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Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses

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Several commonly used medications have been associated with increased cancer risk in the literature. Here, we evaluated the strength and consistency of these claims in published meta-analyses. We carried out an umbrella review of 74 meta-analysis articles addressing the association of commonly used medications (antidiabetics, antihyperlipidemics, antihypertensives, antirheumatics, drugs for osteoporosis, and others) with cancer risk where at least one meta-analysis in the medication class included some data from randomized trials. Overall, 51 articles found no statistically significant differences, 13 found some decreased cancer risk, and 11 found some increased risk (one reported both increased and decreased risks). The 11 meta-analyses that found some increased risks reported 16 increased risk estimates, of which 5 pertained to overall cancer and 11 to site-specific cancer. Six of the 16 estimates were derived from randomized trials and 10 from observational data. Estimates of increased risk were strongly inversely correlated with the amount of evidence (number of cancer cases) (Spearman's correlation coefficient = –0.77, $P < 0.001$). In 4 of the 16 topics, another meta-analysis existed that was larger ($n = 2$) or included better controlled data ($n = 2$) and in all 4 cases there was no statistically significantly increased risk of malignancy. No medication or class had substantial and consistent evidence for increased risk of malignancy. However, for most medications we cannot exclude small risks or risks in population subsets. Such risks are unlikely to be possible to document robustly unless very large, collaborative studies with standardized analyses and no selective reporting are carried out.

Key words: cancer, meta-analysis, pharmacoepidemiology, randomized trials, review

introduction

A number of commonly used medications have been associated with increased risk of malignancy in diverse studies. Such cancer risks are very important to document, if present, because the use of commonly used drugs and biologics continues to increase and the resulting burden of disease due to malignancy can be substantial at the population level [1]. However, for most of the proposed pharmacoepidemiological links of cancer, there has been substantial controversy about their validity and often investigations with varying study designs and populations have arrived at different conclusions. For some of these associations, there are already a very large number of studies and even several meta-analyses thereof. However, even meta-analyses on the same topic may reach contradicting results and conclusions.

In this umbrella review [2], we aimed to collect systematically and critically reassess the results of meta-analyses of common medications that have been associated with increased cancer risk. We aimed to juxtapose the results of meta-analyses on similar drugs and cancer types to see how much they agree or disagree, to understand why disagreements may have arisen, and try to decipher eventually the presence or absence of cancer risks for these pharmacological and biological agents. We examined those associations where there is at least one meta-analysis, including data from randomized trials. For those topics, we evaluated all meta-analyses, regardless of whether they included randomized trials or observational data. We examined in depth those associations where at least one meta-analysis has claimed any nominally statistically significant increased cancer risk. We aimed to see how strong and consistent the evidence was for these claims of significant cancer risks across different types of study designs and different meta-analyses on the same or similar topic.

methods

eligible medications and meta-analyses

We considered medications for which there was at least one meta-analysis of data from randomized, controlled trials on

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that medication or on a respective wider class (e.g., all angiotensin enzyme-converting inhibitors, or all antihypertensives) against placebo or no treatment. Eligible outcomes included cancer—either all malignancies or site and type-specific cancers. We included both drugs and biologics, but excluded sex hormones, supplements and vitamins. We also excluded secondary cancers that have arisen after treatment of a primary malignancy; malignancies occurring specifically after transplantation and associations of medications with the rate of cancer progression or recurrence after a cancer diagnosis.

Whenever a medication or class was identified that had at least one such eligible meta-analysis, we also considered all other meta-analyses of the same medication or class that had assessed the association with any cancer type or overall malignancy. These meta-analyses were considered regardless of whether they included randomized trials, observational studies or both.

Finally, the medication or class was considered eligible for further detailed analyses if at least one meta-analysis claimed a statistically significantly increased risk for one or more types of cancer or for cancer overall.

search strategy and identification of eligible meta-analyses

We used the search strategy [cancer AND (randomized OR randomised)], limited to type of publication = meta-analysis, and also limited to English, human and having an abstract. The results of the search were screened to identify potentially eligible meta-analyses of randomized trials. These articles were then retrieved in full text and scrutinized further to verify eligibility. Then, we carried out searches tailored to each specific medication that already had an identified meta-analysis of randomized trials; we used the search strategy [(medication names and names of medication classes linked by OR) AND cancer], limited to the type of publication = meta-analysis, and also limited to English, human and having an abstract. We screened all the retrieved meta-analyses to identify the ones who had reported nominally statistically significant increased risks for at least one cancer type or cancer overall. When such a meta-analysis was identified, all other meta-analyses on the same medication or class of medication were also considered eligible for detailed data extraction and analysis. Literature searches were carried out in PubMed and were last updated in March 2013.

data extraction

From each meta-analysis article, we extracted information on the following items: first author, journal, year of publication, medication(s) or class(es), cancer type(s), type of studies (randomized or non-randomized), whether any nominally statistically significant increased risk ($P < 0.05$ or 95% confidence interval excluding the null) had been observed for any medication-cancer type pair, and, if so, for which. Then for each medication-cancer type pair with nominally statistically significant increased risk, we noted the number of studies, number of patients with cancer, relative risk and 95% confidence interval for cancer risk, and P value for cancer risk. When the same meta-analysis provided separate data for different cancer types and for all cancer overall, information was recorded separately for each. When the same meta-analysis provided data for different medications in the same class, as well as for sub-classes and larger classes overall, these were also recorded separately. When data were provided separately in the same paper for different types of diseases or disease subgroups, we focused on the data for the more inclusive grouping (i.e., all disease/population settings) that was provided.

Data extraction was carried out independently by two investigators and then the extracted data were compared and discrepancies resolved with discussion. A third investigator arbitrated on any remaining differences.

data analysis

Across all nominally statistically significant estimates of increased risk in meta-analyses of randomized trials, we provide descriptive data on the number of cancer events, P values and relative risk estimates so as to assess the amount of evidence, the statistical strength of the evidence and the size of the harmful effect postulated for them.

For each one of these nominally statistically significant estimates of increased risk, we also noted whether this was the largest (in terms of the number of cancer events) meta-analysis on the same topic and, if not, we compared their results against the results of the largest meta-analysis to see if the largest meta-analysis had found or not an increased risk For nominally statistically estimates of increased risk that were based on observational data, we also noted whether there meta-analyses of randomized data for comparison and selected the largest meta-analysis of randomized data. Compared meta-analyses had to be matched on cancer type and on medication or class of medication. If no such matched meta-analysis existed, we also searched whether any larger meta-analysis existed using a broader definition of cancer and/or broader definition of medication class.

results

meta-analyses of randomized trials and meta-analyses of observational studies

Using the search strategy described in the methods section, we generated a database including 2102 publications. Figure 1 shows the flow chart for the search. Based on our eligibility criteria and additional searches, we identified 60 articles with eligible meta-analyses that included randomized, clinical trials (Table 1) [3–62]. Twelve of these articles also included meta-analysis of observational studies [4, 5, 10, 12, 18–21, 27, 49, 55, 62]. Another 14 articles on meta-analyses of observational studies were also identified [63–76] (Table 1). The meta-analyses addressed diverse medications including antidiabetics, antihyperlipidemics, antihypertensives, antirheumatics, drugs for osteoporosis, and drugs for other conditions.

As shown in Table 1, only 5 of the 60 (8%) articles with meta-analyses of randomized trials claimed some significantly increased cancer risk, while this was more frequent in meta-analyses of observational studies (6 of 26, 23%). Nevertheless, for all categories of medications, the number of articles that found no significant increase or even significant decrease in cancer risk was larger than the number of articles that had found some increased cancer risk. Over 51 articles found no statistically significant differences, 13 found some significantly decreased cancer risk, and 11 found some significantly increased cancer risk (one article reported both increased and decreased risk estimates).

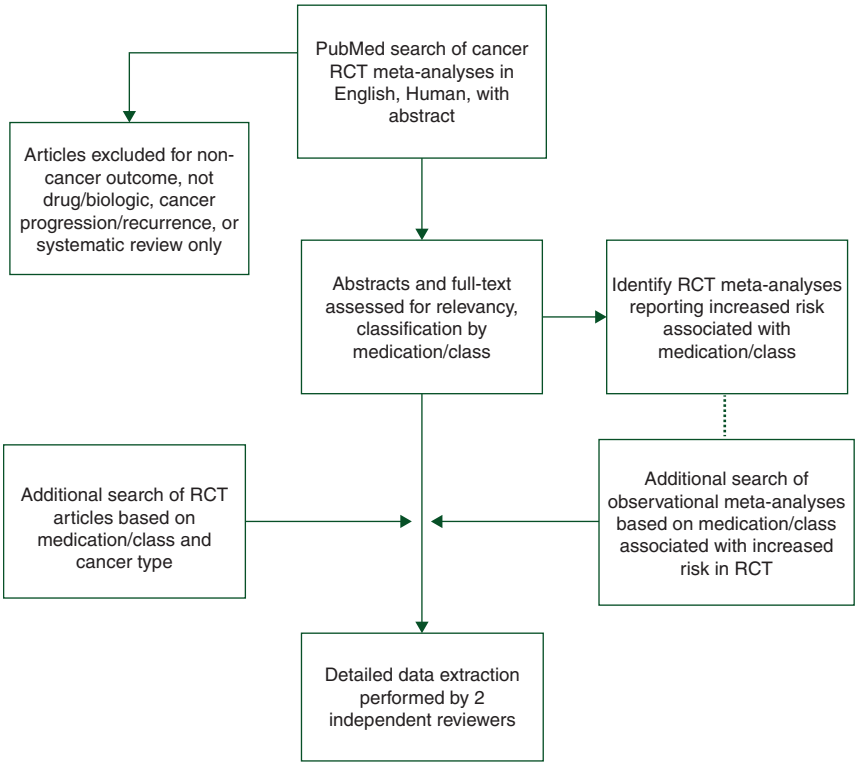

Figure 1. Flow chart for the literature search.

Table 1. Summary of retrieved meta-analyses

Medication class	Number of articles	Increased risk (references)	Decreased risk (references)	Non-significant (references)
Meta-analyses of clinical trials				
Antidiabetic	5		[3]	[4–7]
Antihyperlipidemic	28		[8] (lovastatin and melanoma), [9] (lovastatin and melanoma), [10] (statin and advanced prostate cancer)	[11–35]
Antihypertensive	8	[36, 37]		[38–43]
Antirheumatic	13	[44, 45]		[46–56]
Osteoporosis Treatment	2			[57, 58]
Other treatments	4	[59]		[60–62]
Meta-analyses of observational studies				
Antidiabetic	9	[5, 63–65]	[64] (Insulin use >10 years), [66] (metformin and colorectal cancer), [67] (metformin and liver cancer), [68], [69] (metformin and cancer)	[4]
Antihyperlipidemic	8		[18, 70]	[10, 12, 19–21, 27]
Antihypertensive	3	[71]	[72, 73]	
Antirheumatic	3	[74]		[49, 55]
Osteoporosis Treatment	0			
Other treatments	3			[62, 75, 76]

meta-analyses with significantly increased cancer risks

The characteristics of the 11 articles that claimed nominally statistically significantly increased cancer risks are listed in Table 2. As shown, there were overall 16 cancer type-medication (or medication class) pairs that were nominally significant for increased cancer risk. Of the 16 entries, 5 were on insulin, 3 on tumor necrosis factor (TNF) inhibitor, and the other 8 on drugs with one or two entries each. Of the 16 entries, 5 pertained to overall cancer risk [insulin, angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) combination, ARB, TNF

Table 2. Nominally statistically significantly increased cancer risks in meta-analyses

First author	Year	Medication or class	Cancer type	Design	Studies (*n*)	Patients with cancer (*n*)	RR and 95% CI for cancer risk	*P* value
Colmers [5]	2012	Pioglitazone	Bladder	Co	3	3062	1.22 (1.07–1.39)	0.003[a]
		Thiazolidinedione	Bladder	Co	5	3462	1.15 (1.04–1.26)	0.004[a]
Janghorbani [63]	2012	Insulin	All	CC, Co	15	14 085	1.39 (1.14–1.70)	0.001[a]
		Insulin	Colorectal		5	1854	1.50 (1.08–2.08)	0.015[a]
		Insulin	Pancreatic		2	1062	4.78 (3.12–7.32)	<0.001[a]
Li [64]	2011	Insulin	Pancreatic	CC	3	448	OR = 2.2 (1.6–3.7)	0.002[a]
Deng [65]	2012	Insulin	Colorectal	CC, Co	4	852	1.38 (1.15–1.65)[#]	<0.001[a]
Bangalore [37]	2011	ACEi and ARB combination	All	RCT	2	2479	1.14 (1.02–1.28)	0.024[a]
Sipahi [36]	2010	ARB	All	RCT	5	4112	1.08 (1.01–1.15)	0.016
Corrao [71]	2007	Diuretics anti-hypertensive	Renal-cell cancer	CC, Co	16	6884	1.43 (1.12–1.83)	0.004[a]
		No diuretics anti-hypertensive	Renal-cell cancer	CC, Co	8	3806	1.51 (1.21–1.87)	<0.001[a]
Askling [45]	2011	TNFi	NMSC	RCT	74	65	2.02 (1.11–3.95)	0.030[a]
Bongartz [44]	2006	TNFi	All	RCT	7	32	3.29 (1.19–9.08)	0.022[a]
Mariette [74]	2011	TNFi	NMSC	Co	4	1258	1.45 (1.15–1.76)	<0.001
Heijl [59]	2011	Treatment for AAV	All	RCT	4	46	1.58 (1.17–2.08)	0.003
			NMSC	RCT	4	12	2.78 (1.56–4.59)	0.001

Co, cohort study; CC, case–control study; RCT, randomized, controlled trial; NMSC, non-melanoma skin cancer; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; TNFi, tumor necrosis factor alpha inhibitor; AAV, antineutrophil cytoplasm antibody-associated vasculitis; RR, relative risk; CI, confidence interval; OR, odds ratio.

[a]The *P* value is not given in the article, thus it is approximated by taking the difference (*D*) in the log-transformed upper confidence interval minus the log-transformed lower confidence interval, dividing *D* by 3.92 to get the standard error (SE), and then dividing the log-transformed point estimate by SE to calculate the *z*-score, which is translated to *P* value based on the standard normal distribution. For example: 1.22 (1.07–1.39) log-transformed is: 0.20 (0.07–0.33), thus the standard error is (0.33–0.07)/3.92 = 0.066, and $z = 0.20/0.066 = 3$, thus on a normal distribution table this corresponds to $P = 0.003$.

[b]The published point estimate in Deng et al. [71] is apparently wrong. The reported RR is recalculated based on the results from the four original studies.

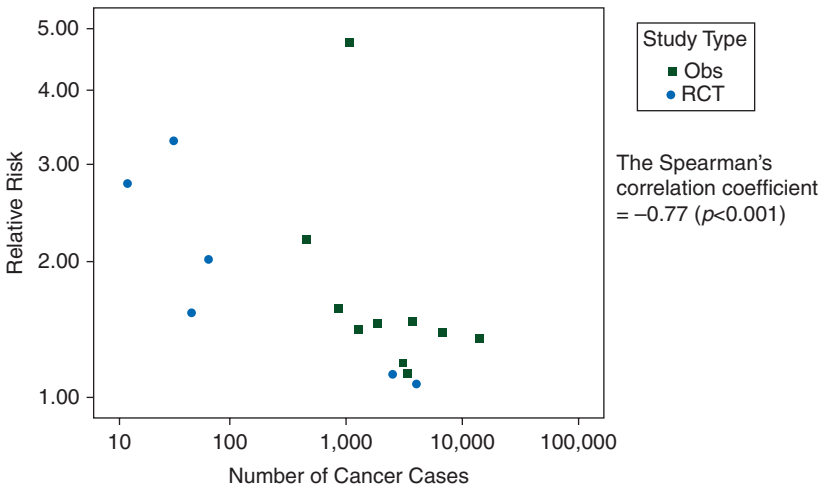

Figure 2. Association between the amount of evidence (number of cancer cases) and estimate of effect (relative risk) in nominally statistically significant estimates of increased risk from meta-analyses.

inhibitor, immunosuppressive therapy in anti-neutrophil cytoplasm antibody-associated vasculitis [AAV]). The other 11 estimates pertained to malignancies of specific sites. Six of the 18 estimates were derived from randomized trials and 10 from observational data. Only one meta-analysis had over 10 000 cancer cases, and 9 had fewer than 2000 cancer cases (4 had even fewer than 100).

Table 3. Meta-analyses with more evidence or better controlled study designs for the topics given in Table 2

First author	Year	Medication or class	Cancer type	Design	Studies (*n*)	Patients with cancer (*n*)	RR and 95% CI for cancer risk	*P* value
Colmers [4]	2012	Thiazolidinedione	All	RCT	3	689	0.92 (0.79–1.07)	0.26
The ARB Trialists [43]	2011	ARB	All	RCT	15	8405	1.00 (0.95–1.04)	0.89
Coleman [41]	2008	Diuretics antihypertensive	All	RCT	21	1925	0.94 (0.73–1.19)	0.62[a]
Mariette [74]	2011	TNFi	All	Co	7	5760	0.95 (0.85–1.05)	0.53

Co, cohort study; CC, case–control study; RCT, randomized, controlled trial; ARB, angiotensin-receptor blocker; TNFi, tumor necrosis factor alpha inhibitor; RR, relative risk; CI, confidence interval.
[a]The *P* value is not reported in the article, thus it is approximated as also described in the footnote of Table 2.

These 16 estimates of increased risk are further illustrated in Figure 2, which shows a very strong inverse relationship between the number of cancer cases and the magnitude of increased risk found by each meta-analysis (Spearman's correlation coefficient = −0.77, $P < 0.001$). Meta-analyses with over 2000 cancer cases had small relative risks (1.08–1.51). $P < 0.001$ was documented only for insulin for colorectal and pancreatic cancer, non-diuretic antihypertensives for renal cell cancer and TNF inhibitors for non-melanoma skin cancer.

comparison against larger-scale or better controlled evidence

Of the 16 topics with at least one nominally significantly increased estimate of cancer risk, we could identify other meta-analyses with larger-scale evidence (larger number of cancer cases) in 2 of them (Table 3). In both, the larger-scale evidence showed no significantly increased risk of cancer, implying false-positive results. This evidence pertained to ARB [43] and TNF inhibitors [74]. The meta-analyses on ARB pertained to data from randomized trials, while the meta-analysis on TNF inhibitors included observational studies. In fact, the point estimate of the TNF inhibitor association in the larger-scale meta-analysis was even protective with a relative risk of 0.95.

For another two topics, where the significantly increased risk had been seen in observational data, data from randomized trials also existed (association of overall cancer risk with thiazolidinediones [4] and diuretic antihypertensives [41]) and in both cases the associations were not statistically significant and the point estimates were suggestive of protection from cancer.

discussion

Our umbrella review has evaluated data from 74 meta-analysis publications on the association of common medications with cancer risk. While 11 articles have reported on a total of 16 increased risk estimates, several of these claimed associations may not be supported by the overall analysis of the literature. The large majority of surveyed meta-analyses have found no significant associations, and the number of meta-analyses that have shown significantly increased risk is similar to those that have shown significantly decreased risk for the same medications. Few claims of increased risk are based on the data from randomized trials and/or large sample sizes. We also documented a very strong inverse relationship between the amount of evidence and effect sizes: when more data were available, estimates of increased risk were much smaller. Finally, for several meta-analyses that claimed increased cancer risk, we found others that were larger and/or included data from better controlled studies and in all these cases, the larger and/or better controlled meta-analyses indicated no increased burden of malignancy.

Our analysis suggests that most associations of commonly used medications with cancer risk, if present, are likely to have small or modest effects. Large estimates of risks in some meta-analyses were documented with limited evidence from small studies. These may correspond to either small or no effects, when large studies are carried out [77]. This may be due to the winner's curse (a regression-to-the-mean phenomenon), where results selected on the basis of statistical significance are expected to have inflated effect sizes, even if some association is genuinely present [78]. Documentation and validation of relative risks in the <1.20 range will require very large datasets, careful designs and protection from selective reporting and other biases to minimize noise. It is possible that several such small relative risks may still remain undetected based on the current evidence which remains underpowered, even when data are combined in meta-analyses. It is also possible that small relative risks can reflect heterogeneity of cancer risks across population subgroups defined on the basis of demographic, clinical and other biological factors such as genetic susceptibility. Conversely, several of the seemingly detected increased risks may reflect the impact of common limitations of pharmacoepidemiology studies, including the lack of control for drug dose and duration, recall bias from self-reported data, short follow-up times, confounding by indication and duration of disease, detection bias, as well as selective reporting and other biases [79] in a setting where there is often substantial unaccounted multiplicity of comparisons that may cause false positives [80, 81]. False positives may manifest as either increased or decreased risk and we observed an equal number of claims of increased and decreased risk in meta-analyses. Feinstein [82] had seen the same phenomenon in an evaluation of observational studies 25 years ago and had suggested that such observational risks may simply reflect false positives. We also suspect that the number of null results in meta-analyses of cancer risk may be substantially underestimated due to reporting bias.

Of the five types of medications that have been associated with significantly increased risk of all malignancies combined, ARB and TNF inhibitors seem unlikely to confer substantially increased overall cancer risk. Very large meta-analyses [43, 74] have found no significant associations and the 95% confidence intervals are very tight, excluding relative risks >1.05. The combination of ACE inhibitors and ARB also has weak evidence with a very small relative risk (1.14) and very modest statistical

significance. At least one other meta-analysis [72] shows no risks or decreased risks with these antihypertensive agents. Insulin therapy seemingly has the strongest evidence for an association with increased overall cancer risk, and this is also reflected in significant associations with specific cancer types, in particular colorectal and pancreatic cancers which have each been documented in two separate meta-analyses [63–65]. However, a recent large randomized, trial on over 12 000 randomized participants (ORIGIN) found no increased risk of cancer with insulin versus standard care over a median follow-up of 6.2 years [83]. Immunosuppressive therapy for AAV also seems to have evidence for an association with increased risk [59], although the number of cancer cases is very small and thus there should be some reservation on the exact magnitude of the effect.

The sporadic associations of medications with specific cancer types at one site should be seen with even greater caution. Given that there are several dozens of cancer sites and types, and perhaps additional subgroup considerations, such associations have an additional layer of multiplicity and a traditional P value of <0.05 is likely to be a very weak discriminating tool for identifying genuine associations. We will focus here on the two site-specific associations that had $P < 0.001$ [84], and which thus account for a Bonferroni correction of 50-fold for the multiplicity of comparisons.

First, the claimed association of TNF inhibitors with increased risk of non-melanoma skin cancer [74] was seen in a meta-analysis with four observational studies and 1258 cases. Despite the strong statistical significance, documentation of non-melanoma skin cancer is likely to be more susceptible to poor data collection for this type of typically non-aggressive cancer. Moreover, the increased risk estimate is seen in the same article [74] where the estimate and 95% CI for overall cancer exclude relative risks >1.05. One cannot also exclude the possibility that some sort of diagnosis bias may exist also in these data, i.e., patients treated with a biologic agent that is considered to potentially increase cancer risk may be more likely to have more thorough screening for suspicious cancerous lesions, referrals for them and diagnosis of non-melanoma skin cancer. Of note, the earliest meta-analysis on TNF inhibitors and cancer had suggested a very large risk with a 3.3-fold increase in overall malignancy incidence, but it was based on the data from only 32 cancer cases [44]. This highlights the major danger of drawing conclusions from early, limited data that may be subject to substantial subsequent regression to the mean [77].

Second, the evidence for an increased risk of renal cell cancer with antihypertensives seems to have strong statistical support [71]. The statistical significance is more prominent for non-diuretics, but practically the risk estimate is the same also for diuretics [71], so it is unclear whether there is any discernible drug specificity for this risk. The evidence for increased risk comes from observational studies, while data on diverse antihypertensives from randomized trials and observational data show mostly no significant risk [4–7, 11, 13–36, 38–42, 46–58, 60–62, 74, 75], and occasionally even decreased risks of cancer [72, 73]. It is unclear whether diagnosis bias may also exist for observational data on renal cell cancer, e.g., some patients with hypertension may be more likely to be subjected to evaluation of their kidneys, and this may result in more renal cell cancers being diagnosed.

Our umbrella review has limitations. Many of them reflect from the limitations of the primary data included in the 75 meta-analyses that we surveyed. Cancer risk may not be possible to detect in studies of short follow-up, and this caveat is very common in randomized trials in particular. Loss to follow-up may compound this problem. Underpowered studies and meta-analyses may fail to detect small or even modest cancer risks. Non-differential misclassification with under-diagnosis of cancer may dilute the estimates of association. Moreover, we did not evaluate the quality or the accuracy of the data and calculations of the 74 meta-analyses, a task that would have been too arduous or even impossible to carry out, given only what was published in the respective article reports. The meta-analysis authors did not have access to original data either and they did not adjust their meta-analysis for multiple testing. Publication and other selective reporting biases are likely to affect several of these meta-analyses, requiring caution in making inferences.

Furthermore, a larger meta-analysis may not necessarily be better than a smaller one with less data. Observational data are likely to be even more biased than randomized data and have a poorer replication record [85]. It is well-documented that observational data may often find stronger effects than randomized trials [86], although this is not so clear for harms [87]. All evidence should be examined comparatively, and we tried to obtain as wide a view as possible given the accumulated published information. Finally, it is possible that for some medication classes, only meta-analyses of observational data exist with no respective randomized evidence and these classes would not have been captured by our searches. This would have required scrutinizing tens of thousands of meta-analyses of observational data with low yield. Nevertheless, our approach has probably captured all the medication classes that have attracted major attention in the literature. It is unlikely that a medication has attracted substantial attention for its association with increased cancer risk in observational data and no one has been tempted to see what the respective data would suggest in its randomized trials.

Allowing for these caveats, our evaluation maps systematically the current landscape of the pharmacoepidemiology of claims of increased cancer risk. Many of the proposed associations with increased risk of malignancy may not be real or may be very modest in magnitude. The available evidence often cannot exclude small risks for many medications, or even modestly large risk in circumscribed population subsets (for example, based on genetic susceptibility). One would have to decide on a case-by-case basis whether small risks are clinically or otherwise important to document robustly. Documentation of relative risks <1.20 will require large studies, long-term follow-up and complete data in collaborative teams carrying out individual-level meta-analyses, where selective reporting of analyses is minimized and ideally eliminated. Bias, multiple testing and multiple modeling are all potential problems and would need to be properly accounted for. Evaluation of population subsets would require strong biologic rationale and careful protection from issues of data dredging and subgroup analyses. Analysis plans should also be transparent and ideally registered upfront [88], and should be clearly stated whether associations with specific cancer types or other forms of secondary analyses are pre-conceived or exploratory ones. The burden of multiplicity of end points and analyses should be carefully considered in making or not making strong conclusions on cancer risks from medications.

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disclosure

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