Review article

The limited oncogenic potential of unilocular adnexal cysts: A systematic review and meta-analysis

Fabio Parazzini\textsuperscript{a,c,*}, Maria Pina Frattaruolo\textsuperscript{b}, Francesca Chiaffarino\textsuperscript{a}, Dhouha Dridi\textsuperscript{b,c}, Elena Roncella\textsuperscript{b,c}, Paolo Vercellini\textsuperscript{b,c}

\textsuperscript{a}Department of Woman, Newborn and Child, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122, Milan, Italy
\textsuperscript{b}Department of Gynecological Surgery and Endometriosis, IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Via Commenda, 12, 20122 Milan, Italy
\textsuperscript{c}Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

A R T I C L E   I N F O

Article history:
Received 3 February 2018
Received in revised form 12 April 2018
Accepted 13 April 2018
Available online xxx

Keywords:
Unilocular ovarian cysts
Malignancy risk
Anechoic unilocular cysts
Postmenopausal

A B S T R A C T

The reported frequency of malignant diseases in unilocular cysts varies in different studies, giving conflicting results. To quantify the risk of malignancies among echoic and anechoic unilocular adnexal cysts, in premenopausal and postmenopausal women, we performed a PubMed/MEDLINE search of papers published in English evaluating the histopathological diagnoses of removed ovarian cysts diagnosed as simple unilocular cysts at pre-operative ultrasound examination. From 34 selected publications, we extracted data on ovarian malignancy in the total series, and separately for premenopausal and postmenopausal women, and women with cysts < 5 cm and ≥5 cm in diameter.

Of the 2177 surgically removed lesions classified as unilocular cysts on pre-operative ultrasound, 24 (1.1%; 95\% CI: 0.74–1.66) were malignant (among these 12 had borderline malignancy: 0.6%). The rates were lower for premenopausal women (6/987, 0.6%) than postmenopausal ones (12/372, 3.2%). Of the 2290 surgically removed lesions classified as anechoic unilocular cysts on ultrasound, 20 (0.9%; 95\% CI: 0.57–1.35) were malignant (among these 8 had borderline malignancy: 0.3%). The rates were lower for premenopausal women (3/907, 0.3%) than postmenopausal ones (13/681, 1.9%) (Pearson chi-square $P=0.002$). When we performed meta-analysis selecting studies including only anechoic unilocular cysts published after 2000 and with 100 or more patients, the estimate was 0.5 (95\% CI 0.1–1.2) with no heterogeneity (heterogeneity chi-square $P=0.175$).

The oncogenic risk of unilocular adnexal cysts is low, suggesting that the final choice about surgical treatment of these cysts should be based on the combination of each patient’s overall risk profile as well as personal priorities.

© 2018 Elsevier B.V. All rights reserved.

Contents

Introduction ........................................................................................................................................................................ 102
Methods ............................................................................................................................................................................... 102
Results ............................................................................................................................................................................... 107
Discussion .......................................................................................................................................................................... 108
Conclusion ............................................................................................................................................................................. 108
Disclosure of interests ....................................................................................................................................................... 108
Contribution to authorship ................................................................................................................................................ 108
Funding ................................................................................................................................................................................. 108
References ......................................................................................................................................................................... 108

* Corresponding author at: Department of Woman, Newborn and Child, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca’ Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122, Milan, Italy.
E-mail address: fabio.parazzini@unimi.it (F. Parazzini).

https://doi.org/10.1016/j.ejogrb.2018.04.019
0301-2115/© 2018 Elsevier B.V. All rights reserved.
Introduction

Ovarian cysts are a common condition. Worldwide, about 7% of women have an ovarian cyst at some point in their lives [1]. In a large American cohort study the incidence of new simple cysts was 8% per year [2], whereas the incidence of ovarian cysts in the menopausal population is likely between 3% and 18% [3]. In case of diagnosis of ovarian cysts, surgical procedure is common. In most cases the indications to surgery include also worries about malignancies. In expert hands approximately 10–25 surgeries will be performed for each malignancy identified. This number may be even higher if simple cystic masses, which represent about 30% of ovarian cysts, are not followed expectantly [4]. In fact, the risk of a unilocular ovarian cyst being malignant is considered very low and it has been suggested that unilocular cysts <5 cm in diameter in postmenopausal women require no intervention other than possibly follow-up scans [4–7].

Along this line, the American College of Obstetricians and Gynecologists (ACOG) stated that simple cysts found on ultrasound may be safely followed without intervention, even in postmenopausal women; however most of them are nowadays removed. Part of these procedures are due to the uncertainties about the risk of malignancies.

In order to review the available evidences on the risk of malignancies among echoic and anechoic unilocular adnexal cysts, both in premenopausal women and in postmenopausal women, we conducted a systematic review and a meta-analysis.

Methods

This review and meta-analysis was restricted to published research articles that evaluated the histopathological diagnoses of ovarian lesions, described as unilocular cysts at pre-operative ultrasound examination.

We performed a PubMed/MEDLINE search of papers published between January 1990 – February 2017, using the terms “unilocular ovarian cysts” or “simple ovarian cysts” combined with “ovarian cancer” or “surgery” or “transvaginal ultrasound”, or “histology”. Only studies published as full-length in English and reporting original data were included. Moreover, bibliographies of the retrieved papers were reviewed, to identify other relevant studies.

The present review and meta-analysis were conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and MOOSE guidelines [8,9].

All published studies evaluating the histopathological diagnoses of removed ovarian lesions, described as simple unilocular cysts at pre-operative ultrasound examination, were included, without any specific restriction regarding the type of echogenicity of cyst fluid and the age of women. The presence or the appearance at pre-operative ultrasound examination of septations, or solid area or papillary projection, or pathological colour doppler analysis or bilateral cysts were exclusion criteria.

Three authors (M.P.F., E.R. and D.D.) conducted an independent screening of all titles and abstracts retrieved from peer-reviewed journals to exclude irrelevant or duplicate citations. Disagreements were resolved by discussion. Data presented exclusively as abstracts in national and international meetings, or case report or review articles that did not include original data were excluded. When we found more than one publication based on the same study population and data, we included only the more recent paper or with the most detailed information.

From each publication we extracted the following information: author, year of publication, study design, number of patients enrolled, age of participants, menopausal status, size of unilocular ovarian lesions (<5 cm or ≥5 cm), echogenicity of cyst fluid at pre-operative ultrasound examination, and histopathological diagnoses of removed adnexal cysts.

The methodological quality of selected studies was assessed using the Methodological Index for Non-Randomised Studies (MINORS), a validated instrument which is designed for assessment of methodological quality of non-randomized studies in surgery [10]. Briefly, the studies were judged on eight pre-defined items and the maximum score was 16.

The primary outcomes assessed were ovarian malignancy in the total series, separately for premenopausal and postmenopausal women, and for women with cysts <5 cm and ≥5 cm in diameters. For each study with binary outcomes, we calculated the 95% confidence intervals (CI) of the estimated proportion. To evaluate the association between ovarian malignancy and menopausal status or cyst diameter, we computed Pearson Chi Square test for heterogeneity and relative P value.

Taking into account the strong improvement that modern ultrasound has had in technical quality and interpretation, we performed a sub-analysis, considering studies published during the 2000 or before and studies published after 2000.

Moreover, to perform meta-analysis of these proportions, we selected only the studies with 100 or more patients and published after 2000 in order to obtain more consistent data. We used Metaprop, a command implemented in Stata to compute meta-analysis of proportions [11]. Freeman-Tukey method was applied to include, in the computation, the studies with outcome proportion equal zero [12]. Estimates of proportion and 95% CI were calculated by using random effect model. To evaluate heterogeneity among studies, heterogeneity chi square value was also reported.

Results

Fig. 1 shows the flowchart of the study selection process. A total of 596 articles were identified by database search as potentially relevant and another 55 citations were found from...
**Table 1**  

<table>
<thead>
<tr>
<th>Source, year</th>
<th>Year of recruitment</th>
<th>Country</th>
<th>Type of study</th>
<th>Clinical criteria</th>
<th>No. of patients enrolled</th>
<th>No. of patients with unilocular cyst operated</th>
<th>Range age (y)</th>
<th>Indicated MP status for patients with unilocular cyst</th>
<th>Cyst diameter (range, mm)</th>
<th>Valuated CA125 level</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granberg et al., 1990 [35]</td>
<td>1987–1988</td>
<td>Sweden</td>
<td>PCS</td>
<td>The tumor was classified as unilocular, unilocular solid, multilocular, multilocular solid or solid.</td>
<td>180</td>
<td>45</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Parker et al., 1994 [36]</td>
<td>NR</td>
<td>Multicentre (USA)</td>
<td>PCS</td>
<td>The criteria for presumptively benign adnexal mass were: cystic masses greater than 3 cm but less than 10 cm, with distinct borders, without solid parts or septations greater than 2 mm, without ascites or matted bowel, and with serum CA 125 levels less than 35 IU/ml. Unilocular cyst (a unilocular cyst without septa and without solid parts or papillary excrescences)</td>
<td>61</td>
<td>61</td>
<td>47–81</td>
<td>Yes</td>
<td>30–100</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Valentin et al., 1994 [37]</td>
<td>NR</td>
<td>Sweden</td>
<td>PCS</td>
<td>Unilocular cyst (a unilocular cyst without septa and without solid parts or papillary excrescences)</td>
<td>149</td>
<td>41</td>
<td>18–84</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Auslander et al., 1996 [38]</td>
<td>1987–1993</td>
<td>Israel</td>
<td>PCS</td>
<td>Cyst with the following characteristics: mean diameter less than 5 cm, smooth-walled, hypoechogenic, aseptate, no solid content, and absence of ascites or any other pelvic finding</td>
<td>51</td>
<td>9</td>
<td>43–85</td>
<td>Yes</td>
<td>15–50</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>Valentin, 1997 [39]</td>
<td>NR</td>
<td>Sweden</td>
<td>PCS</td>
<td>Unilocular cyst (a unilocular cyst without septa and without solid parts or papillary excrescences)</td>
<td>151</td>
<td>33</td>
<td>20–90</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Bailey et al., 1998 [40]</td>
<td>1987–1995</td>
<td>USA</td>
<td>PCS</td>
<td>The morphology index scores off all unilocular cystic tumors ranged from 0 to 5 (mean 1.1)</td>
<td>159</td>
<td>45</td>
<td>50–90</td>
<td>Yes</td>
<td>0–100</td>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>Hata et al., 1998 [41]</td>
<td>NR</td>
<td>Japan</td>
<td>PCS</td>
<td>Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures</td>
<td>171</td>
<td>20</td>
<td>11–82</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Reimer et al., 1999 * [42]</td>
<td>NR</td>
<td>Germany</td>
<td>PCS</td>
<td>Unilocular, some echoes</td>
<td>58</td>
<td>27</td>
<td>48–83</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Bayar et al., 2005 [48]</td>
<td>NR</td>
<td>Turkey</td>
<td>RCT</td>
<td>Simple cyst is a unilocular cyst, smooth-wall, between 3 and 10 cm, with and without internal echoes and benign on Doppler flow velocity</td>
<td>141</td>
<td>28</td>
<td>&lt; 50</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>Exacoustos et al., 2005 [46]</td>
<td>1997–2003</td>
<td>Italy</td>
<td>RCS</td>
<td>Unilocular cyst is a smooth-walled unilocular cyst with clear fluid or dense (echogenic) fluid content</td>
<td>452</td>
<td>227</td>
<td>12–82</td>
<td>No</td>
<td>20–165</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Timmerman et al. 2005 [43]</td>
<td>NR</td>
<td>Multicentre (Europe)</td>
<td>PCS</td>
<td>Unilocular cyst: a unilocular cyst without septa and without solid parts or papillary structures</td>
<td>1066</td>
<td>313</td>
<td>17–94</td>
<td>No</td>
<td>11–410</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jokubkien et al., 2007 [44]</td>
<td>NR</td>
<td>Sweden</td>
<td>PCS</td>
<td>Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures</td>
<td>106</td>
<td>22</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Gramellini et al., 2008 [47]</td>
<td>2004–2006</td>
<td>Italy</td>
<td>RCS</td>
<td>Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures</td>
<td>105</td>
<td>35</td>
<td>18–83</td>
<td>No</td>
<td>13–200</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McDonald et al., 2010 [45]</td>
<td>2001–2008</td>
<td>USA</td>
<td>PCS</td>
<td>Tumor morphology was classified as cystic [. . .]. All tumors classified as cystic were unilocular.</td>
<td>395</td>
<td>123</td>
<td>10–86</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

| Source, year of publication | Head of recruitment | Country | Type of study | Clinical criteria for unilocular cysts | Type of echogenicity | No. of patients with unilocular cyst operated | No. of patients with unilocular cysts examined | Range (median, IQR) diameter (range, mm) | Cutoff diameter > 50 mm | Cutoff diameter ≤ 50 mm | Cutoff diameter < 50 mm | No. of patients enrolled | MP status (range, mm) | Value of evidence | Quality of evidence level |
|-----------------------------|---------------------|---------|---------------|---------------------------------------|---------------------|---------------------------------------------|---------------------------------------------|------------------------------------------|---------------------------------|------------------|------------------|------------------|------------------------|--------------------------|----------------------|-------------------------|
| Table 1/Valentin et al. 2013 [7] | Multicentre (Europe) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

| Values are numbers. Quality of evidence is scored according to the MINORS criteria (Slim et al., 2003). |
| Those studies are included also in Table S3 (for anechoic unilocular cyst analysis). |
| MP = menopausal; NR = not reported; PCS = prospective cohort study; RCT = randomized controlled trial; RCS = retrospective cohort study. |

The number of patients enrolled ranged from 51 to 1148. Four studies were conducted in Sweden, three in USA, two in Italy, two studies were multicountry European studies, one was conducted in Israel, one in Turkey, one in Germany and one in Japan. According to the MINORS criteria, the quality of considered studies was generally good; the score ranged from 8 to 13 being 12 or 13 in 12 papers out of 15.

The definition of unilocular cyst was not uniform. A total of eight studies didn’t report the cyst’s diameter. Only seven studies reported the menopausal status.

Table 2 reports the characteristics of studies including anechoic unilocular cysts. 21 studies were selected. Two studies were also included in Table 1 because they had also data of unilocular cysts with different echogenicity [7,42]. Five studies were conducted in the USA, three in Israel, two in Germany, two studies were multicountry European studies, one was conducted in Sweden, one in China, one in Japan, one in Austria, one in the United Kingdom, one in Spain, one in the Netherlands, one in New Zealand and one in Turkey. 12 were prospective [4,42,49–58], 7 retrospective [7,59–64] cohort studies, and two were clinical case series [65,66]. The number of patients considered ranged from 29 to 2763. A total of 16 studies reported the menopausal status of patients 11 studies didn’t report cysts size.

Table 3 considers the studies including unilocular cysts without any specific restriction regarding the type of echogenicity of cyst fluid. In the studies published before 2000, the number of included women was low and the malignancy rate was 0% except for Reimer et al. [42]. The rate of malignancy among the studies published from 2000 was 9.9%. Overall of the 2177 surgically removed lesions classified as unilocular cysts on ultrasound, 24 (1.1%; 95% CI: 0.74–1.66) were malignant (among these 12 were of borderline malignancy: 0.6%). When we performed the meta-analysis selecting studies published after 2000 and with 100 or more patients, the random pooled estimate was 0.8 (95% CI: 0.4–1.3) with no heterogeneity among studies (heterogeneity chi square = 2.12 P = 0.55) [7,43–46].

The rate was lower for premenopausal women (6/987, 0.6%) than postmenopausal ones (12/372, 3.2%) and the difference was statistically significant (Pearson chi-square P = 0.0002). Similar results we obtained analyzing studies published after 2000: the malignancy rate was 0.6% for premenopausal women (two studies [7,48]) and 2.8% for menopausal women (only one study [7,48]) and the difference was statistically significant (Pearson chi-square P = 0.005). Likewise, the rates were lower in cysts with diameter < 5 cm (5/524, 1.0%) than ≥ 5 cm (12/705, 1.7%) but this difference was not statistically significant (Pearson chi square P = 0.268).

Among studies published after 2000, we identified one study [7] including a large number of women: the malignancy rate in women with cysts with diameter < 5 cm was 0.8% and in cysts with diameter ≥ 5 cm was 1.1%.

Table 4 considers the studies including only anechoic unilocular cysts. The rate of malignancies ranged from 0 to 6.3%. Overall of the 2390 surgically removed lesions, classified as anechoic unilocular cysts on ultrasound, 20 (0.9%; 95% CI: 0.57–1.35) were malignant (among these 8 were of borderline malignancy: 0.3%). When we performed the meta-analysis selecting studies published after
Table 2: Characteristics of the selected studies with anechoic unilocular cyst. Literature data, Jan 1990–Feb 2017.

<table>
<thead>
<tr>
<th>Source, year</th>
<th>Year of recruitment</th>
<th>Country</th>
<th>Type of study</th>
<th>Clinical criteria</th>
<th>No. of patients enrolled</th>
<th>No. of patients with anechoic unilocular cyst operated</th>
<th>Range age (y)</th>
<th>Indicated MP status for patients with anechoic unilocular cyst</th>
<th>Cyst diameter (range, mm)</th>
<th>Anechoic unilocular cyst diameter &lt; 50 mm</th>
<th>Anechoic unilocular cyst diameter ≥ 50 mm</th>
<th>Valuated CA125 level</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenfeld et al., 1990 [65]</td>
<td>NR</td>
<td>Israel</td>
<td>CCS</td>
<td>Unilateral simple cysts with no separations or solid components</td>
<td>29</td>
<td>29</td>
<td>50–76</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxman et al., 1991 [49]</td>
<td>1987–1989</td>
<td>Israel</td>
<td>PCS</td>
<td>A lesion that appeared to be unilocular and clear and lacking papillae or septa was defined as “simple”</td>
<td>102</td>
<td>33</td>
<td>42–90</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obwegeser et al., 1993 [59]</td>
<td>1987–1990</td>
<td>Austria</td>
<td>RCS</td>
<td>Completely anechogenic; no septae; no papillae or other even small echogenic areas; no thickening of cyst wall</td>
<td>144</td>
<td>144</td>
<td>18–81</td>
<td>Yes</td>
<td>40–250</td>
<td>No</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jain, 1994 [50]</td>
<td>NR</td>
<td>USA</td>
<td>PCS</td>
<td>Sonographic criteria for simple cysts included an anechoic cystic mass with a well-defined thin wall and no internal echoes, septations, or mural nodules</td>
<td>42</td>
<td>15</td>
<td>22–55</td>
<td>No</td>
<td>17–55</td>
<td>No</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shalev et al., 1994 [51]</td>
<td>1988–1993</td>
<td>Israel</td>
<td>PCS</td>
<td>Simple cyst (clear cyst with smooth borders)</td>
<td>130</td>
<td>43</td>
<td>&gt; 47</td>
<td>Yes</td>
<td>20–150</td>
<td>Yes</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamashita et al., 1995 [52]</td>
<td>NR</td>
<td>Japan</td>
<td>PCS</td>
<td>At TVUS, a diagnosis of simple cyst was made when an anechoic cystic mass had a well-delineated wall and no internal echoes, septa, or mural nodules.</td>
<td>400</td>
<td>52</td>
<td>13–74</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gerber et al., 1997 [61]</td>
<td>1990–1996</td>
<td>Germany</td>
<td>RCS</td>
<td>Simple ovarian cysts: unilocular, anechoic smooth-walled cystic ovarian tumors and contained no septa or solid areas.</td>
<td>1358</td>
<td>140</td>
<td>13–56</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conway et al., 1999 [53]</td>
<td>1990–1994</td>
<td>USA</td>
<td>PCS</td>
<td>A simple ovarian cyst was defined as being less than 5 cm in the single largest diameter, anechoic, and unilocular with regular borders, with no papillary projections.</td>
<td>116</td>
<td>14</td>
<td>&gt; 40</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimer et al., 1999 [42]</td>
<td>NR</td>
<td>Germany</td>
<td>PCS</td>
<td>Simple cyst (anechoic, smooth-walled, unilocular)</td>
<td>58</td>
<td>16</td>
<td>48–83</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source, year</th>
<th>Year of recruitment</th>
<th>Country</th>
<th>Type of study</th>
<th>Clinical criteria</th>
<th>No. of patients enrolled</th>
<th>No. of patients with anechoic unilocular cyst operated</th>
<th>Range age (y)</th>
<th>Indicated MP status for patients with anechoic unilocular cyst</th>
<th>Cyst diameter (range, mm)</th>
<th>Anechoic unilocular cyst diameter &lt; 50 mm</th>
<th>Anechoic unilocular cyst diameter ≥ 50 mm</th>
<th>Valuated CA125 level</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueland et al., 2003 [66]</td>
<td>1987–2000 USA</td>
<td>CCS</td>
<td>Structural score 0: smooth-wall, sonolucent</td>
<td>442</td>
<td>144</td>
<td>18–85</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Castillo et al., 2004 [56]</td>
<td>1995–2002 Spain</td>
<td>PCS</td>
<td>A simple unilocular adnexal cyst was defined as a sonolucent thin-walled (&lt;3 mm) structure without any septation or solid area or papillary projections arising from both internal or external wall surface</td>
<td>215</td>
<td>45</td>
<td>45–84</td>
<td>Yes</td>
<td>9–94</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Simcock and Anderson, 2005 [63]</td>
<td>1994–1997 New Zealand</td>
<td>RCS</td>
<td>A simple ovarian cyst was defined as unilateral or bilateral, thin-walled, anechoic, non-septated, well-defined structure in the absence of ascites</td>
<td>90</td>
<td>59</td>
<td>15–84</td>
<td>Yes</td>
<td>36–180</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sarkar and Wolf, 2012 [64]</td>
<td>1997–2010 USA</td>
<td>RCS</td>
<td>Simple cyst of ovary was defined as an echo-free cyst with a smooth lining and no septae or solid areas or papillary projections within the cyst cavity.</td>
<td>314</td>
<td>3</td>
<td>35–96</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Valentin et al., 2019 [7]</td>
<td>1999–2007 Multicentre (Europe)</td>
<td>RCS</td>
<td>Unilocular cyst is a cyst with one cyst locule, no solid components and no papillary projections and anechoic. Unilocular cyst (with no septa and no solid part or papillary projections); Echogenicity of the cyst was described as anechoic (black)</td>
<td>1148</td>
<td>326</td>
<td>15–90</td>
<td>Yes</td>
<td>8–340</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Bayoglu Tekin and Dede, 2014 [58]</td>
<td>2006–2007 Turkey</td>
<td>PCS</td>
<td></td>
<td>221</td>
<td>59</td>
<td>18–73</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Values are numbers. Quality of evidence is scored according to the MINORS criteria (Slim et al., 2003).
Those studies are included also in Table S2 (for unilocular cyst analysis).
MP = menopausal; NR = not reported; PCS = prospective cohort study; RCS = retrospective cohort study; CCS = Clinical case series.
2000 and with 100 or more patients, the estimate was 0.5 (95% CI 0.1–1.2) with no heterogeneity (heterogeneity chi-square P = 0.175 [4.7,54,55,62,66].

The rates were lower among premenopausal women (3/907, 0.3%) than postmenopausal ones (13/681,1.9%) (Pearson chi-square P = 0.002). When we considered the studies published after 2000, the malignancy rate in anechoic cysts tended to be lower among premenopausal women (3/657, 0.5%) than postmenopausal ones (7/469, 1.5%) but the difference was not statistically significant (Pearson chi-square P = 0.07). Considering all published studies, the malignancy rates were similar in cases with cysts <5 cm (2/302, 0.7%) or >5 cm (3/303, 1.0%) in diameter (Pearson chi square

Discussion

The general result of this systematic review shows that the oncogenic risk of unilocular adnexal cysts is about 1%, including...
borderline conditions. The risk is higher among postmenopausal women.

The apparent heterogeneity of the results of considered studies – in particular for unilocular cysts – represents a potential limitation of this analysis that can be probably explained by the different study design or patients’ selection. Another limitation is the fact the authors classified unilocular cysts in different way.

This review and meta-analysis may be affected by potential limitation or bias. We considered only publications published in English. Authors may be more prone to publish in an international, English-language journal if results are positive, whereas negative findings are more often published in a local journal [67]. Limiting our analysis to publications in English language journals can therefore restrict the completeness of information. The direction and the strength of this bias is not however clear. Another limitation is the fact that most of studies included a very limited number of subjects. Although systematic reviews with meta-analyses provide an explicit method for synthesizing evidence and overcame the low power of the single studies, they may not be as valuable as a single large observational study.

One problem that arises in large retrospective reviews about ultrasound images, particularly when including older data, is that tumors with morphological properties other than simple unilocular tumors are inadvertently included. In this review we included published papers almost 30 years ago and during this time modern ultrasound has improved in technical quality and interpretation. In order to overcome at least in part this potential bias we have analyzed separately studies published before or after 2000: the rate of malignancy tended to decrease in more recent papers, but the finding was not statistically significant.

Beyond methodological limitations of the available studies on malignant potential of unilocular cysts, the findings of the present systematic review have clinical implications also in terms of value of care, that is the balance between potential benefits, potential harms and costs [68,69].

The critical issue in women with no family history of ovarian cancer is the choice between watchful waiting and surgery [70,71].

In this analysis, the risk of malignancy was limited in premenopausal women (1/300 in patients with anechoic cysts, and 1/160 independently of echogenicity), and substantially higher in postmenopausal ones (between 1/50 in patients with anechoic cysts and 1/30 independently of echogenicity). Expectations of effects of the alternative therapeutic options on mortality from ovarian cancer should take into consideration that about half of the observed tumors were of borderline malignancy.

Conclusion

Within the context of a policy aimed at limiting oncological risk, the ultimate challenge is, on one hand, preventing overdiagnosis and overtreatment and, on the other hand, limiting the long-term burden of treatment associated with prolonged surveillance. The results of this analysis offer quantitative information on the risk of malignancy in unilocular adnexal cysts. The final clinical choice between surgery or expectation should be individualized, based on the combination of each patient’s overall risk profile as well as personal priorities.

Disclosure of interests

FP, MPF, FC, DD, ER and PV declare that there is no conflict of interest.

Contribution to authorship

FP, MPF, PV: conception and design of the study, manuscript preparation; MPF, FC, DD and ER: acquisition data; FP, MPF and FC: analysis and interpretation of data; all the authors: critical revision of the article for important intellectual content, and approval of the final version of the manuscript.

Funding

This study was not funded.

References


