



## Review article

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



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## ABSTRACT

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.

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## 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

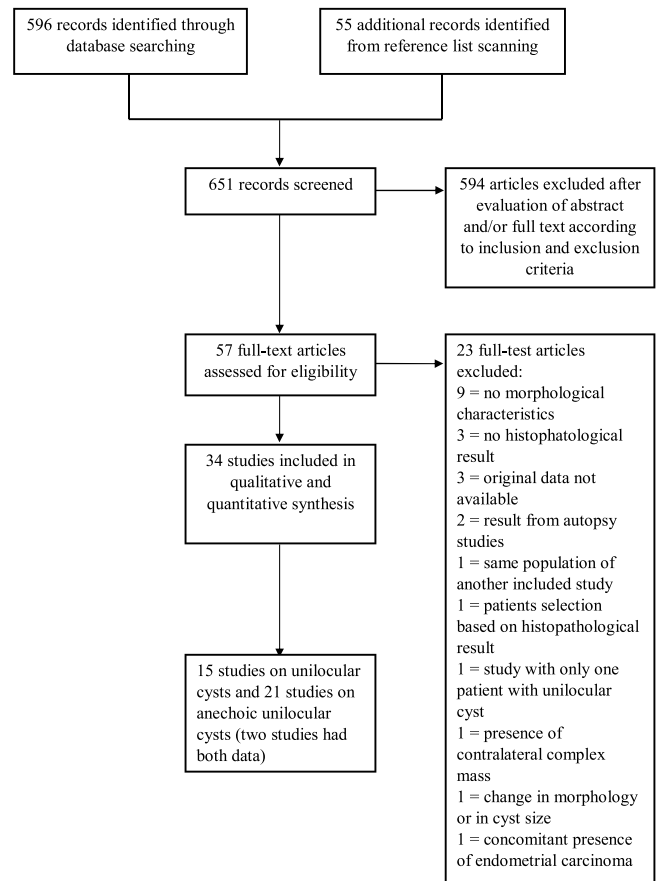


Fig. 1. Flowchart of the study selection process.

(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 flow diagram of the literature search results. A total of 596 articles were identified by database search as potentially relevant and another 55 citations were found from

**Table 1**  
Characteristics of the selected studies with unilocular cyst. Literature data, Jan 1990–Feb 2017.

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with unilocular cyst operated	Range age (y)	Indicated MP status for patients with unilocular cyst	Cyst diameter (range, mm)	Valuated CA125 level	Quality of evidence
Granberg et al., 1990 [35]	1987–1988	Sweden	PCS	The tumor was classified as unilocular, unilocular solid, multilocular, multilocular solid or solid.	180	45	NR	No	NR	No	12
Parker et al., 1994 [36]	NR	Multicentre (USA)	PCS	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.	61	61	47–81	Yes	30–100	Yes	8
Valentin et al., 1994 [37]	NR	Sweden	PCS	Unilocular cyst (a unilocular cyst without septa and without solid parts or papillary excrescences)	149	41	18–84	Yes	NR	No	12
Auslender et al., 1996 [38]	1987–1993	Israel	PCS	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	51	9	43–85	Yes	15–50	Yes	12
Valentin, 1997 [39]	NR	Sweden	PCS	Unilocular cyst (a unilocular cyst without septa and without solid parts or papillary excrescences)	151	33	20–90	No	NR	No	12
Bailey et al., 1998 [40]	1987–1995	USA	PCS	The morphology index scores off all unilocular cystic tumors ranged from 0 to 5 (mean 1.1)	159	45	50–90	Yes	0–100	Yes	13
Hata et al., 1998 [41]	NR	Japan	PCS	Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures	171	20	11–82	No	NR	No	12
Reimer et al., 1999 * [42]	NR	Germany	PCS	Unilocular, some echoes	58	27	48–83	Yes	NR	Yes	10
Bayar et al., 2005 [48]	NR	Turkey	RCT	Simple cyst is a unilocular cyst, smooth-wall, between 3 and 10 cm, with and without internal echoes and benign on Doppler flow velocity	141	28	< 50	Yes	NR	Yes	12

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with unilocular cyst operated	Range age (y)	Indicated MP status for patients with unilocular cyst	Cyst diameter (range, mm)	Unilocular cyst diameter < 50 mm	Unilocular cyst diameter ≥ 50 mm	Valuated CA125 level	Quality of evidence
Exacoustos et al., 2005 [46]	1997–2003	Italy	RCS	Unilocular cyst is a smooth-walled unilocular cyst with clear fluid or dense (echogenic) fluid content	452	227	12–82	No	20–165	NR	NR	No	10
Timmerman et al. 2005 [43]	NR	Multicentre (Europe)	PCS	Unilocular cyst: a unilocular cyst without septa and without solid parts or papillary structures	1066	313	17–94	No	11–410	NR	NR	Yes	13
Jokubkiene et al., 2007 [44]	NR	Sweden	PCS	Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures	106	22	NR	No	NR	NR	NR	No	13
Gramellini et al., 2008 [47]	2004–2006	Italy	RCS	Unilocular cyst is a unilocular cyst without septa and without solid parts or papillary structures	105	35	18–83	No	13–200	NR	NR	Yes	12
McDonald et al., 2010 [45]	2001–2008	USA	PCS	Tumor morphology was classified as cystic [ . . . ]. All tumors classified as cystic were unilocular.	395	123	10–86	No	NR	NR	NR	Yes	12

Table 1 (Continued)

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with unilocular cyst operated	Range age (y)	Indicated MP status for patients with unilocular cyst	Cyst diameter (range, mm)	Unilocular cyst diameter < 50 mm	Unilocular cyst diameter ≥ 50 mm	Valuated CA125 level	Quality of evidence
Valentin et al. 2013 <sup>*</sup> [7]	1999–2007	Multicentre (Europe)	RCS	Unilocular cyst is a cyst with one cyst locule, no solid components and no papillary projections and with a contents of any type of echogenicity	1148	1148	15–90	Yes	8–340	NR	NR	Yes	13

Values are numbers. Quality of evidence is scored according to the MINORS criteria (Slim et al., 2003).

<sup>\*</sup>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.

of reference lists. A total of 594 articles were excluded after evaluation of abstract and/or full text because they did not satisfy the inclusion criteria and 57 articles were assessed for eligibility. Overall, 23 publications were not included in the current review and meta-analysis [4,13–34].

Table 1 reports the characteristics of 15 selected studies considering unilocular cysts independently of the echogenicity. A total of 14 studies had a cohort design, most of these was prospective [35–45], three were retrospective [7,46,47], and one was a randomized clinical trial [48].

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 retrospectives [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 0.9%. 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 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 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.

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with anechoic unilocular cyst operated	Range age (y)	Indicated MP status for patients with anechoic unilocular cyst	Cyst diameter (range, mm)	Valuated CA125 level	Quality of evidence
Schoenfeld et al., 1990 [65]	NR	Israel	CCS	Unilateral simple cysts with no separations or solid components	29	29	50–76	Yes	NR	No	8
Luxman et al., 1991 [49]	1987–1989	Israel	PCS	A lesion that appeared to be unilocular and clear and lacking papillae or septa was defined as “simple”	102	33	42–90	Yes	NR	No	11
Obwegeser et al., 1993 [59]	1987–1990	Austria	RCS	Completely anechogenic; no septae; no papillae or other even small echogenic areas; no thickening of cyst wall	144	144	18–81	Yes	40–250	No	8
Jain, 1994 [50]	NR	USA	PCS	Sonographic criteria for simple cysts included an anechoic cystic mass with a well-defined thin wall and no internal echoes, septations, or mural nodules	42	15	22–55	No	17–55	No	11
Shalev et al., 1994 [51]	1988–1993	Israel	PCS	Simple cyst (clear cyst with smooth borders)	130	43	> 47	Yes	20–150	Yes	11
Kroon and Andolf, 1995 [60]	1983–1992	Sweden	RCS	Completely anechoic, small (less than 50 mm) ovarian cysts	83	43	48–85	Yes	9–50	No	11
Yamashita et al., 1995 [52]	NR	Japan	PCS	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.	400	52	13–74	No	NR	No	12
Gerber et al., 1997 [61]	1990–1996	Germany	RCS	Simple ovarian cysts: unilocular, anechoic smooth-walled cystic ovarian tumors and contained no septa or solid areas.	1358	140	13–56	Yes	NR	No	9
Conwey et al., 1998 [53]	1990–1994	USA	PCS	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.	116	14	> 40	Yes	NR	Yes	12
Reimer et al., 1999 [42]	NR	Germany	PCS	Simple cyst (anechoic, smooth-walled, unilocular)	58	16	48–83	Yes	NR	Yes	10

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with anechoic unilocular cyst operated	Range age (y)	Indicated MP status for patients with anechoic unilocular cyst	Cyst diameter (range, mm)	Anechoic unilocular cyst diameter < 50 mm	Anechoic unilocular cyst diameter ≥ 50 mm	Valuated CA125 level	Quality of evidence
Ekerhovd et al., 2001 [54]	1992–1997	Sweden and Austria	PCS	Cysts were characterized either as single cyst, echo-free, without solid parts or papillary formations	1304	660	14–90	Yes	18–200	NR	NR	No	11
Modesitt et al., 2003 [4]	1987–2002	USA	PCS	A unilocular tumor was defined as a fluid-filled cyst without internal septa, papillary projections, or solid components	2763	106	> 50	Yes	< 100	NR	NR	No	13
Nardo et al., 2003 [62]	1995–2000	United Kingdom	RCS	Only unilocular, echo-free, thin-walled cysts measuring less than 50 mm in diameter and without solid parts or papillary formations were considered in the study	226	138	45–87	Yes	18–80	84	54	Yes	10

**Table 2** (Continued)

Source, year	Year of recruitment	Country	Type of study	Clinical criteria	No. of patients enrolled	No. of patients with anechoic unilocular cyst operated	Range age (y)	Indicated MP status for patients with anechoic unilocular cyst	Cyst diameter (range, mm)	Anechoic unilocular cyst diameter < 50 mm	Anechoic unilocular cyst diameter ≥ 50 mm	Valuated CA125 level	Quality of evidence
Ueland et al. 2003 [66]	1987–2000	USA	CCS	Structural score 0: smooth-wall, sonolucent	442	144	18–85	No	NR	NR	NR	No	11
Xiaoman et al., 2003 [55]	1994–2001	China	PCS	Simple anechoic cysts	221	221	14–74	Yes	NR	76	145	Yes	12
Castillo et al., 2004 [56]	1995–2002	Spain	PCS	A simple unilocular adnexal cyst was defined as a sonolucent thin-walled (<3 mm) structure without any septation or solid area or papillary projections arising from both internal or external wall surface	215	45	45–84	Yes	9–94	NR	NR	Yes	14
De Kroon et al., 2004 [57]	1992–2002	Netherlands	PCS	Simple cyst	406	98	7–88	No	NR	NR	NR	No	12
Simcock and Anderson, 2005 [63]	1994–1997	New Zealand	RCS	A simple ovarian cyst was defined as unilateral or bilateral, thin-walled, anechoic, non-septated, well-defined structure in the absence of ascites	90	59	15–84	Yes	36–180	NR	NR	No	11
Sarkar and Wolf, 2012 [64]	1997–2010	USA	RCS	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.	314	3	35–96	Yes	NR	NR	NR	No	12
Valentin et al. 2013 [7]	1999–2007	Multicentre (Europe)	RCS	Unilocular cyst is a cyst with one cyst locule, no solid components and no papillary projections and anechoic.	1148	326	15–90	Yes	8–340	NR	NR	Yes	13
Bayoglu Tekin and Dede, 2014 [58]	2006–2007	Turkey	PCS	Unilocular cyst (with no septa and no solid part or papillary projections); Echogenicity of the cyst was described as anechoic (black)	221	59	18–73	No	NR	NR	NR	Yes	12

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



**Table 3**  
Studies including unilocular cysts.

Source, year	Malignancies (borderline)/total	% Malignancies (95% CI)
<i>All studies</i>		
Granberg et al., 1990 [35]	0/45	0.0
Parker et al., 1994 [36]	0/61	0.0
Valentin et al., 1994 [37]	0/41	0.0
Auslender et al., 1996 [38]	0/9	0.0
Valentin, 1997 [39]	0/33	0.0
Bailey et al., 1998 [40]	0/45	0.0
Hata et al., 1998 [41]	0/20	0.0
Reimer et al., 1999 [42]	6/27	22.2 (10.6–40.7)
<b>Total papers published before 2000</b>	<b>6/281</b>	<b>2.1 (1.0–4.6)</b>
Bayar et al., 2005 [48]	1 (1)/28	3.6 (0.6–17.7)
Exacoustos et al., 2005 [46]	3 (3)/227	1.3 (0.5–3.8)
Timmerman et al. 2005 [43]	2 (2)/313	0.6 (0.2–2.3)
Jokubkiene et al., 2007 [44]	0/22	0.0
Gramellini et al., 2008 [47]	1 (1)/35	2.8 (0.5–14.5)
McDonald et al., 2010 [45]	0/123	0.0
Valentin et al. 2013 [7]	11 (5)/1148	0.9 (0.5–1.7)
<b>Total papers published after 2000</b>	<b>18/1896</b>	<b>0.9 (0.6–1.5)</b>
<b>Total</b>	<b>24 (12)/2177</b>	<b>1.1 (0.74–1.66)</b>
<i>Premenopausal women only</i>		
Valentin et al., 1994 [37]	0/28	0.0
<b>Total papers published before 2000</b>	<b>0/28</b>	<b>0.0</b>
Bayar et al., 2005 [48]	1 (1)/28	3.6 (0.6–17.7)
Valentin et al., 2013 [7]	5 (4)/931	0.5 (0.2–1.3)
<b>Total papers published after 2000</b>	<b>6/959</b>	<b>0.6 (0.3–1.4)</b>
<b>Total</b>	<b>6 (5)/987</b>	<b>0.6 (0.28–1.32)</b>
<i>Postmenopausal women only</i>		
Auslender et al., 1996 [38]	0/9	0.0
Bailey et al., 1998 [40]	0/45	0.0
Parker et al., 1994 [36]	0/61	0.0
Reimer et al., 1999 [42]	6/27	22.2 (10.6–40.8)
Valentin et al., 1994 [37]	0/13	0.0
<b>Total papers published before 2000</b>	<b>6/155</b>	<b>3.9 (1.8–8.2)</b>
Valentin et al. 2013 [7]	6 (1)/217	2.8 (1.3–5.9)
<b>Total</b>	<b>12 (1)/372</b>	<b>3.2 (1.86–5.55)</b>
<i>Cysts &lt;5 cm in diameter</i>		
Granberg et al., 1990 [35]	0/19	0.0
Auslender et al., 1996 [38]	0/9	0.0
Reimer et al., 1999 [42]	1/10	10.0 (1.8–40.4)
<b>Total papers published before 2000</b>	<b>1/38</b>	<b>2.6 (0.5–13.5)</b>
Valentin et al. 2013 [7]	4 (1)/486	0.8 (0.3–2.1)
<b>Total</b>	<b>5 (1)/524</b>	<b>1.0 (0.41–2.21)</b>
<i>Cysts ≥5 cm in diameter</i>		
Granberg et al., 1990 [35]	0/26	0.0
Reimer et al., 1999 [42]	5/17	29.4 (13.3–53.1)
<b>Total papers published before 2000</b>	<b>5/43</b>	<b>11.6 (5.1–24.5)</b>
Valentin et al. 2013 [7]	7 (4)/662	1.1 (0.5–2.2)
<b>Total</b>	<b>12 (4)/705</b>	<b>1.7 (0.98–2.95)</b>

The bold value indicates a total data.

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  $P=0.656$ ).

## Discussion

The general result of this systematic review shows that the oncogenic risk of unilocular adnexal cysts is about 1%, including

**Table 4**  
Studies including anechoic unilocular cysts.

Source, year	Malignancies (borderline)/total	% Malignancies (95% CI)
<i>All studies</i>		
Schoenfeld et al., 1990 [65]	0/29	0.0
Luxman et al., 1991 [49]	2 (0)/33	6.1 (0.1–9.6)
Obwegeser et al., 1993 [59]	3 (1)/144	2.1 (0.7–5.9)
Jain, 1994 [50]	0/15	0.0
Shalev et al., 1994 [51]	0/43	0.0
Kroon and Andolf, 1995 [60]	0/43	0.0
Yamashita et al., 1995 [52]	0/52	0.0
Gerber et al., 1997 [61]	0/140	0.0
Conway et al., 1998 [53]	0/14	0.0
Reimer et al., 1999 [42]	1 (1)/16	6.3 (1.1–28.3)
<b>Total papers published before 2000</b>	<b>6/529</b>	<b>1.1 (0.5–2.5)</b>
Ekerhovd et al., 2001 [54]	7 (3)/660	1.1 (0.5–2.2)
Modesitt et al., 2003 [4]	0/106	0.0
Nardo et al., 2003 [62]	2 (0)/138	1.4 (0.4–5.1)
Ueland et al. 2003 [66]	0/144	0.0
Xiaoman et al., 2003 [55]	0/221	0.0
Castillo et al., 2004 [56]	1 (0)/45	2.2 (0.4–11.6)
Simcock and Anderson, 2005 [63]	0/59	0.0
Sarkar and Wolf, 2012 [64]	0/3	0.0
Valentin et al. 2013 [7]	4 (3)/326	1.2 (0.5–3.1)
Bayoglu Tekin and Dede, 2014 [58]	0/59	0.0
<b>Total papers published after 2000</b>	<b>14/1761</b>	<b>0.8(0.5–1.4)</b>
<b>Total</b>	<b>20 (8)/2290</b>	<b>0.9 (0.57–1.35)</b>
<i>Premenopausal women only</i>		
Obwegeser et al., 1993 [59]	0/110	0.0
Gerber et al., 1997 [61]	0/140	0.0
<b>Total papers published before 2000</b>	<b>0/250</b>	<b>0.0</b>
Ekerhovd et al., 2001 [54]	3 (2)/413	0.7 (0.2–2.1)
Xiaoman et al., 2003 [55]	0/194	0.0
Simcock and Anderson, 2005 [63]	0/50	0.0
<b>Total papers published after 2000</b>	<b>3/657</b>	<b>0.5 (0.2–1.3)</b>
<b>Total</b>	<b>3 (2)/907</b>	<b>0.3 (0.11–0.97)</b>
<i>Postmenopausal women only</i>		
Schoenfeld et al., 1990 [65]	0/29	0.0
Luxman et al., 1991 [49]	2 (0)/33	6.1 (1.7–19.6)
Obwegeser et al., 1993 [59]	3/34	8.8 (3.0–23.0)
Shalev et al., 1994 [51]	0/43	0.0
Kroon and Andolf, 1995 [60]	0/43	0.0
Conway et al., 1998 [53]	0/14	0.0
Reimer et al., 1999 [42]	1 (1)/16	6.3 (1.1–28.3)
<b>Total papers published before 2000</b>	<b>6/212</b>	<b>2.8 (1.3–6.0)</b>
Ekerhovd et al., 2001 [54]	4 (1)/247	1.6 (0.6–4.1)
Nardo et al., 2003 [62]	2 (0)/138	1.5 (0.4–5.1)
Xiaoman et al., 2003 [55]	0/27	0.0
Castillo et al., 2004 [56]	1 (0)/45	2.2 (0.4–11.6)
Simcock and Anderson, 2005 [63]	0/9	0.0
Sarkar and Wolf, 2012 [64]	0/3	0.0
<b>Total papers published after 2000</b>	<b>7/469</b>	<b>1.5 (0.7–3.0)</b>
<b>Total</b>	<b>13 (2)/681</b>	<b>1.9 (1.56–3.96)</b>
<i>Cysts &lt;5 cm in diameter</i>		
Luxman et al., 1991 [49]	2 (0)/18	11.1 (3.1–32.8)
Kroon and Andolf, 1995 [60]	0/43	0.0
Gerber et al., 1997 [61]	0/59	0.0
Conway et al., 1998 [53]	0/14	0.0
Reimer et al., 1999 [42]	0/8	0.0
<b>Total papers published before 2000</b>	<b>2/218</b>	<b>0.9 (0.3–3.3)</b>
Nardo et al., 2003 [62]	0/84	0.0
Xiaoman et al., 2003 [55]	0/76	0.0
<b>Total papers published after 2000</b>	<b>0/160</b>	<b>0.0</b>
<b>Total</b>	<b>2 (0)/302</b>	<b>0.7 (0.18–2.38)</b>
<i>Cysts ≥5 cm in diameter</i>		
Luxman et al., 1991 [49]	0/15	0.0
Gerber et al., 1997 [61]	0/81	0.0
Reimer et al., 1999 [42]	1 (1)/8	12.5 (2.2–47.1)
<b>Total papers published before 2000</b>	<b>1/104</b>	<b>1.0 (0.2–5.2)</b>
Nardo et al., 2003 [62]	2 (0)/54	3.7 (1.0–12.5)
Xiaoman et al., 2003 [55]	0/145	0.0
<b>Total papers published after 2000</b>	<b>2/199</b>	<b>1.0 (0.3–3.6)</b>
<b>Total</b>	<b>3 (2)/303</b>	<b>1.0 (0.34–2.87)</b>

The bold value indicates a total data.

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 imagines, 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 echogenity), and substantially higher in postmenopausal ones (between 1/50 in patients with anechoic cysts and 1/30 independently of echogenity). Expectations on 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.

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