in our follow-up studies of the natural history of both simple and non-simple ovarian cysts support the current management guidelines of the Royal College of Obstetricians and Gynaecologists[1] (RCOG) and the American College of Obstetricians and Gynecologists (ACOG)[12].

Simple cysts resolved or persisted without progression in all patients who were followed up with no apparent increased risk of malignancy. The resolution rate in one rescan was 26% in our study after 6 to 9 months, similar to that of other overseas studies with an annual resolution rate of 23% to 32%[8,13]. In our study, the follow-up period was relatively short and it was not possible to determine the long-term resolution rate. The University of Kentucky trial further followed up patients and suggested that up to 83% of simple cysts would resolve spontaneously over a mean of 4.6 years of follow-up[13].

On the contrary, the chance of resolution of a non-simple cyst with RMI I score of <200 was less than 6% in our study, which is lower than the 16.1% quoted in a previous study[14]. The figures, however, may not be directly comparable since we took the RMI I score into account and the rescan interval was also different. In view of the low resolution rate, surgical intervention should be included as one of the management options during counselling after the first scan, even when CA-125 level is normal and RMI I score is <200.

Apart from the resolution rate, management of patients with non-simple cyst should take account of the RMI I score. Our data suggest that using the new cut-off RMI I score of 200 to stratify risk of invasive ovarian cancer appears to be reliable[1]. However, patients should be informed during discussion about management of its limited sensitivity[15,16]. A prospective study with a larger sample size should be considered to evaluate this cutoff.

This is the first study to evaluate the prevalence and natural history of ovarian cysts in a Chinese population. A strength of this study is the well-structured clinical protocol for management of women with postmenopausal bleeding, and the standardised follow-up for those with ovarian cysts. All clinical data including history, physical findings, and USG reports were well-documented on a standardised electronic template so data collection was complete and accurate with less than 1% of missing data despite its retrospective nature. All USG scans were performed by an accredited medical doctor and the findings were documented in a standard format.

An ideal study design for this cohort would be to recruit asymptomatic women from the general population into a large screening USG programme. Nonetheless there is a lack of established screening programmes in Hong Kong. In most of the regional hospitals in Hong Kong, under the current clinical practice, ovarian cysts in postmenopausal women are identified either following emergency admission or by referral from an outpatient setting. In this study, we reviewed those women presented with postmenopausal

bleeding as it is an uncommon presenting symptom for ovarian cysts or ovarian cancer, except in rare cases such as a hormone-secreting tumour. The selected patient group in this study therefore represented a generally low-risk Chinese population in current clinical practice in Hong Kong.

This study has some limitations. The final histological pathology was not available for every woman with an ovarian cyst. In addition, with the small sample size and relatively short follow-up period, an accurate malignancy risk as well as long-term resolution rate could not be ascertained.

Conclusion

The incidence of postmenopausal ovarian or adnexal cysts in Chinese women was 6.6% in a single episodic pelvic USG. The incidence of postmenopausal cysts follows the double-peak pattern of the age-related incidence of ovarian cancer in Hong Kong, which increases with age and reaches its highest peak at 60-64 years, and a second peak at 75-80 years. No other risk factors or protective factors for occurrence of postmenopausal cysts were identified. The chance of resolution of ovarian cysts in the Chinese population is comparable with overseas studies. Our finding supports the current management guidelines of the RCOG and ACOG on postmenopausal ovarian cysts and their appropriateness to our local Chinese population.

Declaration

The authors have disclosed no conflicts of interest.

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