

## Researchers and HIPAA

### To the Editor:

Medicaid data have been used for pharmacoepidemiologic research since the early 1980s, and there is now optimism about using Medicare Part D data for such studies. Database studies often require hospital records to validate study outcomes.<sup>1</sup> Unfortunately, the Health Insurance Portability and Accountability Act (HIPAA) has made obtaining medical records much more challenging. We sought to develop and test a mechanism to obtain hospital records for research.

As part of a study of drug-induced sudden death and ventricular arrhythmia, the Centers for Medicare and Medicaid Services (CMS) provided us with Medicaid claims data from 5 states (California, Florida, New York, Ohio, and Pennsylvania) covering 1999–2000. Because Medicaid claims are often incomplete for persons who are also eligible for Medicare,<sup>1</sup> we also obtained Medicare data for all dually eligible persons from those states.

Quality Improvement Organizations (QIOs) are a national network of contractors whose mission is to improve the quality of health care provided to Medicare beneficiaries. As part of this mission, QIOs have traditionally abstracted hospital medical records. More recently, primary responsibility for this role has shifted from QIOs to a single, national CMS-funded Clinical Data Abstraction Center (CDAC), which obtains and abstracts inpatient medical records nationwide.

Our proposed mechanism for obtaining inpatient records was as follows. First, we used Medicaid and Medicare data to identify a list of hospitalization outcomes to be validated. We then provided information about these hospitalizations to the CDAC. This information

included social security number, Medicaid statistical information system identification number and/or Medicare health insurance claim number, sex, date of birth, admission date, discharge date, and hospital identifiers. The CDAC would then contact the hospital and request a photocopy of the relevant record for research purposes. The hospital would photocopy the record and mail the photocopy to the CDAC, which would reimburse the hospital for photocopying and shipping. The CDAC would then redact direct personal identifiers and ship the redacted records to the academic center.

The University of Pennsylvania's institutional review board approved the study and granted waivers of informed consent and HIPAA authorization, and CMS granted the needed data reuse agreement. Once we had executed a business associate agreement with the CDAC, we provided the CDAC with an electronic file containing the information needed to request records. As required by the HIPAA Privacy Rule, we accounted for this disclosure of protected health information.

The CDAC requested 164 inpatient records of 164 patients, and received full inpatient records of 128 (78%) of these. We would expect a higher success rate for more recent records, and a lower rate for less recent ones. The CDAC recontacted nonresponding hospitals, which provided the following reasons for not providing requested records: unable to locate record ( $n = 17$ ), hospital closed or otherwise unable to be contacted ( $n = 4$ ), refused ( $n = 2$ ), and no reason given ( $n = 13$ ). The CDAC charged \$15,000 including hospital reimbursements, which comes to \$117 per chart retrieved.

We believe that this mechanism for obtaining hospital records can greatly enhance the scientific and public health value of data now available from CMS, as well as Medicare Part D data, which we hope will become available soon. We see no reason why other researchers cannot use this same mechanism. A mechanism to obtain outpatient records would also be valuable, since not all outcomes result in hospitalization. However, this may prove more challenging, since outpatient providers,

unlike hospitals, are unaccustomed to responding to requests by the CDAC or QIOs.

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## Coffee and Myocardial Infarction

### To the Editor:

Just before taking my first sip from a cup of coffee, I read the case-crossover study by Baylin et al<sup>1</sup> and its estimated relative risk of 1.5 for myocardial infarction in the hour after doing what I was about to do. I wondered what this result might mean if it were translated into more meaningful terms. Recalling the advice of Cornfield et al<sup>2</sup> to use the risk difference for such a purpose, I realized I needed an estimate of the baseline risk: the risk my cup of coffee would hypothetically be increasing by an estimated 50%.

Schwartz et al found that baseline risks are hard to come by in journal articles in which estimates of ratio effect measures are reported.<sup>3</sup> Sure enough, the paper by Baylin et al<sup>1</sup> gave no hint as to what the 1-hour risk of myocardial infarction might be. I went to a previous paper the authors cited from the same study,<sup>4</sup> then to the paper cited by that paper.<sup>5</sup> No luck. It was a population-based study and myocardial infarction incidence rates had been calculated, but none had been reported.

Clearly, I had to take another tack. Browsing through the web site of the National Heart, Lung and Blood Institute ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)), I stumbled across a document<sup>6</sup> with an appendix giving a brief description of Framing-

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ham risk scoring. Although a “Framingham risk” is an estimated risk of myocardial infarction or coronary death and Baylin et al<sup>1</sup> had studied only the former, I was unfazed. I needed only a ballpark value. After all, the decision in question was just a single cup of coffee for a target population of size  $N = 1$ .

Some illustrative tables in the appendix<sup>6</sup> suggested that a 10-year risk of 10% would not be out of the question. That was the risk given for a man with a Framingham score of 9 or a woman with a score between 19 and 20.

With the help of my trusty calculator, I was able to take it from there. An average decade has  $10(365.25)(24) = 87,660$  hours. Hence, a 10-year risk of 10% would be a 1-hour risk of  $0.1/87,660$ , or about 1 in a million. A 50% increase in such a risk would be an increase of about 1 in 2 million.

Finally, I had an answer to my question. What would it mean for a cup of coffee to increase the 1-hour risk of myocardial infarction by 50%? It would mean an expectation, on average, of about 1 extra heart attack in the hour immediately following the consumption of each 2,000,000 cups of coffee.

Schwartz et al<sup>3</sup> suggested that researchers should routinely provide this kind of information to readers: the absolute differences that are implied by the ratios of risks, rates, and prevalences we typically estimate. I agree. Journals might think about encouraging or even insisting that this information be provided, even if only in very approximate terms like those in my calculations.

In the 2 hours it had taken me to work out that risk difference on my own, my coffee had gone cold. While weighing the risk-benefit tradeoff of getting a fresh cup, I was reminded of something a colleague once told me. He, too, had conducted a case-crossover study of myocardial infarction and coffee, but the results were never published. They were “negative.”

That made my decision even easier.

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## The authors respond:

We agree with Dr. Poole<sup>1</sup> that the absolute risk of having a myocardial infarction is very low. This point was reflected in the commentary by Dr. Siscovick<sup>2</sup> that accompanied our paper<sup>3</sup>; it has also been considered in other publications about triggers of myocardial infarction.<sup>4–6</sup> For example, sexual activity is recognized as a known trigger of myocardial infarction, but, precisely because of the very low absolute risk, and keeping in mind the potential benefits, most people at risk of having a myocardial infarction are not discouraged of having sex.<sup>5,7</sup>

However, Dr. Poole missed the point of our study, which explored a biologic mechanism. In theory, any exposure that increases the sympathetic nervous system could trigger a myocardial infarction provided that there is a vulnerable atherosclerotic plaque. Caffeine in coffee is a known stimulant of the sympathetic nervous system. Based on this biologic mechanism, we showed not only that coffee may trigger a myocardial infarction (regardless of the low absolute risk) but also that this effect is modified by habitual intake of coffee and physical activity.<sup>3</sup> These two modifiers indicate that some habitual lifestyles make people less susceptible to surges in sympathetic activity. In our view, the consistency between the

data and the hypothesized biologic mechanism is a major strength of our study.

It was not our intention to alarm people about having a heart attack after a single cup of coffee. We regret that Dr Poole felt apprehensive about having his daily cup of coffee. It is clear that in order to decrease the absolute risk of myocardial infarction one should focus on the traditional known risk factors: no smoking, healthy diet, weight control, and physical activity—and, by all means, enjoy the small pleasures of life!

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## Statins and Cancer

### To the Editor:

In their recently published case-control trial, Coogan et al., reported that statin use was not associated with the risk of 10 cancers at extra-hepatic sites.<sup>1</sup> Different statins are frequently grouped together as a drug class since they share a major biochemical function—inhibition of hepatic HMG-CoA reductase. However, there is considerable evidence that the hydrophobic and hydrophilic statins differ in their biochemical function at extra-hepatic sites.<sup>2</sup> Grouping these compounds together for the purpose of analyzing a cancer risk in extra-hepatic tissues may mask an effect where one exists.

Hydrophilic pravastatin does not enter most normal extra-hepatic cells or malignant cells of extra-hepatic origin. This precludes a protective effect of this statin on the growth of malignant cells at most extra-hepatic sites. Failure to distinguish cancer risk data between users of hydrophobic and hydrophilic statins, therefore, may temper findings of a protective effect where one exists. Furthermore, it is biologically plausible that hydrophilic statins such as pravastatin that lower serum cholesterol but do not enter most extra-hepatic cells may actually increase the risk of some extra-hepatic cancers. Lowering serum cholesterol causes a compensatory induction of HMG-CoA reductase in extra-hepatic cells. We have shown that mevalonate, the product of this enzyme, can promote the growth of tumors derived from human cells in mice.<sup>3</sup> Although lipophilic statins can readily enter extra-hepatic cells to inhibit HMG-CoA reductase activity and compensate for the induction of this enzyme, hydrophilic statins cannot. Grouping of hydrophilic and hydrophobic statins in studies of their extra-hepatic effects without regard to fundamental differences in their extra-hepatic function may, therefore, obscure findings of risk where one exists.

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3. Duncan RE, El-Soheby A, Archer MC. Mevalonate promotes the growth of tumors derived from human cancer cells in vivo and stimulates proliferation in vitro with enhanced cyclin-dependent kinase-2 activity. *J Biol Chem*. 2004;279:33079–33084.

### The authors respond:

Duncan et al<sup>1</sup> suggested that a protective effect of statins on cancer risk may be more apparent among hydrophobic than hydrophilic statins, and that use of the latter may increase cancer risk. In response we have re-examined the association between cancer risk and use of statins using data from our previous report.<sup>2</sup> We classified simvastatin, lovastatin, and fluvastatin as hydrophobic and pravastatin and rosuvastatin as hydrophilic, based on pharmacokinetic data<sup>3,4</sup> and on classification schemes used elsewhere.<sup>5,6</sup> It is unclear where atorvastatin belongs: Dale et al<sup>5</sup> considered it hydrophilic but other sources describe it as lipophilic<sup>3,4,7</sup> In the

present analysis, atorvastatin users were excluded.

The table shows odds ratios among users of all statins combined as given in the original report,<sup>2</sup> and among subjects who used hydrophobic statins exclusively or hydrophilic statins exclusively.

The odds ratios among hydrophobic statin users are within 10% of those reported among all statin users for cancers of the prostate, colorectum, lung, and pancreas and for leukemia. The odds ratios for breast, endometrial, bladder, and kidney cancers are reduced by 20%–40% compared to those reported for all statin use, but all are near 1.0. The odds ratios among hydrophilic statin users for prostate and colorectal cancer were at or near 1.0 and were increased 2-fold for breast and endometrial cancer, although not statistically significantly so.

Numbers were small, but the fact that some odds ratios decreased among the hydrophobic statin users and increased among the hydrophilic statin users, compared to users of all statins, tends to support the reasoning of Duncan et al.<sup>1</sup> Data from the Women's Health Initiative, wherein a reduced risk of breast cancer was observed among hydrophobic statin users but not among pravastatin users, also suggest that the 2 types of statins should be considered separately.<sup>6</sup> Since atorvastatin is the most widely used statin, consensus should be reached on where it fits in this classifica-

**TABLE 1.** Hydrophobic and Hydrophilic Statin Use Among Cancer Cases and Controls

Cancer Type	All Statins		Hydrophobic Statins		Hydrophilic Statins	
	No.	OR* (95% CI)	No.	OR* (95% CI)	No.	OR* (95% CI)
Prostate	153	1.2 (0.9–1.7)	91	1.3 (0.8–1.9)	18	1.1 (0.4–2.5)
Breast	69	1.2 (0.8–1.8)	40	1.0 (0.6–1.7)	10	2.0 (0.7–5.5)
Colorectal	35	0.8 (0.5–1.2)	22	0.8 (0.5–1.2)	6	1.0 (0.4–2.7)
Lung	31	0.7 (0.4–1.1)	22	0.7 (0.4–1.2)	1	—
Endometrial	19	1.3 (0.7–2.4)	8	0.9 (0.4–2.0)	5	2.3 (0.6–8.4)
Bladder	20	1.3 (0.8–2.3)	13	1.1 (0.6–2.2)	4	—
Kidney	16	1.1 (0.6–1.9)	9	0.9 (0.5–1.9)	0	—
Leukemia	15	1.1 (0.6–2.0)	11	1.2 (0.6–2.3)	1	—
Pancreas	10	0.7 (0.3–1.4)	7	0.7 (0.3–1.6)	0	—
All controls	190	—	130	—	20	—
Female controls	91	—	65	—	9	—
Male controls	99	—	65	—	11	—

\*Adjusted as in original report.<sup>1</sup>

tion scheme. More data are clearly needed to address these questions.

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## Silica and Lung Cancer

### To the Editor:

With interest we read Dr. Stayner's commentary<sup>1</sup> on the large European study by Cassidy and colleagues<sup>2</sup> into occupational exposures to crystalline silica and the risk of lung cancer. On the basis of this study and numerous previous investigations, Dr. Stayner gave a personal "yes" to the following question: "Have we reached a point at which there is enough evidence to conclude that, at least under some circumstances, exposure to silica is causally associated with an increased risk of lung cancer?"

We agree. And yet, there is a critical "but." Importantly, we think that such judgment is not enough in terms of prevention. We don't want to fall into the trap of an inevitable call for further research.

However, in order to make sound public health decisions concerning silica at the low end of the exposure scale we need to answer the following causal question posed earlier by, among others, Checkoway and Franzblau<sup>3</sup>: Is silicosis required for silica-associated lung cancer?

Indeed, silicosis could be part of the pathogenetic chain that leads to silica-associated cancer. Alternatively, or additionally, it could be a complex biomarker of exposures to silica and of susceptibility to lung carcinogens, including silica, or susceptibility to lung alterations and disease, including cancer. Following this rationale leads to 2 public health consequences. If silicosis is necessary to increase the risk of lung cancer, then the public health goal should be to prevent silicosis. But if it is not a necessary exposure, then lung cancer risks may be increased at much lower doses of silica not known to cause silicosis, implying that current exposure standards may not be appropriate to prevent lung cancer.

Unfortunately, the studies to date, including the one by Cassidy et al,<sup>2</sup> do not allow unambiguous answers to the questions regarding the causal path(s) that may lead to lung cancer in silica-exposed workers nor do they provide the much-needed insights into possible effects at the low ends of exposure. (The cumulative exposure distribution presented by Cassidy et al differs considerably from distributions found in other studies, including the cited investigation by Hughes et al.<sup>4</sup>)

Future studies should consider the entire exposure-response range between silica dust exposure, silicosis development and lung cancer occurrence, and researchers should analyze data in terms of processes, taking intermediate confounding<sup>5</sup> and possible threshold effects into account.<sup>6</sup>

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### The author responds:

Erren and his coauthors<sup>1</sup> agree that there is sufficient evidence to conclude that "exposure to silica is causally associated with an increased risk of lung cancer." However, they add that there is still a "critical 'but,'" which is whether silicosis is required for silica-associated lung cancer. I agree with the authors that this is indeed an important unresolved question, which has large medico-legal and regulatory implications. If silicosis were necessary for silica-induced lung cancer, then a case of lung cancer without silicosis might be dismissed as being unrelated to silica. If occupational standards for silica are set at a level that would prevent silicosis, then this would also eliminate excess lung cancer. This is somewhat moot given that the OSHA standard for silica is associated with a substantial risk of silicosis<sup>2–4</sup> as well as lung cancer.<sup>5,6</sup> The question has greater relevance for environmental exposures, which are generally below levels where silicosis has been reported to occur. If their conjecture is true, this may suggest that there is a threshold for silicosis and hence for lung cancer. However, the absence of evidence of silicosis for environmental exposures does not necessarily imply a threshold, and might be explained by limitations of the diagnos-

tic tests or low power of studies to detect weak effects.

Most studies have not found an association between silica and lung cancer among individuals without silicosis,<sup>7–10</sup> while some have.<sup>11</sup> Interpretation of these mostly negative findings is complicated by the facts that silicosis may also be regarded as a marker of heavy exposure to silica and that the diagnosis of lung cancer may increase the likelihood of silicosis detection. Study results indicating an increase in lung cancer among persons without silicosis might be attributable to underascertainment of silicosis based on chest radiographs. Comparisons of findings from pathologic exams at autopsy with chest radiographs have shown that the use of chest radiographs may grossly underestimate the prevalence of silicosis.<sup>12</sup>

Finally, Erren et al<sup>1</sup> suggest that further research is needed to resolve this important issue in order to be able to “make sound public health decisions concerning silica at the low end of the exposure scale.” In 2000 Checkoway and Franzblau<sup>13</sup> suggested that the question of whether or not silicosis required for

elevated lung cancer risk “is virtually unanswerable.” Unfortunately this situation has not improved since their review and is unlikely to change in the near future.

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