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Serum placental-type alkaline phosphatase activity in women with squamous and glandular malignancies of the reproductive tract

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Abstract

Aim—To investigate serum placental-type alkaline phosphatase (PLAP-type) activities in women with squamous and glandular malignancies of the reproductive tract using an immunoradiometric assay.

Methods—PLAP-type immunoreactivity was measured in 180 women with non-ovarian malignancies of the reproductive tract and the values were compared with those from 334 controls. The cases comprised 18 vulval, nine vaginal, 103 cervical, 46 endometrial, and five fallopian tube cancers.

Results—Serum PLAP-type activities were no different from controls in patients with squamous cell tumours. Women with adenocarcinoma of the cervix, endometrium, and fallopian tube had increased values: women with endometrial cancer had a median value nearly four times greater than that of controls. There was no direct correlation between PLAP-type activities and stage of disease in patients with endometrial cancer, but values reverted to normal after treatment.

Conclusions—Serum PLAP-type measurements are of no value in the management of patients with squamous cell tumours of the female reproductive tract. Raised activities can, however, be found in glandular tumours, in particular endometrial cancer where serum PLAP-type measurements may be of value in predicting remission.

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Serum measurement of placental alkaline phosphatase (PLAP) can be used as a tumour marker for testicular and ovarian cancer.¹⁻⁷ In vitro studies have shown that PLAP is also produced by non-ovarian malignancies of the female reproductive tract.^{8,9} Several groups have measured PLAP and PLAP-like material in the serum of patients with non-ovarian gynaecological cancers, but the results have been conflicting.¹⁰⁻¹⁶ A possible reason for the divergent results was that most groups measured the intrinsic alkaline phosphatase activity of the protein, and this may be defective in ectopically produced PLAP.^{17,18} In addition, factors such as smoking, ABO blood group,

and menopausal status may substantially affect circulating concentrations.¹⁸⁻²³

We re-evaluated serum PLAP-type concentrations in women with non-ovarian malignancies of the reproductive tract using an assay that measures immunoreactivity rather than enzymatic activity. Our results have been corrected for smoking habits, menopausal status, and ABO blood group.

Methods

One hundred and eighty patients with non-ovarian malignancies of the female reproductive tract had blood taken before treatment. These included patients with vulval, vaginal, cervical, endometrial, and fallopian tube cancers (17, nine, 103, 46, and five, respectively). In 14 cases of adenocarcinoma of the cervix and endometrium squamous change was found, and these patients were considered separately in the results.

A further 14 samples were collected from the same patients with endometrial cancer following treatment and a period of remission. Three hundred and thirty four women with non-pregnancy related, non-neoplastic, or benign neoplastic gynaecological disease served as controls. The serum PLAP-type activities in some of the control group have been reported before.⁸

Samples were received as coded specimens and stored at -20°C. PLAP-type immunoreactivity was measured by immunoradiometric assay (IRMA).²⁴ This uses the monoclonal antibody H7 (InRo, Sweden) for capture and H17E2 (Unilever UK) for detection. The IRMA has a sensitivity of 0.1 IU/l and has no cross-reactivity with intestinal or tissue non-specific alkaline phosphatase.

PLAP values were measured in international units and expressed as multiples of the regressed control group median (MoM) after correction for smoking, ABO blood group and menopausal status. The equation used was:

$$PLAP = 10^{(-0.065 - (0.14 \times M) + (0.35 \times S) + (0.018 \times A) + (0.22 \times B))}$$

where M = menopausal status (1 = premenopausal, 2 = post-menopausal); S = smoking habits (0 = non-smoker, 1 = smoker); A = number of cigarettes smoked per day; and B = ABO blood group (1 = blood groups A and AB, 2 = O and B). A MoM of 7.4 (100th centile for controls) was used as a cut off. PLAP values were compared

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Table 1 Serum PLAP-type activities in women with non-ovarian malignant disease of the reproductive tract, and statistical comparison with the control group of 334 women

	Per cent positive	Median (MoM)	Range (MoM)	Mann-Whitney U statistic	p value	95% CI in cases (controls)
<i>Uterus</i>						
Adenocarcinoma	37 (13/35)	3.6	0.2-310	9203	<0.0001	0.7-4.9
Adenocarcinoma with squamous change	18 (2/11)	5.2	1.2-46.6	3383	<0.0001	1.8-5.0
All uterus	33 (15/46)	4.8	0.2-310	12972	<0.0001	1.29-4.56
<i>Cervix</i>						
Squamous	3 (2/67)	1.2	0.2-13.2	14690	0.16	-0.1-0.4
Adenocarcinoma	3 (1/33)	1.6	0.2-7.8	7534	0.01	0.6-1.6
with squamous change	0 (0/3)	1.0	0.6-1.6	509	0.99	-0.4-0.6
All cervix	3 (3/103)	1.2	0.2-13.2	25595	0.01	0.0-0.4
<i>Vagina</i>						
Squamous	0 (0/8)	0.7	0.3-1.8	945	0.12	-0.9-0.1
Adenocarcinoma	0 (0/1)	1.4	—	—	—	—
All vagina	0 (0/9)	0.8	0.3-1.8	1180	0.21	-0.8-0.2
<i>Vulva</i>						
Squamous	12 (2/17)	1.1	0.4-13.5	3630	0.12	-0.1-0.7
<i>Fallopian tube</i>						
Adenocarcinoma	40 (2/5)	6.6	2.5-50.1	1554	0.0012	1.5-947

Table 2 Serum PLAP-type concentrations in adenocarcinoma of the cervix and endometrium by stage

Stage	Median MoM for endometrial carcinoma (n, range)	Median MoM for adenocarcinoma of the cervix (n, range)
Unstaged	1.6 (7, 0.7-195)	—
Stage 1	1.7 (18, 0.2-310)	1.1 (16, 0.2-6.1)
Stage 2	6.9 (6, 1.1-94.1)	1.2 (2, 0.8-1.6)
Stage 3	1.3 (3, 0.8-2.2)	1.9 (2, 0.7-3.1)
Stage 4	4.6 (6, 0.4-37.8)	1.1 (1, —)
New recurrence	15.4 (6, 0.3-189)	3.0 (12, 0.2-7.8)

between cases and controls by analysis of MoMs using the Mann-Whitney *U* test.

Results

Serum PLAP-type activities were raised in patients with adenocarcinoma of the cervix, endometrium, and fallopian tube compared with controls (table 1). Values were no different from those of controls in patients with squamous cell carcinoma of the lower genital tract (table 1). The proportion of patients with increased PLAP-type values was highest in women with endometrial and fallopian tube cancers (33 and 40%, respectively) (table 1). Only one of the 33 (3%) patients with adenocarcinoma of the cervix had circulating concentrations greater than the 100th centile for controls, but the median concentrations were significantly higher than those in the controls overall.

There was no difference in circulating PLAP-type values between the control group and women who were in remission after treatment for carcinoma of the endometrium (median MoM = 1.5, *u* = 2867, *p* = 0.25, 95% confidence interval for cases and controls = -0.2 to 0.8, respectively). In all of these cases serum concentrations had fallen and were below the 100th centile for controls.

No correlation with stage was shown in patients with adenocarcinoma of the cervix or endometrium (table 2).

Discussion

These results clearly show that serum PLAP-type measurements are of no value in the management of patients with squamous cell

tumours of the female reproductive tract. Raised values can, however, be found in some glandular tumours, in particular endometrial carcinoma.

Ectopic production of a PLAP-type material was first described by Fishman *et al* in 1968.²⁵ They found raised values in a man with carcinoma of the lung. Since then, PLAP production has been found in a number of tumours, of which ovarian and testicular cancers have been the most extensively investigated.^{1-6 11-16 22 26-32} However, most assays for PLAP-type material measure the enzymatic activity rather than protein mass. This activity may be defective in PLAP expressed in neoplasms.

In carcinoma of the cervix previous studies have yielded varying results. In our study values were raised in glandular but not squamous cell tumours. In the former, activities were greater than the 100th centile for the control group in only 3% of cases. DeBroe *et al* (1988)¹¹ found raised PLAP-type activity in 7% (five of 70) of patients. This is in contrast to Doellgast and colleagues (1984),²⁶ who found raised activities in 41% (28 of 69). Other groups have reported that between 15 and 25% of patients have increased concentrations.^{1 12 13 27} A possible reason for these varied results is the use of different cut off levels. In addition, none of these groups' results were corrected for smoking which is known to cause a 10-fold rise in serum PLAP-type activities.¹⁸⁻²³ There is also a strong association between smoking and the development of cervical cancer independent of PLAP-type activity. One study by Muensch *et al* (1986)²² excluded smokers and found raised PLAP-type activities in 20% of patients (one of five). However, the small number of patients and the absence of histological data make it difficult to draw conclusions from their results.

Only one group (DeBroe *et al*, 1988)¹¹ have measured serum PLAP-type activity in patients with carcinoma of the vulva and vagina. In that study concentrations were not increased in any of their eight cases. This is similar to the present data for PLAP-type immunoreactivity. No group has reported on PLAP activities in carcinoma of the fallopian tube.

In endometrial carcinoma we have shown increased activities in a third (14 of 46) of patients. This is a higher proportion than that found in studies using enzymatic activity. In addition, most of these groups have used a lower cut off level. Cadeaux *et al* (1974)²⁷ found raised values in 11% (five of 44) and DeBroe *et al* (1988)¹¹ in 19% (10 of 54) of patients. Two other groups reported increased concentrations in 15% (eight of 53) and 9% (seven of 77) of patients.¹² This is consistent with *in vitro* studies which showed immunoreactive but not enzymatically active PLAP production in endometrial tissue cultures.⁹

Other markers, such as CA 125 are raised in endometrial cancer. Kenemans *et al* (1988)³³ performed a meta-analysis of results from 16 groups and found high CA 125 concentrations (>35 U/ml) in 27% (66 of 245) of cases of endometrial cancer. However, at this cut off level CA 125 is increased in 20% of patients with benign or non-neoplastic ovarian masses.³³ In our study we used a cut off at the 100th centile of our control group which included patients with benign pelvic masses. Using these stricter criteria, we suggest that PLAP-type immunoreactivity is a better marker for endometrial cancer than CA 125.

If PLAP-type material is to be a useful marker in the management of endometrial cancer, a correlation with tumour bulk and spread would be desirable. In this respect our results in relation to the stage of disease are clearly disappointing. However, all 14 blood samples from patients in remission after treatment, with raised PLAP-type activities before treatment, were normal, suggesting that this test may be of value in determining remission.

In conclusion, measurement of serum PLAP-type immunoreactivity is of little value in patients with squamous cell tumours of the female reproductive tract but may be of value in some patients with glandular malignancies.

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