Association between plasma concentrations of plasminogen activator inhibitor-1 and survival in patients with colorectal cancer

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Invasion by cancer cells requires proteases such as the serine protease plasmin to degrade the cellular matrix. Plasmin is formed from its zymogen, plasminogen, a reaction catalysed by urokinase type plasminogen activator—which is implicated in invasion[1]—and partly regulated by plasminogen activator inhibitors. The active form of the inhibitor complexes with free and receptor bound active urokinase plasminogen activator and is bound by vitronectin in plasma and extracellular matrix.[2]

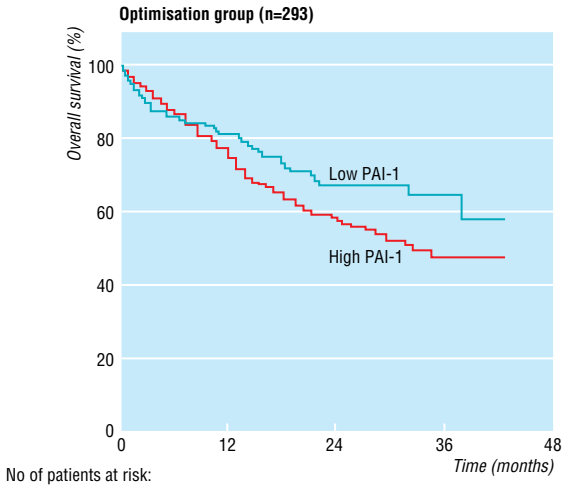
A high concentration of plasminogen activator inhibitor-1 in biopsy specimens from tumours is associated with a poor prognosis,[3] and some patients with ovarian cancer have raised plasma concentrations of plasminogen activator inhibitor-1.[4] We studied the prognostic importance of plasma concentrations of plasminogen activator inhibitor-1 in patients with colorectal cancer.

Subjects, methods, and results

Plasma was collected preoperatively as previously described[5] from 609 patients having elective surgery for colorectal cancer. Plasma concentrations of plasminogen activator inhibitor-1 were measured by a sandwich enzyme linked immunosorbent assay (ELISA) using two monoclonal antibodies.[3] The concentration was expressed as interim units of plasminogen activator inhibitor-1/mg protein.[3]

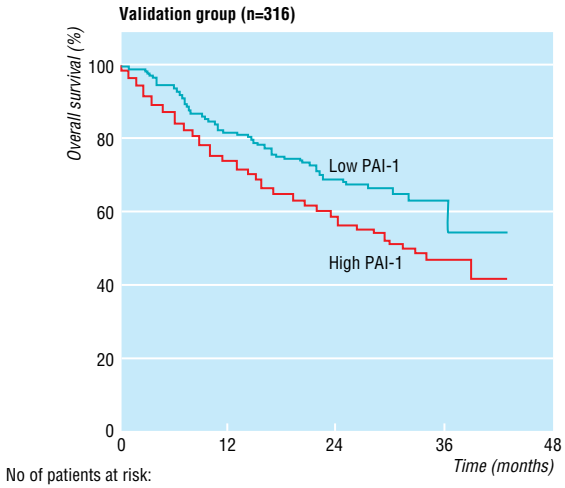
All patients had histologically verified colorectal cancer and complete clinical data. The median follow up time was 25 months (range 13-40). Patients were randomised into two groups. Data on 293 patients (optimisation group) were used to determine the optimal cut off value for plasminogen activator inhibitor-1 in relation to survival using Cox's proportional hazard model, and data on 316 patients (validation group) were used to validate the results obtained from the optimisation group.

High plasma concentrations of plasminogen activator inhibitor-1 were associated with increasing severity of disease (Dukes's stage; χ^2 test, $P = 0.001$). The best cut off value for plasminogen activator inhibitor-1 was 0.5 interim units/mg of protein. With this value the hazard ratio was 1.5 for patients with high concentrations of plasminogen activator inhibitor-1 (178/293 (61%)) compared with those with low concentrations (115/293 (39%)). Applying this value to the validation group gave similar results (hazard ratio 1.5 (95% confidence interval 1.1 to 2.2); $P = 0.02$; 179/316 (57%) *v* 137/316 (43%)) (figure). Cox analysis of the 316 patients in the validation group showed that Dukes's stage was the strongest prognostic variable (hazard ratio 2.9 (2.3 to 3.7)), followed by age (hazard ratio 1.5 (1 to 2.1)).



No of patients at risk:

Low PAI-1	115	93	55	15
High PAI-1	178	133	83	16



No of patients at risk:

Low PAI-1	137	112	70	8
High PAI-1	179	132	81	18

Survival in patients with colorectal cancer according to preoperative plasma concentrations of plasminogen activator inhibitor-1 (PAI-1). See text for definition of groups

Comment

This study shows that high preoperative plasma concentrations of plasminogen activator inhibitor-1 are associated with shorter survival in patients with colorectal cancer. The validity of this result is strongly supported by the fact that the best cut off value for plasminogen activator inhibitor-1 obtained from one patient population gave similar prognostic information about a second independent population. It is further supported by the close correlation between high plasma concentrations of plasminogen activator

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inhibitor-1 and increasing severity of disease according to Dukes's stage, which is an established predictor of poor prognosis in patients with colorectal cancer.

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Contributors: HJN and NB had the original idea for and planned the study. HJN was also responsible for collecting the samples and patient data. FM established the database and participated in planning the clinical trial. JG-H developed the enzyme linked immunosorbent assay and analysed all the samples. IJC and HP were responsible for the statistical analyses of the data. The paper was written jointly by NB, KD, JG-H, OT-U, and HJN. HJN and NB are guarantors of the study.

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1 Danø K, Andreasen PA, Grøndahl-Hansen J, Kristensen P, Nielsen LS, Skriver L.Plasminogen activators, tissue degradation and cancer. *Adv Cancer Res* 1985;44:139-266.
2 Andreasen PA, Georg B, Lund LR, Riccio A, Stacey SN. Plasminogen activator inhibitors: hormonally regulated serpins. *Mol Cell Endocrinol* 1990;68:1-19.
3 Grøndahl-Hansen J, Christensen IJ, Rosenquist C, Brünner N, Mouridsen HT, Danø K, et al. High level of urokinase-type plasminogen activator and its inhibitor PAI-1 in cytosolic extracts of breast carcinomas are associated with poor prognosis. *Cancer Res* 1993;53:2513-21.
4 Casslen B, Bossmar T, Lecander I, Åstedt B. Plasminogen activators and plasminogen activator inhibitors in blood and tumour fluids of patients with ovarian cancer. *Eur J Cancer* 1994;30A:1302-9.
5 Meijer P, Pollet DE, Wauters J, Kluft C. Specificity of antigen assays of plasminogen activator inhibitor in plasma: Innotest plasminogen activator inhibitor-1 immunoassay evaluated. *Clin Chem* 1994;40:110-5.

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How much does relapse after one year erode effectiveness of smoking cessation treatments? Long term follow up of randomised trial of nicotine nasal spray

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Recent research on treatments to stop smoking has focused almost entirely on nicotine replacement, and several meta-analyses testify to the efficacy of four delivery systems.[1] Although the ultimate goal of treatment is lifelong cessation, few trials have published results of abstinence beyond one year. Little consideration has therefore been given to whether the treatment is effective in reducing the major health risks of smoking. This effect would become evident only after many years of abstinence. Our randomised trial showed that the use of nicotine nasal spray compared with a placebo spray was associated with more than double the number of abstainers at one year.[2] We report the results from a longer term follow up to estimate the impact of relapse after one year on effectiveness.

Subjects, methods, and results

A total of 227 heavy smokers entered the trial; 116 were given the nicotine spray and 111 the placebo. Of these, 47 sustained abstinence from smoking for 1 year. They constituted the long term follow up group; 33 were in the nicotine group, 14 in the placebo group. Criteria for long term sustained abstinence were the same as for the first year. Since the follow up was completed mainly over a 2 month period, the time interval from randomisation varied according to when the smoker entered the trial over 15 months. Standard survival methods were used to analyse the data. Survival times of those who were not contacted beyond 1 year (3 subjects in the nicotine group, 2 in the placebo group) and those who had successfully given up were censored at their last follow up. The Kaplan-Meier method was used to estimate cumulative abstinence up to $3\frac{1}{2}$ years.

Mean follow up period was 3 years 4 months (range $2\frac{1}{2}$ to $4\frac{2}{3}$ years) and was shorter by 21 days for the nicotine group. All observed relapses occurred within $3\frac{1}{2}$ years. The table shows that the nicotine spray maintained an advantage over placebo up to $3\frac{1}{2}$ years. Relapse after 1 year's abstinence was similar in the two groups and totalled 23% at 2 years, 38% at 3 years and 48% (95% confidence interval 32% to 64%) at $3\frac{1}{2}$ years. Although subjects had been recommended to use the spray for three months only, they were allowed to continue for 1 year. Of those remaining abstinent in the nicotine group, 19 used the spray for 1 year and 14 for <1 year (range 1-39 weeks). There was no difference in relapse after 1 year in the nicotine group between those who used the spray for 1 year and those who stopped earlier (difference 5%, 95% confidence interval −33% to 43%).

Results of long term follow up of randomised trial of nicotine nasal spray

	Nicotine spray (n=116)	Placebo spray (n=111)	Difference in % (95% CI)
% (No) who sustained abstinence to 1 year	28.4 (33)	12.6 (14)	15.8 (5.6 to 26.1)
Sustained abstinence to 3.5 years (%)*	15.4	6.1	9.3 (0.88 to 17.4)
Cumulative relapse between 1 and 3.5 years (%)*	45.9	52.1	–6.2 (–41.0 to 28.8)

*Kaplan-Meier estimates.

Comment

Our results show that the spray is an effective aid to long term smoking cessation and that those who used the spray for 1 year had a similar relapse profile to those who stopped using it earlier. They also indicate substantial relapse after the time that most studies have completed their final follow up to assess treatment efficacy. Although the success ratio of active to placebo treatment (about 2.5) was unchanged by relapse, the absolute difference was reduced considerably, and hence the estimated number needed to treat to achieve each success was increased (from 6.3 to 10.8).