Cause and Effect in Lung Cancer

Fueling the Fire

One of the applications of epidemiologic research is to determine causality. This can be difficult to do in even the best situation, when a single, identifiable, quickly pathogenic cause is present. In this situation, Koch’s concepts of causality tend to apply: the agent in question is present in all cases, the agent in question leads to only one disease, and the agent in question will cause disease when healthy subjects are exposed. Unfortunately, in a large number of modern diseases, things are not this straightforward. There is frequently more than one cause for any one disease; a single agent may be a potential cause of multiple conditions; and exposure of healthy subjects to a suspected agent does not necessarily cause the disease and is typically not ethical. Considering host, agent, and environmental interactions is even only part of the picture. Accurately assessing exposure, while considering all other possible factors, is fraught with difficulty.1

Given this, when an association between an exposure and disease is found, the term risk factor is frequently used in place of cause. In the study by Delgado et al in this issue of CHEST (see page 124), evidence is presented to suggest that exposure to wood smoke is a risk factor for lung cancer. Wood smoke exposure occurs generally when subjects use solid fuels. Solid fuels include coal and biomass (wood, dung, and crop residues) and solid fuels have been associated with lung diseases. Delgado et al in Mexico City studied 62 patients with lung cancer, mainly adenocarcinoma (72%). They suggested that in 39% of the patients, wood smoke exposure was the etiologic factor. The authors looked for the presence of p53 mutation, phospho-p53, and the protein MDM2 in Western blot assays from blood samples in their 62 patients with lung cancer and in a group of 18 control subjects, which included patients with obstructive lung disease. The abnormalities in the above markers were similar in those patients in whom wood smoke was the etiologic factor and in the group of patients with a significant history of tobacco use.

When evaluating evidence of an association between an exposure and disease, several criteria need to be considered: there should be a strong association that increases as the exposure increases; the exposure must occur before the disease appears; the association should be consistent and specific; the association should not conflict significantly with what is already known of the disease; and the association should be biologically plausible. Each of these criteria may not be satisfied for any one proposed association, but each should be considered. Finally, the association cannot be due to any source of error.1

Errors in epidemiologic research can be random or systematic. They can lead to spurious associations or real associations that do not represent a cause and effect relationship. Random errors lead to spurious associations. Examples of random errors are imprecise or variable measurements of the factor and disease in question, and errors in representatively sampling the study population. Bias is a systematic error that can lead to spurious associations. For example, biases in the selection of the study sample or in the attainment of information may lead to spurious associations. Real associations that do not represent a cause and effect relationship may occur when the disease leads to the exposure (instead of the reverse) or when a confounding variable is present. A confounding variable is a variable known to be associated with the exposure and to be a risk factor for the disease in question. A confounding variable should not be an intermediate step in the path between the exposure and the disease.2–3

References

The above criteria and discussion of sources of error can be applied to the suggestion in the Delgado study that wood smoke is a risk factor for developing lung cancer. Is there a strong association that increases as the exposure increases? Although the number of lung cancer patients with wood smoke exposure is considerable in the current study, the study is not performed in a manner to assess the strength of association. Prior reports describe odds ratios for the development of lung cancer in nonsmokers exposed to wood smoke of 1.4 to 2.5. This is not a terribly strong association but is a significant one. Most individuals in the current study had long-term exposures to wood smoke. Prior reports have shown the risk to increase with the duration of exposure. At least 20 years of exposure was required in one study, while 50 years of exposure was required in another. Furthermore, women tend to be more affected perhaps because they spend proportionally more time exposed to coal, wood, and other biomass smoke at home compared with men.

Does the exposure occur before the disease occurs? Clearly this is true.

Is the association consistent and specific? As noted above, the suggestion that wood smoke exposure is a risk factor for lung cancer is consistent with prior reports. Others have reported coal smoke to be a more significant risk. Specificity is less important; it may strengthen the association but should not be used to rule it out. Wood smoke can be a risk factor for more than one condition such as chronic obstructive lung disease in adults and respiratory infections, predominantly pneumonia in children. The relative risk of obstructive lung disease is elevated to 3.2 (95% confidence interval, 2.3 to 4.8) in women who are nonsmokers but who are exposed to fumes from solid fuels. Other diseases that have been associated with wood smoke and other solid-fuel exposure include asthma, interstitial lung disease, tuberculosis (even after correction for socioeconomic status), and cancer from the aerodigestive system.

Does the association conflict with what is already known about the disease? We do not think so. It is not unreasonable to think that exposure to wood smoke could be a risk factor for the development of lung cancer given what we know about other risks factors for this disease. There may be carcinogens present in wood smoke similar to carcinogens in tobacco smoke. Polycyclic aromatic hydrocarbons and their metabolites have been shown to be higher in individuals exposed to coal smoke. It has been calculated that in some households, cooking with wood stoves for 3 h/d exposes women to similar amounts of benzo[a]pyrene as smoking two packs of cigarettes per day.

Is the association biologically plausible? The current study suggests biological plausibility by demonstrating similar effects on p53, phospho-p53, and MDM2 protein expression in those with lung cancer exposed to wood smoke as occurs in tobacco smokers. This is perhaps the strongest contribution of this study. Others have shown an increased frequency of a genetic polymorphism in glutathione S-transferase (a substance known to detoxify carcinogens) in nonsmokers with >20 years of indoor wood smoke exposures who acquire lung cancer. The organic extracts of particles from wood combustion were shown to induce skin tumors in mice, though not as strongly as smoky coal emissions. Similarly, inhalation of wood smoke induced lung cancer in mice (but not rats) at a rate greater than control mice but less than coal smoke.

Are there sources of error? The current study does not provide enough detail to accurately assess for sources of error. The measurement of exposure and disease are not provided. The methods for sampling and information biases cannot be assessed with the information provided, though could be present. Precautions in study design or analysis used to eliminate the potential for confounding are not detailed. Theoretically, all known lung cancer risk factors could be potential confounders, and we are not provided with information to rule out that possibility. For example, in a study in rural China where wood smoke exposure was high, radon levels were also found to be elevated (the homes were underground) and to be a potential risk factor for the development of lung cancer.

Overall, there is growing evidence for a potential cause and effect relationship between wood smoke exposure and lung cancer. We believe it is fair to say that wood smoke exposure is a risk factor for the development of lung cancer. The major contribution of the study by Delgado et al is in adding to the biological plausibility of the association.

It is worrisome to think of the potential impact worldwide. Fifty percent of all homes in the world and 90% of the rural households utilize solid fuels, with some regions having a disproportionate high use of these types of fuels for economic reasons.

What should or could be done about this exposure is a difficult question given the socioeconomic of the populations exposed. Obviously, suggestion to improve the economic status of the population and educate the population about this hazard is difficult if not impossible. The poor and disadvantage from the economic point of view are the most affected. A question that needs to be answered soon is if there is
an additive effect between wood smoke and tobacco smoke. We hope that the answer will be no.

Peter J. Mazzone, MD, FCCP
Juan Carlos Chagoya, MD
Alejandro C. Arroliga, MD, FCCP
Cleveland, OH

Dr. Mazzone is Director of the Lung Cancer Program, Dr. Chagoya is a Fellow in the Department of Pulmonary, Allergy, and Critical Care Medicine, and Dr. Arroliga is Professor of Medicine, The Cleveland Clinic Foundation, and Head, Section of Critical Care Medicine, Lerner College of Medicine.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence: Alejandro C. Arroliga, MD, FCCP, Professor of Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, GC-156, Cleveland, OH 44195; e-mail: arroliga@ccf.org

References
16 Desai MA, Mehta S, Smith KR. Indoor smoke from solid fuels: assessing the environmental burden of the disease at national and local levels. WHO Environmental Burden of Disease Series, No. 4. Geneva, Switzerland: World Health Organization, 2004

Pretransplant Pulmonary Evaluation of the Blood and Marrow Transplant Recipient

Thousands of patients undergo blood and marrow transplantation (BMT) each year, mainly for malignant hematologic disorders.1,2 Their underlying diseases, intensive chemotherapy, radiation therapy, and conditioning regimen, with or without total body irradiation, are among the factors that place BMT recipients at high risk for posttransplant pulmonary complications. The development of graft-vs-host disease (GVHD) and the frequent use of immunosuppressive therapy increase this risk to an even higher level in allogeneic BMT recipients.3 As a result, pulmonary complications develop in 30 to 60% of BMT recipients.4–6 With the recent developments and wide use of effective prophylaxis against certain infections, the spectrum of pulmonary complications is changing.7,8 The pretransplant pulmonary evaluation should focus on identifying and modifying the factors that increase the risk for posttransplant complications.

Although epidemiologic studies have identified potential risk factors, it is not easy to predict accurately which BMT recipients will have pulmonary and other complications. Recognition of the prognostic factors that accurately predict the development of serious complications following transplant are important for both health-care providers and patients to make informed decisions based on the balance between the risks and benefits. Cardiopulmonary assessment has become a routine part of pre-BMT evaluation. However, there are scarce data addressing the clinical utility of such an assessment.9 Although conflicting results have been published, most studies9–14 show no correlation between pretransplant cardiac findings and posttransplant complications. In contrast, many publications9,15–19 suggest correlation between pretransplant pulmonary abnormalities and posttransplant complications.

In this issue of CHEST (see page 145), White et al