Tumour suppressor genes and risk of metastasis in ovarian cancer

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The silent onset of ovarian cancer often leads to metastatic spread before diagnosis can be made. The cause remains unknown, but molecular studies are beginning to reveal some mechanisms. Inactivation of tumour suppressor genes is thought to be responsible for initiating many forms of cancer. Studies of allele loss indicate areas of genome where inactivation may occur. We recently examined the relation between the clinical stage of epithelial ovarian cancer and allele loss at three loci on chromosome 17: progressive loss was detected with advancing stages of disease.[1]

The clinical stage of a tumour defines the extent of the disease and is the best determinant of prognosis for most forms of cancer. It depends on the time elapsed before diagnosis, hence the value placed on early detection. The histopathological grade, however, better describes the intrinsic nature of the tumour: well differentiated tumours are slow growing whereas undifferentiated, anaplastic tumours metastasise rapidly. Thus poorly differentiated tumours tend to be diagnosed at a more advanced stage. At the molecular level one might anticipate less damage to genetic material with well differentiated tumours.

Methods and results

We collected 52 fresh specimens of ovarian tumours, of which 38 satisfied the pathological criteria of invasive malignant disease. Complete clinical and laboratory data were available for 33 of the cases, but three were homozygous and thus uninformative. The remaining 30 cases were informative at one or more of the three loci examined on chromosome 17 (two polymorphic loci (YNZ22.2 and BHP53) on 17p13 and one at the THH59 locus (17q23-qer)). DNA was extracted from fresh blood samples and was analysed by Southern blot hybridisation. The tumours were classified histologically into well, moderately, and poorly differentiated lesions according to grades I, II, and III respectively.

The greatest allele loss was seen in grade III tumours at all three loci, with the highest loss of over 90% at THH59) (table). Allele loss was least in grade I tumours, with no loss at 17p. Results for grade III tumours were compared with combined results for grade I and II lesions at each locus with Fisher's test of exact probability (two tailed): significantly greater allele loss was associated with grade III lesions at THH59 (11/12 *v* 2/10, p=0·002) and YNZ22 (10/12 *v* 1/10, p=0·002), but the difference between the small number of observations for p53 was not significant (3/5 *v* 1/4, p=0·714). When the results for the three loci were combined the difference between grade III lesions and grade I and II lesions was highly significant (24/29 *v* 4/24; $\chi^2=20{\cdot}44$, df=1; $p<0{\cdot}001$) (95% confidence interval for the difference 45% to 87%).

Allele loss at three loci on chromosome 17 by histopathological grade of tumour among 30 cases of ovarian cancer. Values are proportions of those cases that were informative at each of the loci

Loci on chromosome 17	Grade of tumour		
	III	II	I
THH59	11/12	1/3	1/7
YNZ22	10/12	1/6	0/4
p53	3/5	1/2	0/2
Total	24/29	3/11	1/13

Comment

The histological grade of a tumour is difficult to define and measure accurately, and it may deteriorate with advancing malignancy as cells undergo multiple abnormal divisions. Despite such criticisms, however, most clinical and pathological studies agree that grading is related to survival.[2] In our previous analysis of tumour stages, allele loss on 17p was seen as a late step in the progression of ovarian malignancy. This seems to be ubiquitous in many tumours and is probably related to inactivation of the p53 tumour suppressor gene. Allele loss at THH59 is an earlier step and appears to be specific to ovarian cancer.

Prognostic factors can be analysed more precisely when staging and grading are considered together. Evidence suggests that loss of a putative tumour suppressor gene at THH59 is significantly higher in undifferentiated cancers. These rapidly growing tumours have a greater potential for metastatic spread even in early stage disease. The highly significant difference in the cumulative observations strongly suggest that anaplastic tumours have lost the entire chromosome. The degree of malignancy of the tumour thus depends on the extent of underlying molecular damage.

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1 Eccles DM, Russell SEH, Haites NE, Atkinson R, Bell DW, Gruber L, *et al.* Early loss of heterozygosity on 17q in ovarian cancer. *Oncogene* 1992;7: 2069-72.
2 Anderson MC. In: Sharp F, Soutter WP, eds. *Ovarian cancers—the way ahead.* Section 2. Chichester: Wiley, 1987:63-4.

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MRCGP pass rate by medical school and region of postgraduate training

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Initiatives to measure and enhance the quality of higher education for both undergraduates and postgraduates (academic audit, teaching quality assessment) will shortly start to impact on medical schools in the United Kingdom.

We believe that it would be helpful to consumers of medical education (prospective students), to its providers (medical schools and their curriculum designers, postgraduate training schemes), and to its customers (medical care providers) if comparative output data on medical schools and postgraduate training were available. Without a national medical qualifying examination this is probably possible only by examining the performance of candidates for the major postgraduate examinations of the royal colleges.

Methods and results

To start such a process we analysed the pass-fail result of seven recent diets (December 1988-December 1991) of the membership examination of the Royal College of General Practitioners (MRCGP) by clinical

MRCGP pass rates by United Kingdom medical school of training and region of postgraduate training

Medical School	No taking exam	% Pass	Region	No taking exam	% Pass
Oxford	70	94·3	Devon and Cornwall	109	94·5
Bristol	125	92·8	Overseas	18	94·4
Nottingham	124	91·1	Northern Ireland	141	92·2
Southampton	98	90·8	East Anglia	108	90·7
Cambridge	74	90·5	North West Thames	118	89·8
Royal Free	63	90·5	Trent	206	88·8
Newcastle	138	89·9	Oxford	152	88·8
King's	48	89·6	Northern	225	88·4
St Mary's	77	89·6	Avon and Somerset	138	88·4
Birmingham	120	89·2	North East Scotland	51	88·2
Leicester	72	88·9	Wessex	181	87·3
University College-Middlesex	115	87·8	Yorkshire	139	87·1
Guy's-St Thomas's	151	87·4	South East Thames	112	85·7
Manchester	225	84·9	Wales	129	84·5
Leeds	92	84·8	South East Scotland	126	84·1
Queen's, Belfast	241	84·6	Northern Scotland	42	83·3
Edinburgh	155	83·9	South West Thames	127	82·7
Charing Cross-Westminster	153	83·7	West Midlands	178	82·0
The London	101	82·2	North East Thames	115	81·7
St George's	39	82·1	Armed Forces	20	80·0
St Bartholomew's	104	81·7	North West	238	79·4
Sheffield	119	80·7	Mersey	84	72·6
Aberdeen	102	79·4	West of Scotland	271	70·5
Dundee	86	79·1	Scotland (Tayside)	50	68·0
Wales	95	76·8			
Liverpool	86	72·1	Not known	13	84·6
Glasgow	218	69·3			

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medical school and region of vocational training. To avoid bias, only first time United Kingdom and Irish born takers, currently finishing their training, were included (n=3091).

The summary data are given in the table. Differences were highly significant between medical schools ($\chi^2=92{\cdot}46$; df=26; $p<0{\cdot}001$) and training regions ($\chi^2=100{\cdot}34$; df=23; $p<0{\cdot}001$). Although medical school and training region were related (42% of trainees carried out postgraduate training in the same region as their undergraduate training), there are no differences overall between those who stayed in their region for postgraduate training and those who left. Log-linear modelling using the program GLIM (generalised linear interactive modelling) showed that differences between training regions were significant after differences between undergraduate schools were taken into account ($\chi^2=56{\cdot}6$; df=23; $p<0{\cdot}001$), and differences between undergraduate schools were significant after differences between training regions were taken into account ($\chi^2=49{\cdot}7$; df=26; $p<0{\cdot}01$). The rank ordering of schools and regions was little altered by taking into consideration the effect of the other, and the top and bottom six schools and regions remained the same as in the tables.

Comment

The differences shown in the table may well be the result of true differences in the training ability of medical schools and regions. Alternative explanations are, however, not inconceivable. It might, for example, be the case that good students from high scoring schools consistently tend to opt for general practice.

The proportions of trainees from the different regions who attempt the examination vary (but the available data on which to calculate these are unsatisfactory).[1] The figures also take no account of the academic qualifications of students entering the various medical schools and the relevant "value added," though there are medical schools traditionally admitting well qualified applicants well down the list. (Controlling for this variable is exacerbated by the different school leaving qualifications in the United Kingdom.) Moreover, the relevant training programme may have changed by now.[2] The medical school courses taken by the subjects of this study were those in the early to middle 1980s. Initiatives are currently being taken with a view to improving postgraduate training and assessment.[3]

Taken together with data from the other major postgraduate examinations—for example, the membership of the Royal College of Physicians and the fellowship of the Royal College of Surgeons—these findings will, among other things, be relevant considerations for the location of the expansion of undergraduate medical education recently recommended in the report of the Medical Manpower Standing Advisory Committee.

We thank the examination board of the Royal College of General Practitioners for their encouragement to analyse and publish these data.

1 *Members Reference Book 1992.* London: Royal College of General Practitioners, 1992:48.
2 Rees L, Wass J. Undergraduate medical education. *BMJ* 1993;306:258-61.
3 Campbell LM, Howie JGR, Murray TS. Summative assessment: the West of Scotland Pilot Project. *Br J Gen Practice* (in press).

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Correction

Is screening and intervention for microalbuminuria worthwhile in patients with insulin dependent diabetes?

An authors' error and an editorial error occurred in this paper by K Borch-Johnsen and others (26 June, pp 1722-3). On p 1723 the last sentence of the first paragraph should have read: "The impact of treatment was calculated by using three different levels of effect, decreasing the proposed progression rate of 20% in microalbuminuria by 33%, 67%, and 100% (see table II) [not table I]." Also on p 1723 the symbols in the legend to figure 2 were incorrectly designated. The legend should have read: "Median life expectancy at onset of diabetes in patients developing microalbuminuria without intervention (□) and at treatment effect 33% (■) and 67% (○). Life expectancy of general population of Germany shown for comparison (●)."

National Health Service breast screening programme results for 1991-2

A typesetting error occurred in this article by J Chamberlain *et al* (7 August, pp 353-6). In table I the United Kingdom (all ages) percentage response rate should read 71·26, not 51·26.