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Editorial Comment

Calcium channel blockers, verapamil and cancer risk

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The Rotterdam Study reported in this issue of the *European Journal of Cancer* is a prospective population-based cohort investigation of over 3200 elderly patients aged over 70 years followed-up between 1991 and 1999, and provides additional useful information on the use of calcium channel blockers (CCB) and the risk of cancer in the elderly [1]. 302 incident cancers were observed during the 8-year follow-up. Of these, 29 were observed among CCB users, corresponding to a crude relative risk (RR) of 1.3, and a multivariate one of 1.2 [95% confidence interval, (CI) 0.8–1.8]. None of the individual cancer risks was significantly related to CCB use, but skin cancer showed a significant excess in the crude RR and in one of the multivariate models used. Since the incidence of skin cancer is largely influenced by diagnostic attention and accuracy [2], which may be greater in subjects under a long-term pharmacological treatment than in the general population, such an excess in skin cancer incidence is probably, at least in part, spurious, and may account for some of the observed excess risk in the all cancer incidence calculations. The RR was 1.5 for urinary tract cancers, non-significant. These include kidney cancer which has been associated with hypertension [3–5], and hence to the underlying condition leading to treatment with CCB.

The results of the Rotterdam Study are in broad agreement with those of major studies providing data on CCB and cancer risk, indicating some excess risk of kidney cancer, but no or a modest excess of other cancer sites [3,8–11]. RRs of the order of 1.1–1.2 are in any case extremely difficult to interpret in terms of causal inference from observational epidemiological data [6,7], and could be due to detection or information bias.

After the first report from a cohort of 5052 subjects aged 70 years or older from Massachusetts [8], including 420 cases of cancer (47 among CCB users), and showing a multivariate RR of 1.7 for all CCB (1.2 for diltiazem, based on 13 events, 1.7 for nifedipine, based on 16 events, and 2.5 for verapamil, based on 18 events), the most relevant evidence on CCB and cancer risk comes from another cohort [9], and two case-control [10,11] studies.

The cohort investigation was a 6-year follow-up of the Nurses' Health Study [9] and included 852 incident cases and 335 deaths from cancer. The RRs of all cancers among CCB users were 1.02 for incidence and 1.25 for mortality, and there was no significant association with any of the individual cancers or groups of cancers considered, i.e. breast, lung, colon or lymphoid neoplasms.

The case-control study from the United Kingdom General Practice Research Database (GPRD) (10) included 446 cases of cancer and 1750 hypertensive controls. Relative to users of β-blockers, the RR estimates for all cancers combined were 1.27 and 0.70 for users of CCB and acetylcholinesterase (ACE) inhibitors, respectively. None of the estimates were significant, and there was no relationship between the duration of CCB use and cancer risk (RR = 1.23 for 4 years). Furthermore, none of the individual cancer sites showed a significant excess risk.

The largest study on CCB and cancer risk was a case-control investigation conducted in Baltimore, New York and Philadelphia [11], including a total of 9513 patients with cancer and 6492 controls. The RR estimates for all cancers combined were 1.1 for users of CCB since 1 year (481 cases), 1.1 for users of β-blockers (1059 cases), and 1.1 for users of ACE inhibitors (348 cases). Among CCB users, the RR was 1.2 for a duration of 5 years. With reference to the type of CCB, the RR was 1.0 for any use of diltiazem, 1.0 for nifedipine, and 1.2 for

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verapamil. The RR for 5 years of use of verapamil was 1.1, and none of the estimates for duration of use were significant for any of the CCB. Thus, the recent use of CCB, use for 5 or more years, and use of individual CCB were not associated with cancer incidence in that uniquely large dataset. Among individual cancer sites, only kidney cancer showed a significant excess risk among users of CCB (RR = 1.8), of β-blockers (RR = 1.8) and of ACE inhibitors (RR = 1.9). Such an apparent association, however, was attributed to the well known relationship between hypertension and kidney cancer risk [3–5].

Furthermore, in the International renal cell-cancer study [3] the apparent excess risk observed with the use of CCB was similar to that of other anti-hypertensive medications, as well as of hypertension per se.

It appears, therefore, that CCB are not appreciably and consistently related to the risk of cancer. A specific association with verapamil, as suggested by the Rotterdam study [1], remains open to discussion, since some excess risk was observed in this cohort (based on nine cases) as well as in the Massachusetts one (based on 18 cases) [8]. However, the largest available dataset, i.e. the multicentric United States case-control study based on 172 cases among users of verapamil [11] found no consistent excess risk. It is difficult, moreover, to postulate any specific role for verapamil as opposed to other CCB on the process of carcinogenesis on the basis of different biological mechanisms, which remain largely undefined for all CCB.

Thus, the current status of our knowledge of CCB and cancer risk underlines the substantial difficulties in drawing any firm conclusions based on modest associations from observational epidemiological studies [6,7].

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