Antihypertension and Colorectal Cancer Prevention: Getting Two Birds With One Stone?

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As a classical antihypertensive drug, angiotensin I-converting enzyme inhibitor (ACEI) has been suggested to protect against cancer ever since Lever et al.’s landmark report in 1998 of a 28% reduced cancer incidence among ACEI users compared with general control subjects (1). Despite the ongoing enthusiasm, most prospective studies failed to find any secondary benefit of ACEI use on colorectal cancer (CRC) or overall cancer risk (2–4). Similarly, null associations have been observed for another antihypertensive drug, angiotension receptor blocker (ARB), with CRC risk in all but one prospective study (5). In a recent meta-analysis of 70 randomized controlled trials, no evidence of benefit was observed on any cancer (including CRC) incidence or mortality after ACEI or ARB therapy, although an increased overall cancer risk was suggested for the combinations of ACEI plus ARB in a fixed-effects model (6). Several limitations of this secondary analysis of trials have been noted, including short duration of included trials, cancer as a nonpredefined outcome, domination of results by one trial, and incomplete inclusion of studies (7,8).

In the current issue of the Journal, Makar et al. (9) report findings from a nested case–control study within a large primary care database in the United Kingdom that examined the association between ACEI/ARB therapy and risk of CRC. The study found a 16% reduction in CRC incidence after 3 or more years of ACEI/ARB therapy among patients with a diagnosis of hypertension or hypertension-related complication. The magnitude of this reduction increased with longer exposure and higher dose of therapy.

The large computerized database used by this study offers several important advantages, including a large sample size, a representative study population, and systematic and accurate collection of medication information. However, some limitations of the study need to be considered. First, it is not clear how occasional and regular drug users were distinguished for exposure definition, especially when combined use of multiple antihypertensive drugs is common. For example, a person using ACEI as an auxiliary therapy sporadically during the past 3 years has a substantially different exposure history from the person using the drug every day in the same period. Second, as in other observational studies, confounding is a concern of this study, especially when only a moderate association is observed. A previous study using the same database reported that users of ACEIs and ARBs were more likely to be obese, to have ever smoked, to have diabetes, and to use aspirin, statins, and nonsteroidal anti-inflammatory drugs than users of other antihypertensive drugs (4). Whereas obesity, smoking, and diabetes are important risk factors for CRC, long-term use of aspirin and nonsteroidal anti-inflammatory drugs can substantially reduce CRC risk. Given the complex lifestyle and medication pattern, it is difficult to determine the direction of aggregate confounding. Although the investigators considered several potential confounders, according to the criterion of “including only factors leading to change of at least 10% in the association,” only the average number of physician contacts after the incident diagnosis of hypertension was adjusted in addition to the matching factors (ie, sex, age, calendar period and duration of follow-up after diagnosis of hypertension before the index date). Although physician visits might reflect disease severity to a certain extent, many factors can influence patients’ contacts with doctors, and thus adjustment for this single composite factor may not address the complicated confounding pattern in this study. On the other hand, adjustment for physician visits could induce selection bias because both drug use and subclinical symptoms or important risk factors (eg, family history) for CRC can lead to more frequent physician visits (10). This is more notable when a statistically significant association with 3 or more years of ACEI/ARB therapy emerges only after such adjustment (crude relative risk \[ \text{RR} = 0.92, 95\% \text{ confidence interval [CI]} = 0.79 to 1.08; \text{adjusted RR} = 0.84, 95\% \text{ CI} = 0.72 to 0.98), whereas statistically significant associations with some other agents disappear after the adjustment (for ≥5 years of diuretics use: crude RR = 0.80, 95\% CI = 0.65 to 0.98; adjusted RR = 0.85, 95\% CI = 0.70 to 1.05; for ≥5 years of beta-blocker use: crude RR = 0.80, 95\% CI = 0.67 to 0.95; adjusted RR = 0.85, 95\% CI = 0.71 to 1.01). Again, aggregation of small biases can induce a spuriously moderate association.

Given the findings by Makar et al. (9), an obvious question arises: What is the mechanism if ACEI/ARB therapy really reduces CRC risk among hypertension patients? Accumulating data indicate that the renin-angiotensin system (RAS), the target of ACEI and ARB action, is frequently dysregulated in malignancy. Abnormalities in the RAS signaling influence proliferation and apoptosis of cancer cells and promote angiogenesis and formation of cancer inflammatory microenvironment (11). Some experimental data suggest an anticarcinogenic role of RAS inhibitors in colorectal tumors, although the exact mechanisms remain largely unclear. Recent in vivo evidence demonstrates that ACEI or ARB administration substantially reduces the total number of colonic premalignant lesions and decreases oxidative stress and expression of inflammatory cytokines in metabolically disordered mice, suggesting that suppression of inflammation might mediate the effect...
Despite the encouraging findings, more research needs to be done before recommending clinical use of ACEI/ARB for CRC chemoprevention. Cancer incidence should be monitored as a secondary outcome in the ongoing and future clinical trials of antihypertensive drugs. At the same time, further observational studies should be conducted by using the existing cohorts or administrative health databases. When doing this, rigorous study design and analysis are needed to minimize the influence of confounding and biases, as proposed in the recent guidelines for good pharmacoepidemiology practices (14). Furthermore, the potential interaction with lifestyle factors (eg, obesity) and genetic susceptibility warrants more investigation. A recent study suggests that a polymorphism in the ACE gene modifies the association between ACEI/ARB therapy and CRC risk (15). In addition, the stage at which these medications might impact the adenoma-carcinoma sequence is speculative. ACEI use has been shown to be associated with decreased risk of recurrence of advanced adenomatous colon polyps (16), and a recent cross-sectional study in a CRC screening program found that ACEI therapy was associated with lower prevalence of advanced neoplasia at colonoscopy (CRC or intermediate- or high-risk dysplastic polyps) (17). Given the sparse data, more prospective studies are needed. Regarding mechanistic research of RAS inhibitors, current focus is still on cancer progression and metastasis, thus highlighting the need for more translational studies to examine CRC initiation-related change upon ACEI/ARB therapy and decipher the involved mechanisms, if such effect exists.

In summary, given that 40% of adults aged 25 years and older in the world have raised blood pressure, any protection of antihypertensive drugs against CRC, even small in magnitude, can produce substantial public health benefits. The promising findings by Makar et al. (9) should provide a stimulus for further work. However, at this moment clinicians should not recommend that their patients take ACEI/ARB for prevention of CRC until further conclusive evidence is obtained.

References


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