EDITORIALS

Passive Smoking and Lung Cancer Risk: What Is the Story Now?

William J. Blot, Joseph K. McLaughlin

In this issue of the Journal, Boffetta et al. *(1)* report results from a large-scale multicenter epidemiologic investigation in Europe launched 10 years ago under the auspices of the International Agency for Research on Cancer (IARC) specifically to evaluate risks of lung cancer associated with exposure to environmental tobacco smoke (ETS). The results have been eagerly awaited because of the size of the study, the special attempts to minimize misclassification of cigarette smoking status, and the ability to control for various potential confounding factors.

While the IARC study is among the largest and most exhaustive examinations of passive smoking's effects on lung cancer, no single study can provide definitive closure to the debate regarding ETS as a cause of cancer among nonsmokers. Nevertheless, the new findings add considerably to the total body of evidence available for assessing whether ETS can be considered a lung carcinogen. The European data show that risk of lung cancer was modestly elevated among nonsmokers exposed as adults at home or in the workplace, with risk tending to rise with the amount of ETS exposure (although not consistently with all measures used), and that there was no increase in risk associated with exposures to ETS in childhood.

As co-authors, we came to the writing of this editorial about the importance of the IARC findings and their place in context with the general literature on passive smoking and lung cancer from different perspectives and initial opinions. One of us (W. J. Blot) had conducted epidemiologic studies on this issue, served as a consultant to the U.S. Environmental Protection Agency in its review of ETS and lung cancer, helped to identify relevant issues in risk assessment for a law firm involved in litigation against the tobacco industry, and acknowledged the possibility that long-term exposure to ETS could increase risk of lung cancer *(2)*. The other (J. K. McLaughlin) had no involvement in studies of ETS and was skeptical of a causal connection. During the course of our review of the article by Boffetta et al. and of the overall epidemiologic and biologic literature on ETS and lung cancer, our views merged. We both came to the conclusion that there was a convincing mosaic of evidence demonstrating that prolonged ETS exposure during adulthood can lead to an increase in risk of lung cancer.

The new European data show that the increase in risk of lung cancer associated with ETS is small, a finding consistent with most other studies. On average, the increase among passive smokers appears to be on the order of about 20%. This is a low excess risk to detect reliably in epidemiologic studies, and it is well below the greater than 10-fold increased risk of lung cancer observed in the average smoker. In 1981, the first two studies reporting elevated rates of lung cancer among nonsmoking women married to smokers in Japan *(3)* and Greece *(4)* cited a nearly doubled risk of lung cancer associated with passive smoking. These initial findings were greeted with skepticism because it was not commonly believed that ETS exposures by nonsmokers typically would be sufficient to double cancer risk. Subsequent studies *(5)* and the current study by Boffetta et al. *(1)* have indicated that the initial risk estimates were indeed too high. Of course, there may be instances where exceptionally heavy ETS exposure may double the risk of lung cancer; however, in the typical spousal- and workplace-exposure situations, the excess risk is probably modest. Furthermore, Boffetta et al. show that lung cancer risk declines following cessation of exposure to ETS, and they found no excess 15 or more years after cessation.

Because a small increase in risk of a disease can be accounted for by subtle biases in study design, conduct, or analysis or by confounding by other risk factors associated with the exposure of interest, there has been intense debate about whether the increased risk of lung cancer observed among nonsmokers exposed to ETS is in fact due to the ETS exposure. It has been noted that nonsmokers married to smokers may differ from nonsmokers married to nonsmokers in ways that could influence lung cancer risk (e.g., the former group may have lower intakes of fruits and vegetables) *(6)* and that misclassification of some smokers as nonsmokers may have upwardly biased results of previous studies *(7)*. The IARC study provides evidence that bias and confounding are unlikely to account for the observed association between passive smoking and lung cancer. Still, evaluating causation in situations where epidemiologic studies identify moderately strong associations (e.g., relative risks of 2–3) is difficult enough, but when observed relative increases in risk are quite small (such as when relative risks equal 1.2), the assessment becomes even more problematic.

Thus, how can a scientist reasonably conclude that exposure to ETS can cause lung cancer? If the only data to evaluate the risk of lung cancer related to ETS exposure were from the study reported in this issue of the Journal or from similar case–control or cohort studies carried out elsewhere over the past decade and a half, a judgment about the causal nature of the association would be tenuous at best. However, risk associated with ETS need not be evaluated in isolation and separately from risk as-

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sociated with cigarette smoking, the primary cause of lung cancer in all western populations.

Despite differences in the relative constituents of ETS and inhaled tobacco smoke *(8)*, breathing ETS can be considered as roughly equivalent to low-intensity cigarette smoking. Various attempts have been made at equilibrating average ETS exposure with low-level smoking. The calibration is typically based on comparisons of relative concentrations of cigarette smoke components in the bodily fluids of passive versus active smokers. Levels of cotinine, the major metabolite of nicotine, in blood, urine, or saliva are most commonly compared, but other compounds, including protein and DNA adducts, have also been employed as markers of tobacco smoke exposure. Multiple studies using such biomarkers have clearly documented that nonsmokers exposed to ETS do indeed inhale and metabolize tobacco smoke *(8)*.

The cotinine research suggests that passive smokers have bodily levels of this nicotine metabolite averaging about 1% those of active smokers *(5,8,9)*. Moreover, studies of 4-aminobiphenyl (a carcinogenic component of cigarette smoke)–hemoglobin adduct levels *(10)* indicate that passive smokers have as much as 14% of the concentrations of active smokers. Because of the numerous carcinogenic compounds in cigarette smoke, it is not clear which of the several biomarkers is the most relevant to examine. Nevertheless, if it is assumed that typical passive smokers continually received roughly the same exposure as smokers of about 0.1–0.3 cigarette per day (corresponding to 0.5%–1.5% of the number of cigarettes smoked by the pack [20 cigarettes]-a-day smoker), then an approximately 20% excess risk of lung cancer is not unexpected. Indeed, extrapolating (extrapolations are needed because the numbers of smokers of such low levels are too few for direct observation) from the known 15- to 20-fold increased risks of lung cancer among current pack-a-day smokers *(11)*, the predicted increases among passive smokers range from 7% to 28% (calculated as follows: 7% = 0.1 cigarette/20 cigarettes × 1400%, and 28% = 0.3 cigarette/20 cigarettes × 1900%, where 1400% and 1900% are the excesses corresponding to relative risks of 15 and 20, respectively, among pack-a-day current smokers).

Such predictions depend on the assumption of a linear relationship between the amount smoked and lung cancer risk. On the other hand, nonlinear models, especially threshold models of disease risk, whereby there is no increase in disease incidence below a certain level of exposure, are plausible. It is generally difficult to discriminate epidemiologically between linear versus threshold models because data at low doses are often scanty. In evaluating the tobacco–lung cancer association, however, there are now ample direct observations of increased risk among passive smokers to indicate that, if there is a tobacco smoke threshold for lung cancer, it is at a level below that experienced by nonsmokers who have spent their adult lives with smokers.

When all the evidence, including the important new data reported in this issue of the Journal, is assessed, the inescapable scientific conclusion is that ETS is a low-level lung carcinogen. Thus, the reduction in risk of lung cancer following cessation of exposure to ETS in the IARC study is a hopeful sign and suggests that measures aimed at the reduction of smoking may benefit not only smokers but also persons with whom they live and work.

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The Retinoblastoma-Like Protein Family: Still in the Shadow of the RB Gene?

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Exactly 10 years ago, the field of cancer biology received a quantum boost with the realization that viral proteins from three unrelated DNA tumor viruses had evolved the capacity to transform cells by binding to a set of cellular proteins that included the retinoblastoma (RB) tumor suppressor gene product *(1–3)*. From a biochemical perspective, this observation allowed the development of a working model where RB can mediate growth inhibition or promote cellular differentiation by reversibly binding to an increasingly complex list of cellular proteins *(4,5)*. From a clinical perspective, this observation has led to the identification of several promising targets for cancer treatment *(6)*, but it has also raised the controversial question of what role ubiquitous DNA tumor viruses may play in human disease *(7–9)*. Over the past several years, two other RB-like gene products,

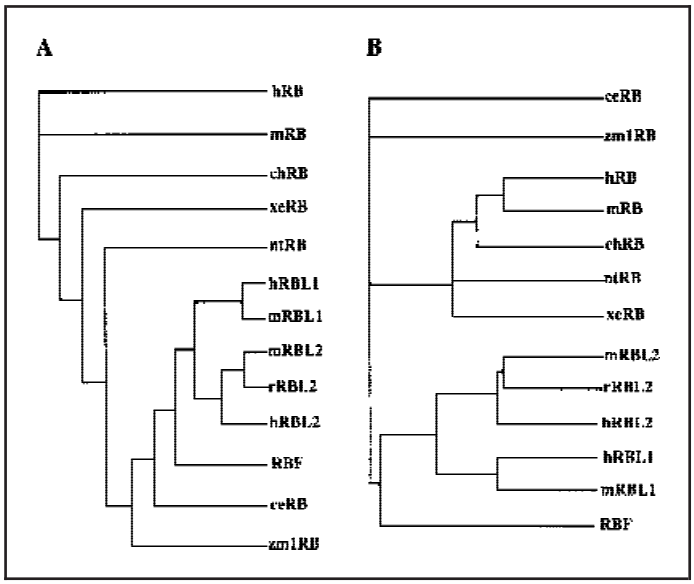

Fig. 1. Phylogenetic analyses demonstrate that the only *Drosophila* RB-like product identified to date (RBF) is more closely related to RBL1/RBL2 than to RB. RB-like protein sequences from the GenBank/European Molecular Biology Laboratory (EMBL) databases were subjected to a clustalw alignment and trees were constructed by use of two different algorithms: either the pauptree **(A)** or pileup **(B)** programs (GCG/Oxford Molecular Company, Madison, WI). Human (document identification No. 190958, hRB), murine (132165, mRB), chicken (631029, chRB), *Xenopus* (348583, xeRB), and newt (1666661, ntRB) homologues for the RB gene; human (1172848, hRBL1) and murine (1871224, mRBL1) homologues for RBL1/p107; human (138150, hRBL2), murine (1255232, mRBL2), and rat (2760811, rRBL2) homologues for RBL2/p130; *Drosophila* RB-like gene (1403031, RBF); *Caenorhabditis elegans* RB-like gene (1946998, ceRB); maize RB-like gene (2352795, zm1RB).

kinase-4 inhibitor (CDKN2a), also serves to accomplish this goal. Therefore, it is surprising that human mesothelioma, which has been linked most tightly with SV40 infection *(7)*, also demonstrates 100% inactivation of the CDKN2a gene in primary tumors *(25)*, which raises questions about the role of TAg in these tumors.

In summary, the requirement for RBL1 and RBL2 inactivation to unmask the fully transformed phenotype of virally infected animal cells *(23,24)* and other recent developments in double-gene knockout murine models *(14)* are exciting findings that are beginning to lead these RB-like members out of the shadow of the RB gene. Focusing higher scrutiny on these genes is overdue, especially if one considers that a phylogenetic analysis shows that RB-like genes from the earliest non-chordate species, such as *Drosophila*, show a closer relationship to RBL1/RBL2 than to the RB product shown in Fig. 1. Regardless of whether or not the RBL1 and RBL2 genes are shown to be frequent targets for mutations in human cancer, our understanding of the RB tumor suppressor pathway will be incomplete until the deceptively subtle contributions of the RBL1 and RBL2 genes are uncovered.

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