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Ovarian Cancer Screening: the Role and Drawbacks of Ultrasonography and Feasibility in Low Resource Settings

Chukwuemeka Anthony Iyoke[1,*], Osaheni LuckyLawani[2], George Onyemaechi Ugwu[1], Euzebus Chinonye Ezugwu[1], Leonard Ogbonna Ajah[2], Robinson Chukwudi Onoh[2]

[1]Department of Obstetrics and Gynaecology, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria
[2]Department of Obstetrics and Gynaecology, Federal Teaching Hospital, Abakaliki, Nigeria
*Corresponding author: caiyoke@yahoo.co.uk

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Abstract **Context**: Although there have been reports of increasing incidence of ovarian cancer in developing countries, no developing country has been involved in current trials of ovarian cancer screening. **Aim**: To review the evolution of the role and drawbacks of ultrasonography in ovarian cancer screening and the feasibility of implementing current potential screening strategies inlow resource settings. **Methods**: An electronic literature search for all articles written in English language on ovarian cancer screening from 1960-2013. Information from appropriate articles were collated and analysed for content. **Results**: Ultrasound was used as the first-line or second-line test in the most popular multicentre multimodal trials of ovarian cancer screening. It has a high sensitivity but a low specificity. The low specificity of ultrasound screening necessitates the use of further measures to aid the triaging of ultrasound positive cases, which add to the overall cost of screening. There is yet scant evidence of the cost effectiveness of multimodal screening for ovarian cancer. Current potential strategies for ultrasound-based screening for ovarian cancer demand the training and employment of large numbers of highly skilled personnel as well as the acquisition of high resolution scanners and technology for biochemical assay of tumour markers. **Conclusion**: Transvaginal ultrasonographyhas evolved into a potentialtool for ovarian cancer screening and ovarian cancer screening strategies based on CA125 assays and ultrasonography would demand substantial resources. If and when reduction in mortality and cost-effectiveness of this approach to screening are proven, itmay not be feasible in developing countries.

Keywords: *transvaginal ultrasound, ovarian cancer, screening, CA125, low-resource countries*

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1. Introduction

Recent trials of ovarian cancer screening have shown that current modalities for screening increase the detection of early stage ovarian cancer [1]. Five-year survival for early stage cancer is significantly higher than for late disease [1]. This survival advantage for patients diagnosed with early stage ovarian cancer suggests that screening programs that detect early stage disease might have an impact on disease mortality [2]. Evidence from screening women with family history of ovarian cancer or with confirmed inherited high-risk genes such as BRCA 1, 2 showed that 4-monthly CA125 followed by ultrasound for positive cases increased the rate of complete cytoreductive surgery to 92% compared to 62% for annual screens [3,4]. However, till date, the ability of screening to decrease overall mortality from ovarian cancer in populations at risk is not yet established [1,2]. The United States Preventive Services Task Force (USPSTF) "recommends against screening for ovarian cancer in asymptomatic women, except those with known genetic mutations that increase their risk for ovarian cancer (for example, BRCA mutations)" [5].

In the last three decades, the potential usefulness, acceptability and limitations of ultrasound individually or as part of a multimodal approach to ovarian cancer screening have been well documented [6-10]. A challenge arising from the limitations of ultrasound is how to minimize the false positive tests associated with ultrasound screening. The low specificity of ultrasound screening makes it unsuitable as a sole screening modality and necessitates the application of further measures such as clinical assessment, biochemical assay of tumour markers, morphologic indices, logistic regression models, risk of malignancy indices to aid the triaging of ultrasound positive cases. The aim is to further identify all benign lesions among all cases that initially tested positive to ultrasound screening. Such benign lesions can then be safely managed conservatively by serial scans.

For ultrasound screen-positive benign lesions involving simple cysts, further management is well defined because the natural history of small simple ovarian cysts is, perhaps, conclusively determined: they either disappear or persist and they do not transform to cancer [11,12]. Conservative management of simple cysts is therefore the rule. When such lesions involve benign septated (complex) cysts, further management has been shrouded in uncertainty because the natural history of such lesions is less clear: disappearance, persistence and transformation to cancer have all been described. Whereas in the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) trial, no increased risk of cancer was found compared to women without cysts, analysis of United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) data reached a similar conclusion but suggested that septated (multilocular) cysts did transform to mostly borderline and few early type I ovarian cancer [1,13]. A recent study has also shown transformation of conservatively-managed septated cysts to ovarian cancer through increasing complexity in morphological features [14]. The link between benign complex cysts and ovarian cancer therefore remains controversial today as it was two decades ago [15].

We reviewed literature on the evolution of ultrasonography as a possible screening tool for ovarian cancer and the management of ultrasound positive screening tests. We highlight in particular the dilemmas that may confront ultrasound practitioners and gynaecological oncologists involved in the selection and treatment of women that are triaged to conservative management following positive ultrasound screening tests. We explored the feasibility of mounting ovarian cancer screening based on CA125 and ultrasonography in developing countries, especially in Sub Saharan Africa.

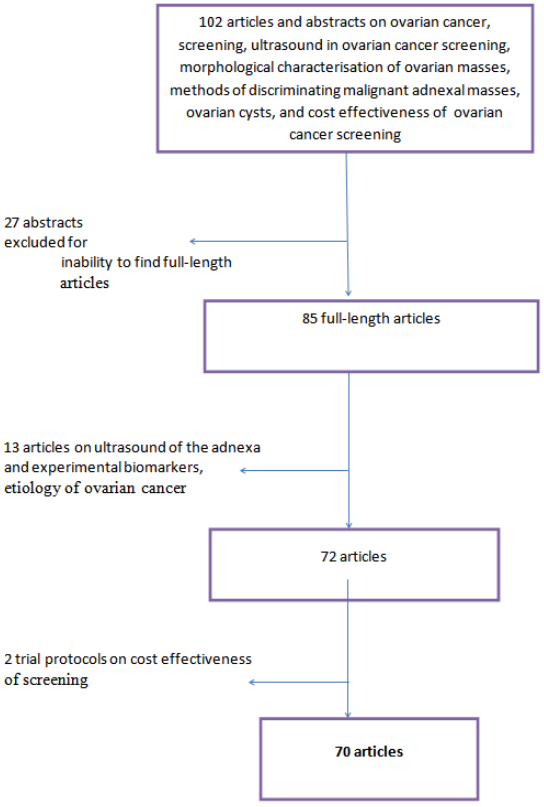

Figure 1. Flow chart of reviewed literature

2. Search Methodology

The information contained in this review were obtained through electronic literature search conducted in major data bases including PubMed, Medline, EMBASE, Scopus, CINHAL, Cochrane database and central register of controlled trials using the following search terms individually and in combination: *ovarian cancer, simple ovarian cysts, complex ovarian cysts, screening trial, ultrasonography, transvaginal ultrasound, multimodal, PLCCO trial, cost effectiveness of screening, UKFOCCS, UKCTOCS.* All relevant peer-reviewed English language articles and publications were identified, retrieved and reviewed. We also obtained further articles by reviewing the bibliographies of the relevant published articles. Figure 1 shows a flow chart of the results of literature search.

3. History of Ovarian Cancer Screening

The history of screening for ovarian cancer can be broken into three phases based on the major focus of efforts at screening. The first phase would be the period from the 1950 to 1980 during which efforts at screening were made, at best, at informal, individualized and opportunistic level. Methods used included digital pelvic examination and cul-de-sac aspiration [16,17]. These methods had low sensitivity and specificity and were abandoned due either to complications arising from them and/or poor patient acceptability and compliance [18]. The introduction of ultrasound into medicine during this period resulted in transabdominal ultrasound being used to characterize abdominal and pelvic masses including ovarian tumours in symptomatic women [19, 20].

The second period was the period between 1980 and 1990 during which formalised intense efforts at discovering and establishing appropriate modalities for screening for ovarian cancer began all over the world. During this period real time ultrasonography evolved with the introduction of the transvaginal probe. Similarly the antigen CA125 was discovered and its role as a biomarker identified [21]. In 1985, the first randomized clinical trial of ovarian cancer screening commenced enrolment in Shizouka district of Japan and the trial ran till 2002. This was a multimodal screening using pelvic examination and ultrasonography as a primary modality and CA125 as a secondary modality [22]. In 1989, a pilot randomized controlled trial of multimodal screening utilizing CA125 as primary modality and ultrasonography as secondary modality commenced in the United Kingdom [23]. A number of biomarkers other than CA125 were also tried as possible screening tests for ovarian cancer [24].

The third period from 1990 till date represent the period when real efforts were made at undertaking randomized controlled studies to determine the effect of ovarian cancer screening on mortality from ovarian cancer in at-risk populations. Also intense activity went on in developing new biomarkers and in introducing the use of proteomics to identify antigen profiles related to ovarian cancer. In order to address the inadequacies in the use of absolute values of CA125 for screening, measurement of the rate of rise of the serum levels of the protein was devised. This measurement, called Risk of Ovarian cancer algorithm has

been shown to be more specific for ovarian cancer than absolute point measurements since serum levels of CA125 remain steady or decline over time in benign ovarian conditions [25,26]. To further increase the sensitivity and specificity of serum screening, a number of tumour marker panels were tried. Combinations of tumour markers such as CA125, Human Epididymis protein4, Transthyrenin, etc have been tried. To date, no tumour marker panel has been shown to be superior to CA125 followed by transvaginal ultrasound scan [24]. Several novel screening methods have been proposed and a number of these have been tested. Assay of biomarkers in urine of postmenopausal women is said to hold some attraction because of its simplicity and non-invasiveness [27].

Two large randomized controlled trials of ovarian cancer screening were commenced. The PLCO trial began recruitment in 10 centres in the United States in 1993 and final results were reported in June 2011 [28,29]. The trial has determined that ovarian cancer screening did not reduce ovarian cancer mortality in the population, but genuine concerns have already been raised about the methodological approaches that led to this conclusion [30]. A larger trial powered to determine the effect of screening on mortality, the UKCTOCS, commenced recruitment in 13 centres in the UK in 2001 and concluded screening in December 2011 [31]. Unlike the PLCO trial, the UKCTOCS would also determine the relative efficacy of ultrasonography compared to multimodal screening involving CA125 as primary modality followed by ultrasonography where CA125 is abnormal. The final results of the UKCTOCS are expected in 2015.

3.1. The Evolution of Transvaginal Ultrasonography as a Screening Tool for Ovarian Cancer

Table 1 shows a selection of studies that underlined the evolution of ultrasonography as a potential tool for ovarian cancer screening. In addition to the studies listed in the table, other studies had also shown that the cost of screening with ultrasonography compared well with other methods. A major area of concern with transvaginal ultrasound screening remained the significant level of false positive tests which could result in many unnecessary interventions and surgeries. The vital place of ultrasound scan in screening for ovarian cancer was, perhaps, further underscored by the fact that assay of CA125 detects only 50-60% of early ovarian cancers [40]. Thus, although ultrasound scan could give rise to many false positive results, its capacity to detect adnexal lesions even when CA125 assay was normal made ultrasonography an important complement to CA125 for ovarian cancer screening.

Table 1. Showing some key studies that described the evolution of ultrasonography as a potential screening tool for ovarian cancer

Year & country of study	Authors	Title of study	Key findings(reference)
1982, UK	Campbell S, Goswamy R, Goessens L Whitehead M	Real time ultrasonography for determination of ovarian morphology and volume. The Lancet, 1982: 425-426	Demonstrated the correlation between ovarian volume measurements by ultrasound and measurements of the ovary during surgery. The study indicated the possible use of real time ultrasonography as an early screening test for ovarian cancer in asymptomatic women[32].
1986, Sweden	Andolf E, Svalenius E, Astedt B.	Ultrasonography for early detection of ovarian carcinoma. BJOG: An international journal of Obstetrics and Gynaecology, 1986; 93: 1286-1289.	Ultrasound was a possible diagnostic aid in early ovarian cancer [34]
1988, UK	Goswamy RK, Campbell S, Whitehead	Ovarian size in postmenopausal women. BJOG: An international journal of obstetrics and Gynaecology, 1988; 195: 795-801	Reported the first screening for ovarian cancer with ultrasonography [33]
1988, UK	Jacobs I, Stabile I, Bridges J.	Multimodal screening for ovarian cancer. The Lancet, 1988: 268-72	Demonstrated that CA125 and Ultrasonography each test lacked the specificity to screen for ovarian cancer individually but that CA125 and ultrasound achieved acceptable specificity together [35]
1990, UK	Campbell S, Royston P, Bhan V, Whitehead MI, Collins WP	Novel screening strategies for early ovarian cancer by transabdominal ultrasonography. BJOG: An International Journal of Obstetrics & Gynaecology, 1990; 97: 304-311	Supported possible role for ultrasonography for ovarian cancer screening[36]
1990, USA	van Nagell Jr JR, Higgins PV, Donaldson ES et al.	Transvaginal sonography as a screening method for ovarian cancer; a report of first 1000 cases. The Lancet, 1990; 65:573-577.	Reported the usefulness of ultrasonography in detecting early stages of ovarian cancer
1993, USA	van Nagell Jr JR., DePriest PD, Gallion HH, Pavlik EJ.	Ovarian Cancer Screening. Cancer 1993; 71: 1523 - 8.	
1995, USA	van NagelI Jr JR, Gallion HH, Pavlik EJ, DePriest PD	Ovarian Cancer Screening. Cancer 1995; 76:2086-91.	high resolution transvaginal ultrasonography was uninvasive, painless, well accepted by women and was able to determine precise ovarian dimensions that correlated well with measurements of the ovary obtained during surgery [38,39]
1996, USA	van Nagell Jr JR, DePriest PD, Puls LE et al.	Ovarian cancer screening in asymptomatic postmenopausal women by transvaginal sonography. Cancer, 1996; 68: 458-462.	Reported the usefulness and acceptability of ultrasonography for screening postmenopausal women for ovarian cancer
1997, USA	DePriest PD, Gallion HH, Pavlik EJ	Transvaginal sonography as a screening method for the detection of early ovarian cancer. Gynecologic Oncology, 1997; 65: 408-414	transvaginal sonography reduced stage at detection and case-specific mortality and recommended a multi-institutional ovarian cancer screening trial to determine effect on mortality in the population[37]

4. Management of Positive Ultrasound Screening Tests

A few challenges confront the gynaecologist following a positive ultrasound screening for ovarian cancer. The first challenge is the necessity to avoid any delay in intervention that may lead to disease progression; the second is to avoid unnecessary surgical interventions in those who may have had false positive screening tests and the third and the least recognized is the challenge posed by the unpredictability of the biologic behaviour of cases that are triaged to conservative management. As a consequence of the third challenge, it has been observed that a "proportion of women and clinicians will opt for surgery once a complex adnexal lesion is detected even if it is likely to be benign" [31].

4.1. Triaging Ultrasound Positive Results

Triaging is important in order to refer those with a high likelihood of cancer to Oncology centres early enough in order to maximize the benefit of screening and also to avoid unnecessary surgeries in those with false positive results. Avoiding unnecessary surgical interventions requires taking extra steps to further identify those who are most likely to have benign lesions among the screen positive tests. This could involve repeat ultrasound scan by an expert ultrasound practitioner, clinical examination by a gynaecologist as well as biochemical assays of CA 125. In addition to these, several procedures are available as adjuncts to aid the triaging of adnexal masses (screen positive cases) to either surgical intervention or conservative management. These include the use of morphologic indices, risk of malignancy indices and mathematical models etc. Although many of these were described for symptomatic ovarian masses, they can also be used in screen positive cases and therefore merit elaboration.

4.1.1. Morphologic Indices

These techniques include the use of scoring systems based on morphological features noted on ultrasound images to distinguish between benign and malignant ovarian lesions. Sonographic morphological features of ovarian cysts such as the thickness of cyst wall, presence of papillary growths on cyst wall, presence of solid components within the cyst, presence and number of loculations, sonoluscency of cyst fluid and presence of shadowing have been incorporated into scoring systems. There are many scoring systems now but the commonest include the Granberg score, Sassone score, the Kentucky score, Lerner's score, Ferrazzi's score, Alcazar score [41-47].

The Granberg score is a single index scoring system based on locularity of the adnexal cyst with unilocular cyst given a score of zero, unilocular solid score of 1, multilocular cysts score of 2 and multilocular solid and pure solid cysts given score of 3 and 4 respectively [41]. The Granberg score has a sensitivity and specificity of 87% and 49% respectively for a score of 2 (multilocular cysts) for a positive predictive value of 31% [41]. The Granberg score is one of the earliest morphologic scoring indices and has been largely superseded by later scoring indices. The Sassone score utilizes features including inner wall structure, wall thickness, septal thickness and echogenicity scored on a scale of 1 to a maximum of 5 where applicable [44]. For a cut off of score of 9, it has a sensitivity, specificity and positive predictive value of 74%, 65% and 36 respectively. The Kentucky score uses 3 parameters namely cystic wall structure, ovarian volume, and septal structure [43]. For a cut off score of 5 it has a sensitivity, specificity and positive predictive value of 88%, 40% and 28% respectively. The Alcazar score includes features from Doppler studies such as velocimetry and blood flow location [47]. The efficacy of all these scoring systems when used alone is hampered by an overlap between the appearances of benign and malignant adnexal masses [48].

4.1.2. Risk of Malignancy Indices

To increase the sensitivity and specificity of morphological scoring systems, some scientists have combined ultrasound features with other parameters such as clinical features or assay of biomarkers to create risk scoring indices. The risk of malignancy index devised by Jacobs and co-workers, for instance, combines scores based on menopausal status, ultrasound features and CA125 level [49]. It had a sensitivity of 85% and specificity of 97% [49]. Since the introduction of this index, several other risk-of-malignancy indices have been introduced, each new index seeking to improve on diagnostic accuracy by improving on the specificity or sensitivity of previous ones [50,51,52]. While the original risk of malignancy index by Jacobs and co-workers is referred to as RMI 1, other RMIs have followed the RMI 1 thus: RMI 2 by Tingulstad and colleagues 48, RMI 3 also by Tingulstad and colleagues [51] and RMI 4 by Yamamoto and co-workers [52]. A recent comparison of the performances of RMIs 1-4 showed that there was no statistically significant difference in their ability to discriminate between malignant and non-malignant adnexal masses [53]. The sheer multiplicity of indices underlies the inadequacy of each RMI and this has limited the usefulness of these aids for the triaging of ovarian lesions diagnosed during screening.

4.1.3. Mathematical Models

4.1.3.1. Logistic Regression Models

In order to further improve clinical decision making following a positive screening test, logistic regression models using socio-demographic and clinical features were introduced to assist in discriminating between malignant and benign ovarian lesions prior to surgery. Several authors have introduced or validated previously devised logistic regression equations and found them to demonstrate a high sensitivity, specificity and positive predictive value [47,54,55,56]. Prospective validation has been possible with the IOTA logistic regression equation [53]. The logistic regression model proposed by Tailor and co-workers had a sensitivity of 93.3% and specificity of 90.4% [56], while the IOATA logistic regression had a sensitivity of 93.0% and a specificity of 76% [54]. Alcazar and colleagues introduced Doppler flow characteristics and reported a sensitivity of 84.6% and specificity of 100% [47].

4.1.3.2. Computer-based mathematical techniques

In addition to morphological scores, risk of malignancy indices and logistic regression equations, other techniques such as self-teaching computer based neural networks [57] and the use of least support square vector machines are other mathematical devices that have been introduced to the distinguish between benign and malignant adnexal tumours prior to surgery [58]. Timmermann and co-workers obtained a sensitivity of 95.9% and specificity of 93.5 for artificial neural networks in discriminating between malignant and benign ovarian masses [57]. These techniques are advanced statistical applications that cannot be easily understood by most clinicians and this limits their usefulness for routine clinical practice.

5. Predicting the Biologic Behaviour of Triaged Benign Cysts

Appreciation of the precise biologic behaviour of benign ovarian cysts is important for conservative management. Overall, the biologic behaviour and outcomes of conservative management have tended to differ between benign simple cysts and benign complex cysts.

5.1. Simple Ovarian Cysts

Prior to the advent of transvaginal sonography, studies based on transabdominal ultrasound scan showed that small anechoic ovarian cysts were seldom malignant in elderly women. In a retrospective study of 152 symptomatic Swedish women aged 50 years or more presenting in the Gynaecology clinic, in whom cystic lesions without solid parts had been diagnosed, Andolf and Jorgensen found no malignancies in 58 completely anechoic lesions less than 5 cm and of small lesions less than 5 cm with some echogenicity or septa, they found 1 borderline tumour [59]. In contrast they found 5 malignancies in a group of 32 women who had cysts measuring more than 5 cm with some echogenicity and 8 malignancies among 18 lesions greater than 5 cm with septa [59]. The study excluded those with multicystic lesions without solid parts. The study demonstrated that small unilocular anechoic cysts were hardly malignant. However, since no follow up on these simple cysts was done, no conclusion could be drawn on their biologic behaviour from this study.

With the advent of transvaginal sonography, Sasaki and colleagues conducted a follow up study of 225 pre and postmenopausal women with ovarian cysts less than 6 cm with change in size as the main outcome measure [60]. After 6.25 years, 29 lesions had progressed (13%), 14% had persisted while 73% regressed with 48% regressing within 6 months [60]. Of the 29 the progressed, 9 had surgery and no cancer was found [60]. The other 20 lesions that progressed were not accounted for. The design of the study that sought change in size as main outcome measure clearly limited the conclusions that could be drawn from the study and the inability to explore a majority of the lesions that progressed deprived the study of a window view into the possible relationship of a progressing simple cyst with malignant transformation.

A study to measure the occurrence and natural history of simple ovarian cysts in older women participating in a large randomized trial of ovarian cancer screening, Greenlee and co-workers found that among 15,735 women whose ovaries were visualized, 2,217 had a simple cyst at first scan and that those with one simple cyst had 33% regression after one year and those with two or more cysts had less regression after one year [61]. Only six percent of simple cysts developed complex cysts or solid areas after one year compared to 7% of two simple cysts and 11% of multiple cysts [61]. Interestingly, only 1% of those who had no cysts initially developed cysts with complex or solid parts. Overall the study concluded that the development of malignancy did not differ significantly between those who had simple cysts and those who had no cysts at all at the initial scan after a median follow up of 7 years [61]. Perhaps because of the finding that the development of complex cysts or cysts with solid areas occurred more in those who had simple cysts at the initial scan than in those with no cysts at all, it affirmed the conclusion of previous studies that simple cysts rarely led to cancer but cysts that persist should be followed up [61].

A prospective cohort study that assessed the malignant potential of ovarian inclusion cysts in postmenopausal women aged 50 years or more who were participants in the UKCTOCS found no increase in relative risk of cancer between those with inclusion cysts and those without after a median follow up of 6.13 years [62]. They however found that the risk of ovarian cancer increased in those who had ovaries with both inclusion cysts and simple/complex cysts as opposed to those who had inclusion cysts alone [62].

These two large series support view that simple cysts are probably not premalignant. However, they tend to suggest that those that have simple cysts that persist tend to develop complex cysts more than those who do not have cysts and that those with complex cysts tend to have increased incidence of subsequent malignancy.

5.2. Septated (Complex) Ovarian Cysts

Data on conservatively-managed complex ovarian cysts with benign ultrasound morphology are scanty and their contribution to the development of ovarian cancer is still not clear. This partly explains why surgical rates are high in trials of ultrasound screening for ovarian cancer. Unlike simple cysts that generally tend to regress, a recent study of pre and postmenopausal women showed that 62% of complex cysts persisted over a mean period of 77 months [63].

In order to determine whether asymptomatic ovarian abnormalities detected on ultrasonography in postmenopausal women are precursors to ovarian cancer, Hartge and co-workers studied complex cysts defined as having septa, irregular thick wall or solid component using correlation analysis and logistic regression [64]. They used known risk factors for ovarian cancer such as old age at examination, age at menopause, family and personal history of breast or ovarian cancer and history of infertility as predictor variables [64]. The study concluded that complex ovarian cysts did not appear to be immediate precursors of ovarian cancer because risk factors for ovarian cancer such as a family history of ovarian cancer were not associated with complex cysts in their series [64].

In a study to determine the risk of malignancy in septated cystic ovarian tumours by Saunders and

colleagues, 1319 women with septated cystic tumours were placed on long term surveillance for ovarian malignancy [63]. Of 2288 tumours, 1114 regressed spontaneously while 1756 persisted [63]. Patients were followed for 4 -252 months with a mean of 77 months and only one patient developed epithelial ovarian cancer and the others were free of cancer after 7642 follow-up years [63]. The study concluded that septated ovarian cysts had very low risk of malignancy [63]. The fact that only one case of cancer developed among 1756 tumours after a mean follow up of 77 months is an interesting finding that suggests that such cysts pose little or no risk of malignancy [63]. However, the study included both premenopausal-who have no increased risk of ovarian cancer- and postmenopausal women. The study also did not describe the changes, if any, in the features of the cysts with time and so no information on transformation of such cysts other than into cancer was provided. A mean follow up of 77 months (71/2 years) would be enough time for changes to be noted in the morphological features of the cysts.

On their part, Sharma and co-workers determined the risk of malignancy in asymptomatic postmenopausal women with ultrasound detected ovarian cysts detected during the prevalence screen of the UKCTOCS trial [62]. They found that of 1095 women with septated cysts without solid elements, four developed primary ovarian cancer and all 4 were initially managed conservatively and all had an increase in size or changes in features of the cysts prior to diagnosis of cancer [62]. The change in morphology prior to diagnosis of cancer could suggest some form of malignant transformation of previously benign cysts [62].

6. Implications of Current Potential Screening Strategies for Low-Resource Settings

6.1 Cost Effectiveness of Ovarian Cancer Screening

Few studies have directly addressed the cost effectiveness of ovarian cancer screening [65,66,67,68]. A cost-effectiveness analysis is defined by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) as an economic study design in which the consequences of different interventions are measured using a single outcome, usually in "natural" units such as life-years gained or cases detected [65]. Alternative interventions are then compared in terms of cost per unit of effectiveness. For ovarian cancer, it would mean the cost of detecting one case of ovarian cancer. Three categories of costs are considered: (i) cost associated with the screening tests themselves, (ii) costs associated with evaluation of positive screens, and (iii) cancer treatment costs [66]. Using stochastic modelling, Urban and colleagues have estimated that using a multimodal strategy with CA125 assay followed by ultrasound for positive cases would cost US $51,000 per year of life saved [67]. Generally, estimates range 100,000 – 250,000 (USD) per life year saved, although it has been suggested that the cost per year of life saved through screening must be <150,000 US dollars to be cost-effective, putting into consideration the cost of interventions, unnecessary surgeries and complications of surgery. However, cost-effectiveness might vary according to different medical environments in different nations

6.2. Feasibility in Low Resource Settings of Current Screening Strategies under Trial

Contrary to previous beliefs, there are indications that the prevalence of ovarian cancer may be increasing in developing countries as a shift to sedentary lifestyles and western diets and social habits spreads [69,70,71]. There is therefore the need for a more than cursory attention to be paid to this disease in developing countries. Despite this development, no trial of ovarian cancer screening has been reported from any developing country.

The implications of current ovarian cancer screening protocols for developing countries are multifold. First, the sheer capital outlay required for large trials is beyond the capacity of most developing economies in terms of funds and personnel required. The UKCTOCS trial needed hundreds of millions of pounds and thousands of highly-skilled health personnel including sonographers, gynaecologists and secretarial staff. Cost-effectiveness studies on ovarian cancer screening appear to have been based on procedural costs alone, in line with the NICE definition. For low-income countries a wider perspective of cost must be applied. Unlike in developing countries, the cost of acquisition of equipment and training of personnel, both of which are not on the ground in most low-resource countries, must be factored in. It might therefore not be possible, nor cost-effective for any developing country in Sub-Saharan Africa to acquire and expend such resources on such a rare disease as ovarian cancer.

Since neither ultrasound nor assay of CA125 possesses sufficient specificity individually to be used alone for screening, multimodal approach to ovarian cancer screening has come to stay. Ultrasound screening is an expensive endeavour given the cost of modern high resolution machines required for precise ovarian morphological characterization. Besides, the high level of ultrasound skill required for transvaginal scanning of postmenopausal women may not be widely available in many developing countries. Assay of CA125 also requires high tech laboratories with appropriately trained personnel. If CA125 assay wassensitive and specific enough on its own, it might still be too expensive for many developing country economies. The necessity for further tests and scans after the initial positive tests increases the cost of screening.

7. Conclusion

Transvaginal ultrasonography remains a potential tool for ovarian cancer screening. It has a high sensitivity. However, its low specificity suggests that it is best used as an adjunct to other screening methods. Confronted with the challenges of high false positive rates, further clinical assessment and biochemical tests are mandatory following positive ultrasound test both to achieve a high specificity and to ensure appropriate triaging and management of

positive results. These extra measures add to the cost of screening. Globally very few studies have evaluated the cost effectiveness of ovarian cancer screening, and there is no clear agreement that current multimodal strategies are cost effective since no mortality benefit has been demonstrated. For developing countries, the technological and human resources needed for current potential screening strategies could make screening for ovarian cancer unattainable.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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