Epidemiology—Found in Translation

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Summary: We highlight the value of carefully designed observational epidemiologic analyses in translating basic science discoveries to clinical application and in providing the impetus for exploring underlying mechanisms for observed associations. Coupling epidemiologic data with an in vitro screen of commonly used therapeutic agents may identify novel applications for further clinical testing. Cancer Discovery; 1(1); 21–2. ©2011 AACR.

Commentary on Platz et al., p. 68 (4).

In a widely publicized special news report in Science in 1995, Taubes (1) raised the concern that epidemiology had “exhausted its potential”; that the discipline generated “conflicting results,” which “confuses” the public; and that all basic associations had already been found. Trichopolous (2) sounded a more encouraging note in a BMJ editorial the following year. He believed that the opportunity for continued innovation was adequate and that epidemiology was likely to expand and flourish but that consumers of epidemiologic results should keep in mind the limits of epidemiologic investigations. In recent years, epidemiology, often accompanied by a molecular component, has taken a more proactive stance, incorporating advanced technology into population studies to engage basic questions of cancer mechanisms. Although no one could have accurately forecasted the revolutionary impact that high-throughput technologies would have on epidemiologic research over the following 2 decades, the molecular epidemiology approach positioned the field for the pivotal role that epidemiology now plays in bridging basic and clinical research.

In a parallel manner, translational medicine moves “from bench to bedside” or from laboratory experiments through clinical trials to actual point-of-care patient applications. This approach is intrinsically transdisciplinary, as it involves integrative studies with a particular emphasis on investigation of problems that “explicitly destabilize disciplinary boundaries while respecting disciplinary expertise” (3). The article by Platz and colleagues (4) in this issue of Cancer Discovery epitomizes this approach. These authors have integrated data from an efficient, high-throughput in vitro drug screen with available data from a large prospective cohort study in a successful proof-of-principle study.

The notion of exploring epidemiologic associations of common medications with common disease risks in large populations to uncover new disease prevention and treatment indications has strong historical precedent. On the basis of epidemiologic observations, the analgesic aspirin has been used for more than a decade for both primary prevention and prevention of further heart attacks and strokes among persons with a history of these events (5). Raloxifene, a selective estrogen receptor modulator (SERM) originally approved for the prevention of osteoporosis, is now approved by the FDA for breast cancer chemoprevention in high-risk women. This recommendation derives from observational studies within the Multiple Outcomes Raloxifene Evaluation trial for Osteoporosis (6) and the Raloxifene Use for The Heart trial (7), which both demonstrated substantially reduced risks of invasive breast cancer in postmenopausal women. The National Surgical Adjuvant Breast and Bowl Project Breast Cancer Chemoprevention Study of Tamoxifen and Raloxifene confirmed these results, demonstrating about a 50% reduction in risk among women at high risk of breast cancer (8).

Nevertheless, widespread adoption of even commonly used medications for cancer chemoprevention remains a challenge. This problem with adoption has been the experience with tamoxifen, another SERM, which was the first drug for breast cancer chemoprevention for women at high risk. To date, the use of tamoxifen as a preventive cancer agent has been very low, attributed in part to the risk for severe and life-threatening adverse events from tamoxifen, which include endometrial cancer, thromboembolism, and stroke (9). The case of tamoxifen (as well as aspirin and nonsteroidal anti-inflammatory drugs for colon cancer prevention) illustrates the difficulty in identifying agents with a favorable benefit–risk profile that would be acceptable for specific populations to take for years to prevent a disease they may actually never have developed anyway. Another example is finasteride, a 5α-reductase inhibitor approved by the FDA for the treatment of benign prostatic hyperplasia and male pattern baldness, which was associated with a 25% reduction in risk of prostate cancer in the Prostate Cancer Prevention Trial (PCPT). Its disadvantages include a risk, albeit low, of sexual side effects, gynecomastia, and cardiac failure and a slight but significant risk of high Gleason-grade tumors among men taking the compound. These negatives have been enough to prevent approval of the drug for prostate cancer chemoprevention (10).

Some notable developing success stories have come to light. Metformin, one of the most widely prescribed oral hypoglycemic agents, has recently received increased attention because of the potential antitumorigenic effects observed in
in vivo and in vitro investigations and in large observational cancer risk cohort studies. More than 10 ongoing clinical trials are now examining the use of metformin in the treatment of a number of different cancers (11).

We return to the report by Platz and colleagues (4), which clearly demonstrates that epidemiologic methods in an observational cohort study have value in confirming a laboratory-driven hypothesis. This study was not an exercise in data mining or a fishing expedition, which certainly strengthens the results of their cohort analysis. In contrast to many epidemiologic studies, the laboratory data of these researchers provide strong a priori hypothesis-driven evidence of biologic plausibility.

Digoxin is one of the oldest drugs in the pharmacopeia, and its antiproliferative activity is well documented. The reduction in risk for prostate cancer noted for digoxin users in the cohort was of a magnitude similar to that of the PCPT trial data mentioned above. As with any observational study, biases could partially account for these findings. Digoxin users were more likely to be white, less likely to have a family history of prostate cancer, and more likely to use cholesterol-lowering drugs and aspirin regularly, all factors that could contribute to the findings reported by Platz and colleagues (4). In addition, digoxin users tended to be older (and therefore may have surpassed the peak age of receiving a diagnosis of prostate cancer) or, because of their cardiac problems, may not have lived long enough to develop prostate cancer, circumstances also possibly contributing to a reduced risk of prostate cancer in digoxin users. The investigators attempted to adjust for these factors and conducted additional analyses, such as a prostate-specific antigen screening and risk from other cardiac drugs, which all supported their results, but the possibility of residual confounding always remains.

Screening of clinically used drugs with well-established toxicologic, pharmacokinetic, and pharmacodynamic profiles, as was the approach adopted by Platz and colleagues, has a clear advantage. This versatile molecular–integrative approach has implications for both the cost and the duration of drug research and development. A major factor contributing to the logistic and financial bottlenecks in drug development is the time-consuming and less-than-optimal processes for preclinical and clinical testing of drugs. The Pharmaceutical Research and Manufacturers of America have estimated that, on average, the industry spends $0.8 to $1.7 billion and 12 to 15 years of research and development to bring a product to market. Most of the promising candidates must then be tested in animal models, another cost-limiting factor in large-scale drug-screening efforts. The approach taken by Platz and colleagues is also more relevant than are in silico technologies for predicting preclinical toxicologic end points, clinical adverse effects, and metabolism of pharmaceutical substances (12).

This article provides evidence for the rich potential applications of integrative epidemiology (13, 14). The integrative approach strives to reveal basic science findings and simultaneously validate results in well-designed, rigorously controlled epidemiologic settings. Such extensions of the traditional epidemiology paradigm engage genomic, epigenomic, and expression profiles to amplify mechanistic insights. Data (including high-dimensional data) can be combined to reveal new relationships. The participation of scientists in diverse disciplines encourages creative approaches to problem solving, and new informatics tools and data sharing dramatically expand the scope and size of collaborations, enhancing power and study efficiency. Finally, this approach may yet reveal whether risk factors that cause malignancy also contribute to its progression and outcome.

Looking ahead, we see that other malignancies and medications will need to be explored using similar approaches, with an emphasis on refining analyses and mining of existing data. Given the explosion in new technology development and the availability of large population databases, informatics tools are urgently needed to access, store, and manipulate data and to provide broad availability to the community of scientists while simultaneously addressing ethical concerns and removing barriers to legitimate research.

As the U.S. population ages, with a concomitant increase in the prevalence of chronic conditions and in the use of pharmaceuticals to treat these conditions, opportunities abound to study the potential benefits of common medications for cancer prevention, to evaluate novel treatment strategies, and to provide a clearer understanding of mechanisms of action of target drugs and related compounds.

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

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REFERENCES
