ARBs and Risk of Cancer - Meta-analysis

Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010 Jun 11. [Epub ahead of print]

ABSTRACT [from authors, except for gray shaded areas]

BACKGROUND: Angiotensin-receptor blockers (ARBs) are a widely used drug class approved for treatment of hypertension, heart failure, diabetic nephropathy, and, recently, for cardiovascular risk reduction. Experimental studies implicate the renin-angiotensin system, particularly angiotensin II type-1 and type-2 receptors, in the regulation of cell proliferation, angiogenesis, and tumour progression. We assessed whether ARBs affect cancer occurrence with a meta-analysis of randomised controlled trials of these drugs.

METHODS: We [the authors] searched Medline, Scopus (including Embase), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the US Food and Drug Administration website for studies published before November, 2009, that included any of the seven currently available ARBs. Randomised controlled trials with an ARB given in at least one group, with a follow-up of at least 1 year, and that enrolled at least 100 patients were included. New-cancer data were available for **61,590** patients from five trials. Data on common types of solid organ cancers were available for **68,402** patients from five trials, and data on cancer deaths were available for **93,515** patients from eight trials.

FINDINGS: **Telmisartan** was the study drug in 30,014 (**85.7%**) patients who received ARBs as part of the trials with new cancer data. Patients randomly assigned to receive ARBs had a significantly increased **risk of new cancer occurrence** compared with patients in control groups (**7.2%vs 6.0%**, **risk ratio [RR] 1.08, 95% CI 1.01-1.15; p=0.016**). When analysis was limited to trials where cancer was a **prespecified endpoint**, the **RR was 1.11 (95% CI 1.04-1.18, p=0.001**). Among specific solid organ cancers examined, only new **lung-cancer** occurrence was significantly higher in patients randomly assigned to receive ARBs than in those assigned to receive control (0.9%vs 0.7%, RR 1.25, 1.05-1.49; p=0.01). No statistically significant difference in cancer deaths was observed (1.8%vs 1.6%, RR 1.07, 0.97-1.18; p=0.183).
[**NNH: 143/ 4 years** 95% CI 76-793 for one excess cancer over all trials.] Trial main text.
[**NNH: 105/4 years** 95% CI 63-271 for 1 excess cancer in 3 trials where cancer was a pre-specified endpoint; n=40739] Trial main text

INTERPRETATION: This meta-analysis of randomised controlled trials suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis. Given the limited data, it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug. These findings warrant further investigation.

FUNDING: None. PMID: 20542468 http://www.ncbi.nlm.nih.gov/pubmed/20542468

As is typical with suggestive but inconclusive findings of harm from meta-analysis, there has been a fair bit of question as to whether or not clinicians and patients should be concerned enough to change therapeutic approaches. The table below outlines some considerations on both sides.

Favoring MORE concern that ARBs may ↑ cancer risk	Favoring LESS concern that ARBs may ↑ cancer risk
o Risk of new cancer for trials where cancer (ca) was a pre-specified secondary endpoint was even stronger than the data for overall. (All trials where ca was pre-specified were on side of ↑ ca. TRANSCEND, ONTARGET, LIFE).	o None of the trials had cancer pre-specified as the 1° endpoint, and none designed specifically for ca.
o Data based on large scale RCTs, as opposed to observational data.	o Although statistically significant, the 95% CI's are close to the point of "no difference"
o ACEIs have been around for longer, have been well studied and have not been associated with an increased cancer risk. ACEIs have excellent clinical outcome evidence and are usually reasonable initial drugs of choice relative to ARBs.	o Cancer deaths were not statistically increased
o ARBs are extensively used for long periods of time in a large number of people; therefore, suspicions of possible harm would have a major impact at a population level; caution advised till investigated.	o Lack of "dose response" ca association
o Concern is for ARBs in general, and telmisartan specifically (~ 85% of patients in these studies).	o Trend in PROFESS trial differs from other trials
o Also concerns about ?↑CV events with olmesartan http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm215222.htm	o Only 1 type of cancer – lung ca, had a statistically significant increase in risk. The trend toward ↑ prostate ca was not statistically significant.*
o Evidence has limitations, but it's the best we have.	o Would ACEI related cough confound the outcome of lung ca? e.g. Would patients on an ACEI & with cough end up being switched to an ARB, and would some of these turn out to be lung cancer?
o Some specialists are concerned (e.g. S. Nissen's accompanying editorial in Lancet Oncology).	o Patients tolerate ARBs relatively well, and somewhat better than ACEI for some; extensively used by clinicians and patients
	o Comparison "control" groups in trials will have been treated with different treatments (e.g. other antihypertensives).
	o This evidence has many limitations (e.g. 4yr time period not long enough for drug to be cause of ca; potential for selective reporting)
	o Some specialists are not so concerned, especially those who often are speakers in ARB marketing. (E.g. debate on theheart.org. http://www.theheart.org/article/1091359.do)
	o Concept of competing risks: if you don't die of CV disease, you will die of something else…

*Total # of specific solid organ ca driving the total: Prostate: 436 vs 256 RR 1.15 (95%CI: 0.99-1.34); Lung: 361 vs 195 RR 1.25 (95% CI:1.05-1.49); Breast: 154 vs 119 RR 1.04 (95% CI: 0.74-1.32).
Link to RxFiles ACEI & ARB Drug Comparison Chart, June 2010 (from 8th Edition book): http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-HTN-ace-arb.pdf

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Additional References:

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