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False Positives in Cancer Epidemiology

Joseph K. McLaughlin and Robert E. Tarone

Abstract

**Background:** A recent attempt to estimate the false-positive rate for cancer epidemiology studies is based on agents in International Agency for Research on Cancer (IARC) category 3 (agent not classifiable as to its carcinogenicity to humans) in the IARC Monographs Program.

**Methods:** The estimation method is critiqued regarding biases caused by its reliance on the IARC classification criteria for assessing carcinogenic potential.

**Results:** The privileged position given to epidemiologic studies by the IARC criteria ensures that the percentage of positive epidemiologic studies for an agent will depend strongly on the IARC category to which the agent is assigned. Because IARC category 3 is composed of agents with the lowest-assessed carcinogenic potential to which the estimation approach in question could be applied, a spuriously low estimated false-positive rate was necessarily the outcome of this approach.

**Conclusions:** Tendentious estimation approaches like that employed will by necessity produce spuriously low and misleading false positive rates.

**Impact:** The recently reported estimates of the false-positive rate in cancer epidemiology are seriously biased and contribute nothing substantive to the literature on the very real problems related to false-positive findings in epidemiology. *Cancer Epidemiol Biomarkers Prev; 22(1); 11–15. ©2012 AACR.

A recent article (1) attempted to estimate the false-positive rate for cancer epidemiology studies based on agents in International Agency for Research on Cancer (IARC) category 3 (agent not classifiable as to its carcinogenicity to humans) in the IARC Monographs Program. The estimation method used was based on the assumption that the IARC classification of agents about their carcinogenic potential (or any similar human endeavor at reaching consensus) provides a scientifically sound basis for assessing the false-positive rate in cancer epidemiology studies. Any such consensus effort uses classification criteria, and we critique the proposed false-positive rate estimation method because of potential biases induced by its reliance on the IARC criteria for assessing carcinogenic potential. The IARC criteria give epidemiologic studies epistemic priority in working group deliberations, and accordingly, the IARC category to which an agent is assigned will depend strongly on the percentage of positive epidemiologic studies for that agent. Because IARC category 3 is composed of agents with inadequate evidence of cancer risk from epidemiologic studies, we argue that the reported false-positive rate estimates based on this IARC category seriously underestimate the actual false-positive rate in cancer epidemiology investigations.

The false-positive rate was estimated as the percentage of positive studies among all epidemiologic studies assessing cancer risk for agents classified in IARC category 3, the IARC category corresponding to the lowest-assessed carcinogenic potential to which the proposed method could be applied (1). For an agent to be assigned to category 3, there must be inadequate evidence of carcinogenicity in both humans and animals. Because IARC gives the greatest probative weight to epidemiologic evidence, any agents, including noncarcinogens, with multiple-positive epidemiology studies would by IARC definitional criteria almost always be assigned to an IARC category indicative of a higher assessment of carcinogenic potential than that of category 3. An agent with even a few positive epidemiologic findings will likely be assigned to category 2b (possibly carcinogenic to humans), category 2a (probably carcinogenic to humans), or sometimes category 1 (carcinogenic to humans). By the IARC classification criteria, agents in category 3 will have almost no positive epidemiology studies, and thus the evaluation by the authors of the percentage of positive epidemiologic studies for category 3 agents was guaranteed in advance to provide a misleadingly low estimate of the false-positive rate.

The fundamentally flawed nature of the estimation method used in the article (1) is best understood by considering the approach its authors indicate that they would have preferred to use to estimate the false-positive rate. They indicate that ideally they would have estimated...
the false-positive rate as the percentage of positive epidemiologic studies for category 4 agents (agents probably not carcinogenic to humans). They could not use this approach, because of the 950 agents evaluated to date by IARC, only 1 agent resides in category 4, and there was no epidemiologic study investigating possible cancer risk associated with this agent (Appendix 1). In order for an agent to qualify for IARC category 4, there must be evidence suggesting a lack of carcinogenicity in both humans and experimental animals. Obviously, if there was even a single epidemiologic study with a positive finding for an agent and any cancer, then that agent would by definition not be eligible for category 4 (unless there were a large number of methodologically superior negative epidemiologic studies of the same agent). Thus, because of the stringent (i.e., virtually impossible to meet) IARC criteria for category 4 agents (and assuming that there were any such agents evaluated in epidemiologic studies), the estimated false-positive rate for epidemiologic studies would have been approximately 0 if the authors’ preference could have been met (1). The fact that no agent actually investigated in an epidemiologic study has ever been assigned to category 4, is itself strong evidence supporting the seriousness of the problem posed by false positives in cancer epidemiologic studies. Even a noncarcinogen is likely to show some evidence of a positive association for some type of cancer in occupational or environmental epidemiologic studies as such investigations are currently conducted and interpreted (2–4).

No scientifically sound evaluation of true false positives can be based on the IARC consensus approach about carcinogenic potential. To provide a reasonable and valid estimate of the false-positive rate in cancer epidemiologic studies, the true state of nature would have to be known (i.e., which agents are real carcinogens and which are noncarcinogens), and the approach (1) reviewed here would have to be applied to all actual noncarcinogens that have been evaluated by IARC, regardless of the present IARC category to which they have been assigned. Because of the aforementioned priority given to epidemiologic evidence by the IARC criteria, the categories to which true noncarcinogens are assigned depend strongly on the percentage of positive epidemiologic studies that have investigated them. Hence, the percentage of positive studies would be lowest for category 3 agents (i.e., the method used by the authors), and would increase successively for agents in categories 2b, 2a, and 1. Most of the agents in category 2b probably do not cause cancer in humans in the usual definition of “probably,” and several agents in category 2a, and even a few agents in category 1, probably do not cause cancer in humans (Appendix 2). True noncarcinogens classified in IARC categories 1 and 2 would be particularly informative, because they would lay bare the pitfalls of virtually all of the mechanisms that produce false positivity, particularly the bandwagon effect in research once suspicion is raised about an agent by a governmental agency, activist group, or nongovern-
category 4 (i.e., evidence suggesting a lack of carcinogenicity is required) and the subjective application of IARC criteria in practice. There were no epidemiologic studies of caprolactam (i.e., no studies suggesting lack of carcinogenicity in humans), but it was put in category 4 on the basis of an option permitting an agent with inadequate human evidence to be assigned to category 4, provided there is evidence suggesting lack of carcinogenicity of the agent in animals. The National Cancer Institute (NCI) conducted a study in male and female mice and rats that found generally lower tumor rates in animals exposed to caprolactam (18). The only compound-related effects reported in the study, however, were dose-related decreases in body weight for both rats and mice exposed to caprolactam, and a dose-related decrease in food consumption in rats. Lower tumor rates should be expected in rodents with restricted food consumption and reduced weight gain, and thus the NCI rodent experiments are not interpretable as providing evidence against carcinogenicity of caprolactam. On the basis of the IARC evaluation criteria, it seems that caprolactam should have been assigned to IARC category 3.

Appendix 2

Coffee is classified by the IARC Monographs Program as an agent that is possibly carcinogenic to humans (i.e., category 2B). Few agents have been investigated more widely in epidemiologic studies than coffee. There is strong evidence that coffee consumption is inversely associated with endometrial cancer risk (19) and substantial evidence for an inverse association between coffee intake and liver cancer (20, 21). A recent comprehensive meta-analysis reported an inverse association between exposure to coffee and total cancer risk, and evaluation by organ site led to the conclusion that “coffee drinking was associated with a reduced risk of bladder, breast, buccal and pharyngeal, colorectal, endometrial, esophageal, hepatocellular, leukemic, pancreatic, and prostate cancers” (22). It seems that coffee may be the only agent evaluated by IARC for which the epidemiologic evidence meets the criteria for category 4, yet it currently resides in category 2B based on the IARC working group deliberations. The sheer number of cancer sites with evidence of protection from coffee drinking is surprising, and many of the reduced relative risk estimates may have been the result of residual confounding or confounding that reflects as yet unrecognized differences between coffee drinkers and people who do not drink coffee. Nevertheless, the weight of the epidemiologic evidence indicates that coffee probably does not cause cancer in humans. Cell phone exposure has been widely investigated in epidemiologic studies, with sporadic reports of increased risk estimates, most coming from case–control studies conducted by a single research group (23). The inconsistent evidence of a possible association between cell phone use and brain or salivary gland cancer risk from case–control studies is negated by the absence of any recent increase in national population cancer rates in developed countries (23–28). No increase in population rates has been observed through 2009 in countries, such as those in Scandinavia where cell phone use began early, despite the fact that increased relative-risk estimates for cell phone use and brain tumor risk were being reported in case–control studies based on cases diagnosed as early as 1994 through 1996 (29). The absence of any temporal increase in brain cancer rates in the presence of ubiquitous cell phone use contrasts with the increase in national rates of lung cancer observed in the 1930s resulting from increased cigarette smoking after World War I, particularly in view of the fact that the prevalence of cell phone use far exceeds the maximum peak prevalence of cigarette smoking during the twentieth century (particularly among women and children). The stable trends in national brain cancer rates are even more surprising if cordless phone use also increases brain cancer risk as some have claimed (30). Continued monitoring of national cancer rates for sites plausibly affected by cell phone exposure should continue, but at present the epidemiologic evidence is consistent with the conclusion that cell phone use probably does not cause cancer in humans.

Comprehensive reviews indicate that, even for some agents classified in IARC category 1, the epidemiologic evidence of carcinogenicity is weak and inconsistent (31, 32). The interpretation of epidemiologic evidence is particularly problematic for formaldehyde (31, 33, 34). Formaldehyde was originally placed in category 1 on the basis of evidence of increased nasopharyngeal cancer (NPC) risk, primarily on the basis of a single NCI cohort study of industrial workers with occupational formaldehyde exposure (35). As has been noted previously, however, all of the evidence of increased NPC risk in this study came from only 1 of the 10 plants included in the study (31, 33, 34). The standardized mortality ratio (SMR) for formaldehyde-exposed workers in plant 1 in the NCI study is 9.1 [95% confidence interval (CI), 3.3–19.8] based on 6 cases. In the remaining 9 plants of the NCI study, the SMR for exposed workers is 0.6 (95% CI, 0.1–2.3) based on 2 cases. Including all occupational cohort studies from around the world, but excluding plant 1 of the NCI cohort, the summary SMR for formaldehyde-exposed workers is 0.6 (95% CI, 0.2–1.6) based on 4 NPC cases (31, 35–40). Follow-up of an expanded cohort of workers from plant 1 of the NCI cohort study yielded an SMR of 4.4 (95% CI, 1.8–9.1) based on 4 NPC cases (41). The elevated SMR in plant 1 of the NCI study was observed despite the fact that no uniquely dangerous characteristics of formaldehyde exposure have been documented in that facility (34). Furthermore, 3 of 7 workers with NPC had formaldehyde
exposure of duration 3 months or fewer, and a fourth had formaldehyde exposure of duration 8 months (33). IARC (42) recently concluded that formaldehyde also causes leukemia in humans, primarily on the basis of an NCI case-control study of embalmers (43). Embalmers are reported to have the highest peak exposure to formaldehyde of any occupation (43), and peak exposure was the exposure metric that showed the strongest association with NPC risk in the NCI industrial cohort study (35). Thus, embalming would seem to be an optimal occupation in which to investigate possible NPC risk. The NCI embalmer case-control study had numerous methodologic problems that are beyond the scope of this appendix, but IARC nonetheless gave it great weight in evaluating the inconsistent epidemiologic evidence of leukemia risk, including it in the discussion of cohort studies because it was treated as a case-control study nested within a cohort (42). Inexplicably, the embalmer case-control study was ignored in the IARC discussion of NPC risk (42), perhaps because the reported OR for NPC of 0.1 (95% CI, 0.01–1.2) among embalmers (43) was hard to reconcile with the consensus IARC working group conclusion that formaldehyde exposure is a cause of NPC in humans. A scientifically sound summary of the epidemiologic evidence about NPC risk would conclude that something in or around plant 1 of the NCI cohort study may have led to increased risk of NPC (41), but that formaldehyde, even at high-occupational exposure levels, probably does not cause NPC in humans.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: J.K. McLaughlin, R.E. Tarone
Development of methodology: R.E. Tarone
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.E. Tarone
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.E. Tarone
Writing, review, and/or revision of the manuscript: J.K. McLaughlin, R.E. Tarone
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