Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study

International Ovarian Tumour Analysis (IOTA) group

EDITORIAL by Biliatis and Ratnavelu

Correspondence to: B Van Calster
ben.vancalster@med.kuleuven.be

Cite this as: *BMJ* 2014;349:g5920
doi: 10.1136/bmj.g5920

The authors are listed in the full paper on thebmj.com

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g5920

thebmj.com

- Routine testing for women with ovarian cancer (*BMJ* 2014;348:g1200)
- London hospital widens access to genetic tests for ovarian cancer (*BMJ* 2014;348:g1179)
- Computer assisted diagnosis of ovarian cancer in primary care (*BMJ* 2012;344:d7628)
- Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm (*BMJ* 2012;344:d8009)

STUDY QUESTION

Can we preoperatively predict the likelihood of an ovarian tumour being benign, borderline, or a stage I, advanced stage, or secondary metastatic cancer?

SUMMARY ANSWER

The Assessment of Different NEoplasias in the adneXa (ADNEX) risk model accurately determines the nature of an ovarian mass. The model differentiates well between benign and all malignant tumours and offers fair to excellent differentiation between borderline tumours, stage I, advanced stage, and secondary metastatic cancer.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Currently many women with ovarian cancer are not referred to receive specialist care in a gynaecological oncology centre. In contrast with existing prediction models, ADNEX can subclassify malignancies. Hence the model may improve referral and subsequent management decisions and so positively impact on morbidity and mortality.

Participants and setting

This study enrolled women with an ovarian (including para-ovarian and tubal) mass who underwent a standardised ultrasound examination and were later selected for surgery. Data were collected in 24 centres (oncology centres and other hospitals) in 10 countries.

Design, size, and duration

This prospective diagnostic study from the International Ovarian Tumour Analysis (IOTA) group included 5909 patients. Based on histological classification and surgical staging of the mass at the local centre, tumours were classified as benign, borderline, stage I invasive, advanced stage invasive, or secondary metastatic cancer (reference standard). Using a priori selected clinical and ultrasound predictor variables, a risk model was built on data collected between 1999 and 2007 (n=3506) and temporally validated on data collected between 2009 and 2012 (n=2403). The model was then updated on all 5909 patients to make full use of the available data.

Main results and the role of chance

The ADNEX model contains nine predictors: age, serum CA-125 level, type of centre (oncology *v* other), maximum lesion diameter, proportion of solid tissue, more than 10 cyst locules, number of papillary projections, acoustic shadows, and ascites. On temporal validation, the area under the receiver operating characteristic curve for the classic discrimination between benign and malignant tumours was 0.94 (95% confidence interval 0.93 to 0.95). Using a previously proposed 10% risk cut-off for the overall risk of malignancy, sensitivity was 96.5% (95% confidence interval 95.2% to 97.6%) and specificity was 71.3% (68.9% to 73.7%). The discrimination performance between the different subtypes is shown in the table. Calibration curves showed that the estimated risks were accurate.

Bias, confounding and other reasons for caution

All prediction models for the diagnosis of ovarian tumours are developed on patients selected for surgery. The lack of central review of pathology may have introduced bias—for example, because pathologists may have difficulty in distinguishing borderline tumours from stage I cancer or benign tumours. Experienced ultrasound operators examined all tumours. Based on other results, however, we expect the performance of the ADNEX model to be maintained by ultrasound examiners with differing experience and training if they are familiar with the IOTA definitions and examination technique as published elsewhere.

Generalisability to other populations

The inclusion of 24 oncology and non-oncology centres from 10 countries suggests generalisability in secondary and tertiary care.

Study funding/potential competing interests

This study is supported by and performed independently from the Flemish government (FWO, IWT, iMinds), the Swedish Medical Research Council, the Malmö and Skane University Hospitals, the Swedish Government, and the NIHR Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

Discrimination performance of ADNEX model on validation data, and after updating on pooled data

Performance measures	Validation data (n=2403)	After updating on pooled data (n=5909)
Benign *v* malignant:		
AUC	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)
Sensitivity (%) for 10% risk cut-off*	96.5 (95.2 to 97.6)	96.4 (95.4 to 97.2)
Specificity (%) for 10% risk cut-off*	71.3 (68.9 to 73.7)	73.2 (71.8 to 74.6)
AUC between subtypes:		
Benign *v* borderline	0.85 (0.82 to 0.88)	0.88 (0.87 to 0.90)
Benign *v* stage I	0.92 (0.90 to 0.93)	0.93 (0.92 to 0.94)
Benign *v* stage II-IV	0.99 (0.98 to 0.99)	0.99 (0.98 to 0.99)
Benign *v* metastatic	0.95 (0.93 to 0.97)	0.96 (0.95 to 0.97)
Borderline *v* stage I	0.75 (0.69 to 0.79)	0.75 (0.71 to 0.79)
Borderline *v* stage II-IV	0.95 (0.93 to 0.96)	0.93 (0.91 to 0.95)
Borderline *v* metastatic	0.87 (0.82 to 0.91)	0.88 (0.85 to 0.91)
Stage I *v* stage II-IV	0.87 (0.83 to 0.90)	0.85 (0.82 to 0.87)
Stage I *v* metastatic	0.71 (0.65 to 0.76)	0.75 (0.70 to 0.78)
Stage II-IV *v* metastatic	0.82 (0.78 to 0.86)	0.80 (0.76 to 0.83)

AUC=area under the receiver operating characteristic curve. 95% confidence intervals are shown in parentheses.
*Patients with overall risk of malignancy of at least 10% are classified as having a malignant tumour.

Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study

Hannah Christensen,[1] Caroline L Trotter,[2] Matthew Hickman,[1] W John Edmunds[3]

[1]School of Social and Community Medicine, University of Bristol, Bristol BS8 2PS, UK
[2]Disease Dynamics Unit, Department of Veterinary Medicine, University of Cambridge, Cambridge CB3 0ES, UK
[3]London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
Correspondence to: H Christensen **hannah.christensen@bristol.ac.uk**

Cite this as: *BMJ* 2014;349:g5725
doi: 10.1136/bmj.g5725

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g5725

thebmj.com

- No evidence for political manipulation regarding the new group B meningococcus vaccine (*BMJ* 2014;348:g2929)
- No conspiracy regarding recommendation for a group B meningococcus vaccine (*BMJ* 2014;348:g2859)
- Introducing a new group B meningococcus vaccine (*BMJ* 2014;348:g2415)
- Meningitis B vaccine to be introduced in UK after U turn on its cost effectiveness (*BMJ* 2014;348:g2327)

STUDY QUESTION

What is the public health impact and cost effectiveness of introducing universal vaccination against meningitis with Bexsero in England?

SUMMARY ANSWER

Models predict that infant immunisation would maximise case reduction in the short term and could be cost effective in England assuming a low vaccine price (range £3-£22) and the inclusion of a quality of life adjustment factor.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The first broadly protective vaccine against meningococcal group B disease (Bexsero) was licensed in Europe in January 2013; in July the Joint Committee on Vaccination and Immunisation advised against the introduction of the vaccine in the UK on cost effectiveness grounds. Models incorporating new evidence suggest infant immunisation would be most effective in the short term and could be cost effective; the committee's final statement on Bexsero recommended vaccination at 2, 4, and 12 months of age, subject to the vaccine being procured at a cost effective price.

Main results

Routine infant immunisation resulted in the greatest case reduction in the short term (26% of cases averted in the first five years with a 2, 3, 4, and 12 month vaccination programme). This strategy could be cost effective at £3 (€3.8; $4.9) a vaccine dose given several favourable assumptions and the use of a quality of life adjustment factor. Predicted cases averted under a 2, 4, and 12 months strategy are only 0.3% lower than for the 2, 3, 4, and 12 months schedule, because similar levels of protection are assumed. If the vaccine disrupts carriage, a combined infant and adolescent programme would prevent more cases in the long term (52% after 30 years) and could be cost effective at £4 a vaccine dose. If we assume the vaccine reduces acquisition by 30%, adolescent vaccination alone is the most favourable strategy economically but takes more than 20 years to substantially reduce cases.

Design

We used an age structured (0-99 years) transmission dynamic model of meningococcal carriage and disease in England and modelled the effects of different introductory Bexsero vaccination programmes.

Sources of effectiveness

The modelled health impact of vaccination was assessed through cases averted and the cost per quality adjusted life years (QALYs) gained. Strategies below £20 000 per QALY gained were deemed cost effective.

Data sources

Model parameters and scenarios included recent evidence on the vaccine characteristics, disease burden, costs of care, litigation costs, and loss of quality of life from disease, including impacts on family and network members. The models were considered over a 100 year time horizon, with costs and benefits discounted back to 2011 at a rate of 3.5% in the base case,

Results of sensitivity analysis

The results were highly sensitive to vaccine profile assumptions. The ability of the vaccine to disrupt transmission is critical to the effectiveness and cost effectiveness of adolescent programmes but had limited impact in infant programmes. Reduced vaccine strain coverage and duration of protection made vaccination less economically attractive and, in some scenarios, cost ineffective. None of the strategies considered was cost effective at the current vaccine list price (£75 a dose).

Limitations

Our models did not consider the potential negative impact of the loss of natural boosting from carriage or strain replacement, thus might be optimistic. Parameter uncertainty was considered through extensive scenario, rather than probabilistic analysis.

Study funding /potential competing interests

HC is funded by a National Institute for Health Research (NIHR) postdoctoral fellowship. MH is a member of the NIHR School of Public Health Research; HC and MH are members of the NIHR Health Protection Research Unit in Evaluation of Interventions.

Comparison of vaccination strategies (vaccination *v* no vaccination over 100 years) against meningococcal disease with Bexsero assuming 30% vaccine efficacy against carriage acquisition

		3.5% discounting for costs and benefits		1.5% discounting for costs and benefits	
Scenario	Undiscounted, cases averted	Cost (£)/QALY gained	Vaccine price (£) for cost/QALY gained <£20 000	Cost/QALY gained (£)	Vaccine price (£) for cost/QALY gained <£20 000
2, 3, 4, and 12 months	52 152	221 000	3	151 400	8
2, 4, and 12 months	51 789	163 100	7	110 800	13
13 years	62 165	104 900	14	62 100	27
2, 3, 4, and 12 months and 13 years	91 304	199 000	4	131 600	9

Clinical and social outcomes of adolescent self harm: population based birth cohort study

Becky Mars,[1] Jon Heron,[1] Catherine Crane,[2] Keith Hawton,[3] Glyn Lewis,[4] John Macleod,[1] Kate Tilling,[1] David Gunnell[1]

EDITORIAL by House

[1]School of Social and Community Medicine, University of Bristol, Oakfield House, Bristol BS8 2BN, UK
[2]Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK
[3]Centre for Suicide Research, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK
[4]Mental Health Sciences Unit, University College London, London, UK
Correspondence to: B Mars
becky.mars@bristol.ac.uk

Cite this as: *BMJ* 2014;349:g5954
doi: 10.1136/bmj.g5954

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g5954

thebmj.com

- People who self harm have a high mortality from natural causes (*BMJ* 2012;345:e6447)
- Effect of assertive outreach after suicide attempt in the AID (assertive intervention for deliberate self harm) trial (*BMJ* 2012;345:e4972)
- Longer term management of self harm: summary of NICE guidance (*BMJ* 2011;343:d7073)

STUDY QUESTION

What are the clinical and social outcomes in early adulthood of self harm in adolescence when studied in a community sample and are there differences in outcomes according to self reported suicidal intent?

SUMMARY ANSWER

In the general population, self harm in adolescents is a risk marker for a range of adverse outcomes in early adulthood. Risks were generally strongest in those who self harmed with suicidal intent; nevertheless self harm without suicidal intent was also associated with poor outcomes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Approximately 1 in 6 adolescents reports having self harmed at some point in his or her life; most self harm is carried out without suicidal intent and less than 20% seek help from clinical services. Previous studies have found associations between suicide attempts in adolescence and poor outcomes in adulthood, but little is known about long term outcomes of self harm without suicidal intent and whether outcomes differ among those who self harm with and without suicidal intent.

Participants and setting

Members of the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK birth cohort of children born in 1991-92. The study is ongoing, examining the influences on health and development across the life course.

Design, size, and duration

Lifetime history of self harm with and without suicidal intent was available for 4799 participants who completed a self harm questionnaire at age 16 years. Logistic regression was used to examine associations between self harm with and self harm without suicidal intent at age 16 years and mental health problems, substance use, educational attainment, occupational outcomes, and future self harm at age 18-21 years.

Main results and the role of chance

Self harm with suicidal intent and without suicidal intent in adolescence were associated with an increased risk of developing mental health problems, future self harm, and problem substance misuse, with stronger associations found for suicidal self harm than for non-suicidal self harm. For example, in models adjusted for confounders the odds ratio for depression at age 18 years was 2.21 (95% confidence interval 1.55 to 3.15) in participants who had self harmed without suicidal intent at age 16 years and 3.94 (2.67 to 5.83) in those who had self harmed with suicidal intent. Suicidal self harm, but not self harm without suicidal intent, was also associated with poorer educational and employment outcomes. After adjustment for socioeconomic position and previous depression symptoms, there was little attenuation in results. Excluding participants with pre-existing problems from the analysis did not greatly alter the effect estimates.

Differences in association of self harm with suicidal intent and self harm without suicidal intent in adolescence with mental health, substance use, educational, and occupational outcomes in early adulthood (results after imputation)

	Odds ratio* (95% CI)	
Suicidal self harm *v* non-suicidal self harm	Adjusted for sex	Adjusted for sex, SEP, and depression symptoms†
CIS-R depressive disorder (age 18)	2.04 (1.35 to 3.06)	1.78 (1.18 to 2.71)
CIS-R anxiety disorder (age 18)	2.32 (1.57 to 3.42)	2.07 (1.39 to 3.10)
Self harm in past year (age 21)	2.74 (1.87 to 40.2)	2.54 (1.72 to 3.77)
Harmful alcohol use (age 18)	1.18 (0.66 to 2.13)	1.03 (0.57 to 1.87)
Problem cannabis use (age 18)	2.32 (1.31 to 4.10)	2.10 (1.17 to 3.75)
Smoking regularly (age 18)	1.42 (1.00 to 2.00)	1.32 (0.93 to 1.87)
Illicit drug use (age 18)	1.21 (0.81 to 1.82)	1.21 (0.80 to 1.83)
Did not achieve ≥5 GCSEs or equivalent A*-C grades (age 15-16)	2.71 (1.87 to 3.94)	1.81 (1.16 to 2.82)
Did not achieve ≥3 A level qualifications (age 19)	1.79 (1.22 to 2.63)	1.41 (0.91 to 2.19)
Not in education, employment, or training (age 19)	1.61 (0.84 to 3.06)	1.39 (0.72 to 2.68)

CIS-R=clinical interview schedule, revised; SEP=socioeconomic position (includes maternal education and parental social class), assessed during pregnancy.
*Values >1.00 indicate risk of a particular outcome is greater in those who self harmed with suicidal intent than in those who self harmed without suicidal intent.
†Educational and occupational outcomes additionally adjusted for IQ at age 8 years.

Bias, confounding, and other reasons for caution

As with all prospective studies loss to follow-up occurred, which may have biased our findings. However, we performed analyses using imputed data, which should correct for biases found in the complete case analyses under the missing at random assumption. Also, although we controlled for several important covariates, we are unable to rule out the possibility of residual confounding. Finally, retrospective recall of suicidal intent accompanying self harm may be unreliable.

Generalisability to other populations

This study was conducted in a general population sample of adolescents. Caution is required in generalising to clinical samples or to adult populations.

Study funding/potential competing interests

This study was funded by the Medical Research Council (grant MR/J012661/1). The UK Medical Research Council, the Wellcome Trust (grant 092731), and the University of Bristol provide core support for the Avon Longitudinal Study of Parents and Children. We are independent of the funders and report no competing interests.