IOTA and Models for Screening for Ovarian Cancer

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Ovarian Cancer: "Silent Killer" No More?

By Christine Lagorio

Survival rates are poor, with only 30% of those diagnosed surviving for more than five years.

However identifying the disease before it has spread can mean nine in ten women make the five-year mark.

"The symptoms shout out at you, but you have to listen to your body..."
“Silent Killer” to “Whispering Disease”

Listening to your body.. new, persistent, and increases in severity

- Abdominal pressure, fullness, swelling or bloating
- Pelvic discomfort or pain
- Persistent indigestion, gas or nausea
- Changes in bowel habits, such as constipation
- Changes in bladder habits, including a frequent need to urinate
- Loss of appetite or quickly feeling full
- Increased abdominal girth or clothes fitting tighter around your waist
- A persistent lack of energy
- Low back pain

Goff et al. Cancer, 2000, 89: 2068–75
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, Females, UK
Mortality: Incidence Ratio

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>0.67</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>0.18</td>
</tr>
<tr>
<td>Cervix</td>
<td>0.39</td>
</tr>
</tbody>
</table>

UK Office of national statistics, 2001
Rationale for Screening

Most deadly gynaecological cancer

Usually advanced disease at diagnosis

Stage shift may improve survival...
Challenge of OC Screening

Adequate sensitivity
  ◦ Detect preclinical or early disease
  ◦ Lead time of marker

High specificity
  ◦ If test positive - surgery
  ◦ Minimum specificity of 99.6% to achieve PPV of 10% (10 surgeries/case diagnosed)
  ◦ Even 98% specificity – 50 surgeries for one case detected
Screening Strategies

Clinical examination, biochemical markers, morphological and vascular features

Simple models
- discrete cut-off values such as CA-125, pulsatility index, resistance index

Intermediate models
- morphology scoring systems and the risk of malignancy index

Advanced models
- include artificial neural networks and multiple logistic regression models
Clinical Examination

“Palpable ovary syndrome”

Sensitivity of pelvic examination for detection of OC is unknown

150 pts EUA - ovaries were detected clinically in <30% of women ≥55 years

“..no predictive value for cancer”

Ueland, 2005
Biochemical Markers

CA 125

30-35 U/ml in PM women

Raised in 50% stage I

Raised >90% cases of advanced disease

Lead time 1.5 – 1.9 years

Bast 1983 MD
Anderson Cancer Center
Biochemical Markers
CA 125

Final diagnosis in women with raised Ca 125 in clinical practice (N = 751)

Moss 2005
**Morphological Markers**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Smooth capsule</td>
<td>Irregular</td>
</tr>
<tr>
<td>Mobile</td>
<td>Fixed</td>
</tr>
<tr>
<td>Thin walled, cystic</td>
<td>Solid, thick walled</td>
</tr>
<tr>
<td>Unilocular</td>
<td>Multilocular</td>
</tr>
<tr>
<td>No projections</td>
<td>Papillary projections</td>
</tr>
<tr>
<td>No ascites</td>
<td>Ascites</td>
</tr>
</tbody>
</table>
Adequately describe morphology and ovarian volume:

- Septum
  - Complete or incomplete
- Papillary projections
- Cystic vs. solid
- Other features
  - Evidence of metastases
  - Presence of ascites
  - Bilateral lesions
  - Consistency

Ultrasound Obstet Gynecol 2000; 16
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number</th>
<th>Ca</th>
<th>Ca %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilocular cyst</td>
<td>86</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unilocular solid</td>
<td>34</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Multilocular cyst</td>
<td>60</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Multilocular solid</td>
<td>70</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>50</td>
<td>31</td>
<td>60</td>
</tr>
</tbody>
</table>
Table 2. IOTA Group ultrasound ‘rules’ to classify masses as benign (B-rules) or malignant (M-rules) \(^{38,51}\)

<table>
<thead>
<tr>
<th>B-rules</th>
<th>M-rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilocular cysts</td>
<td>Irregular solid tumour</td>
</tr>
<tr>
<td>Presence of solid components where the largest solid component (&lt;7) mm</td>
<td>Ascites</td>
</tr>
<tr>
<td>Presence of acoustic shadowing</td>
<td>At least four papillary structures</td>
</tr>
<tr>
<td>Smooth multilocular tumour with a largest diameter (&lt;100) mm</td>
<td>Irregular multilocular solid tumour with largest diameter (\geq 100) mm</td>
</tr>
<tr>
<td>No blood flow</td>
<td>Very strong blood flow</td>
</tr>
</tbody>
</table>

**Rule 1:** \(1 \leq M\) features in the absence of a B feature, classified as malignant.

**Rule 2:** \(1 \leq B\) features in the absence of an M feature, classified as benign.

**Rule 3:** If both M features and B features were present, or if none of the features was present, the simple rules were inconclusive.
1938 women with adnexal mass examined with ultrasound

Sensitivity and specificity for histologically confirmed malignancy

- 1396 (72%) had benign tumours
- 373 (19.2%) had primary invasive tumours
- 111 (5.7%) had borderline malignant tumours
- 58 (3%) had metastatic tumours

The simple rules yielded a conclusive result in 77% masses

- Sensitivity of 92% [89-94%]
- Specificity of 96% [94-97%]

Timmerman BMJ 2010
Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group

...Simple rules has potential to improve the management of women with adnexal masses

...inconclusive result - experienced ultrasound examiner was most accurate diagnostic test

Timmerman  BMJ 2010
Combining Biochemistry and Morphology

Multimodal screening
- Sequential CA125 and TVS - spec 99.9%, PPV 26.8% (4 operations / case OC)
- ROC algorithm – age and serial CA125 profile

Jacobs 1993, 1996
78,216 women 55-74y either annual screening (n=39,105) or usual care (n=39,111) followed 12 years
- CA-125 for 6 years and TV ultrasound for 4 years

Participants and their practitioners received and managed abnormal results

Buys et al. JAMA, 2011
Rate of diagnosis and death NS

3285 women false-positive results
  ◦ 1080 underwent surgery
  ◦ 163 at least 1 serious complication (15%)

Screening with CA-125 and TVS did not reduce ovarian cancer mortality.

False-positive screening test result associated with complications.

Buys et al. JAMA, 2011
UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

202,638 Women randomised to three groups 2:1:1

Half of the participants (n = 101,359) randomised to no intervention

Rest were divided between two screening strategies

Group 1 (n = 50,640) annual CA 125 followed by TVU if abnormal - multimodal screening (MMS) group

Group 2 (n = 50,639) annual TVU

Average follow-up 11.1y

Menon, Jacobs. Lancet Oncol. 2009
UKCTOCS

Significantly better specificity for MMS when compared to the ultrasound-only group

>40% of all cancers diagnosed Stage 1

Surgeries needed to diagnose one cancer
- 35 in ultrasound group
- 3 in MMS group
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UK CT OCS): a randomised controlled trial

Mortality reduction of 15% with MMS (95% CI –3 to 30; p=0.10) and 11% with USS (–7 to 27; p=0.21)

Death from ovarian cancer of MMS versus no screening with exclusion of prevalent cases showed significantly different death rates (p=0.021)

Reduction of 8% in years 0–7 (–27 to 43) and 28% in years 7–14 (–3 to 49) in favour of MMS

“Our findings suggest that a multimodal approach to screening might detect ovarian cancer sufficiently early to reduce mortality.”
Figure 3: Rates of ovarian cancer
The figure including confidence limits is in the appendix (p 14).
MMS = multimodal screening. USS = ultrasound screening.
Ov Ca Screening Guidelines

Risk near that of the general population (RR < 3X general public)
  ◦ Screening not recommended, annual gynaecologic examination

Increased risk (RR 3-6X general public)
  ◦ No evidence that screening will decrease deaths
  ◦ CA-125 and/or TVS - within the framework of research studies

Women with inherited risk (RR >6X general public)
  ◦ Combination of TVS and CA-125 testing
  ◦ BRCA1 begin between 30 and 35 and BRCA2 begin between 35 and 40

https://www.mskcc.org/cancer-care
Screening Conclusion

Promising evidence of late ↓ mortality
Offer only to appropriately counselled women
When to start / finish?
How often?
Clinical Management

The Management of Ovarian Cysts in Postmenopausal Women
Green-top Guideline No. 34
July 2016

Management of Suspected Ovarian Masses in Premenopausal Women
Green-top Guideline No. 62
RCOG/BSGE Joint Guideline | November 2011

RCOG 2016

RCOG 2011
Ovarian Cyst in PM women

Common problem

TVS part of clinical examination

PLCO trail - 21% women had abnormal ovarian morphology
Risk of Malignancy Index

\[ \text{RMI} = \text{U} \times \text{M} \times \text{CA125} \]

\( \text{U} = 0 \) (score of 0); \( \text{U} = 1 \) (score of 1); \( \text{U} = 3 \) (score of 2–5)
- multilocular cyst; solid areas; evidence of metastases; ascites; bilateral

\( \text{M} = 3 \) for all PM women

- CA125 not used in isolation, normal value does not fully exclude ovarian cancer
- Not enough evidence to use other tumour markers: HE4, CEA, CDX2, CA72-4, CA19-9
<table>
<thead>
<tr>
<th>Risk</th>
<th>RMI</th>
<th>Women (%)</th>
<th>Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;25</td>
<td>40</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Moderate</td>
<td>25–250</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>High</td>
<td>&gt;250</td>
<td>30</td>
<td>75</td>
</tr>
</tbody>
</table>

Davies 1993
Postmenopausal ovarian cyst (cystic lesion 1 cm or more)

Measure CA125
TVS ± TAS
Calculate RMI I

RMI I < 200
(low risk of malignancy)

Cysts fulfilling ALL of the following criteria:
asymptomatic, simple cyst, < 5 cm, unilocular, unilateral

Consider conservative management

Cysts with ANY of the following features:
symptomatic, non-simple features, > 5 cm, multilocular, bilateral

Consider surgery salpingo-oophorectomy (usually bilateral)

RMI I ≥ 200
(increased risk of malignancy)

CT scan (abdomen and pelvis)
Referral for gynaecological oncology MDT review

MDT review
High likelihood of ovarian malignancy

MDT review
Low likelihood of ovarian malignancy
...a fierce belief that something must be done to rectify the miserable inadequacies of current medical responses to ovarian cancer