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Gastrointestinal Cancer and the Long-term Use of Pravastatin in the Elderly

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To the Editor:

We have no doubts about the benefit of pravastatin on cardiovascular morbidity and mortality among subjects aged 70 to 82 years as reported in the PROSPER study (1). However, we are uneasy about the safety of pravastatin as reflected by the significantly higher incidence of cancer (8.5%) in patients treated with pravastatin compared with those on placebo (6.8%) ($p = 0.02$).

Although any p-value cannot totally exclude a random error effect, we do not agree with the authors, who argue that this is most likely a chance finding. The results of the LIPID trial on pravastatin already showed that older persons had a significantly higher overall incidence of cancer compared with younger persons ($p < 0.001$) (2). This difference was also thought to be a chance finding. We are not convinced by the authors' arguments referring to their meta-analysis and some large-scale trials, because the subjects in most of these trials are much younger and therefore less susceptible to cancer (3–5) and because the follow-up period tends to be relatively short.

The authors claim that the high incidence of cancers in the pravastatin group was not confined to any particular site. However, compared to the placebo group, the incidence of gastrointestinal cancer was higher in the pravastatin group (relative risk = 1.46; 95% CI = 1.00–2.13). We compared the incidence of gastrointestinal cancers over the 4-year study period and found that during the first year there was a similar incidence in the placebo group (558 per 100 000 persons) compared to the treatment group (528 per 100 000 persons) ($p = 0.88$). During the complete study period the incidence of gastrointestinal cancers remained around that level in the placebo group (see Fig. 1). From the second year on, the incidence in the treatment group increased, resulting in a relative risk of 2.74 for the fourth year (Table 1). A similar picture was found for all cancers starting from the third year. In a linear regression analysis, the year explained 90% of the variance of the yearly relative risks for both gastrointestinal and all cancers ($p = 0.05$).

If pravastatin has a carcinogenic effect, it is to be expected that no differences in cancer incidence could be observed during the first year of the study but only after a longer period. By including the cancer figures for the first year the magnitude and the significance of any later differences could be masked, and for this reason we recalculated the significance between the placebo and the treatment groups over the last 3 years. We found 29 gastrointestinal cancers in the placebo group and 50 in the pravastatin group. The differences are significant when calculated for either the placebo group (n = 2 913) compared with the treatment group (n = 2 891) ($p = 0.016$) or when calculated per person-year in the placebo group (6 155 person-years) compared with the treatment group (6 102 person-years) ($p = 0.016$).

We are aware of the fact that our levels of significance are fairly low. However, we believe that higher significance levels could be obtained over a longer study period and with more subjects. Before a definite conclusion about the safety of pravastatin in the elderly can be drawn, more long-term observations are needed.

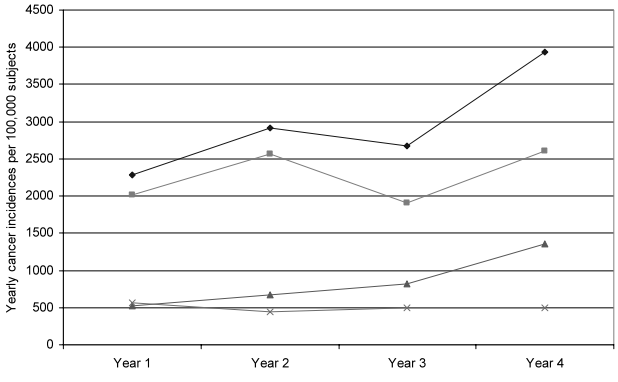

Fig. 1. Yearly incidences per 100 000 inhabitants for all cancers and for gastrointestinal cancers in the placebo group and in the pravastatin group over the 4 study years. —◆— All cancers in the pravastatin group. —■— All cancers in the placebo group. —▲— Gastrointestinal cancer in the pravastatin group. — × — Gastrointestinal cancer in the placebo group.

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Table 1

Cancer incidence (number of cases/person-years and relative risk with 95% confidence interval) in the PROSPER study

Years	All cancers			Gastrointestinal cancers		
	Pravastatin	Placebo	RR* (95% CI)	Pravastatin	Placebo	RR* (95% CI)
1	65/2 839	58/2 869	1.13 (0.80–1.56)	15/2 839	16/2 869	0.95 (0.47–1.91)
2	79/2 704	70/2 729	1.14 (0.83–1.56)	18/2 704	12/2 729	1.51 (0.73–3.14)
3	69/2 584	50/2 622	1.40 (0.98–2.01)	21/2 584	13/2 622	1.64 (0.82–3.27)
4	32/814	21/804	1.51 (0.88–2.59)	11/814	4/804	2.72 (0.87–8.49)
All 4	245/8 941	199/9 024	1.24 (1.03–1.49)	65/8 941	45/9 024	1.46 (1.00–2.13)
Last 3	180/6 102	141/6 155	1.29 (1.04–1.60)	50/6 102	29/6 155	1.74 (1.10–2.74)
Last 2	101/3 398	71/3 426	1.43 (1.06–1.94)	32/3 398	17/3 426	1.90 (1.06–3.41)

*RR = relative risk.

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