

# Wood Smoke: Protocol for Evaluating Human Cancer Studies

Addendum: Female breast cancer studies

*Report on Carcinogens Monographs*  
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National Institute of Environmental Health Sciences  
*Your Environment. Your Health.*

# 1. Evaluating Human Cancer Studies of Exposure to Wood Smoke: Addendum

## Background and Objectives

### Background

Wood smoke is a complex mixture consisting of particulate matter, gasses, and hundreds of different chemicals, including U.S. EPA hazardous pollutants and carcinogens (e.g., PAHs, benzene). In the United States, wood smoke is emitted primarily from wood stoves, fireplaces, and boilers used for heating; however, some restaurants use wood for cooking. Over 2 million U.S. households use wood as their primary heating fuel. Biomass and coal together comprise solid fuel. Biomass fuels are considered fuels such as wood, charcoal, animal dung, and agricultural residues. Recently, concerns about woodstove use in the United States have attracted [media attention](#) (Kruzman 2022). Wildfires are increasing in severity and numbers due to climate change.

IARC (2006, published in the (2010) monograph) has characterized indoor emissions from household combustion of biomass fuel (primary wood) as *probably carcinogenic to humans* (2A). The IARC working group concluded there was limited evidence for a causal association with lung cancer.

Because exposure to wood smoke poses a potential carcinogenic hazard for people living in the United States, NIEHS is conducting a cancer hazard evaluation of wood smoke for potential listing in the [Report on Carcinogens](#), a congressionally mandated, science-based public health document. Our review focuses on wood smoke because wood, but not other biomass fuels, is used widely in the United States. The overall cancer hazard evaluation will (1) assess and integrate the evidence from human and animal cancer studies and mechanistic studies, and (2) apply the [RoC listing criteria](#) to the assessment to reach a listing recommendation. A separate evaluation will be conducted for exposure to wildfires if the database is adequate.

Methods for evaluating human cancer studies were published in the [RoC protocol: Human cancer studies on exposure to wood smoke](#) on April 5, 2022 (now referred to as the primary human cancer studies protocol) and focused on esophageal, lung, and nasopharyngeal cancers, which had adequate databases to review at that time. Since this time, additional studies on wood smoke exposure have been published, creating an adequate database to evaluate female breast cancer. In this protocol addendum, we report on breast cancer-specific issues and refer to the primary protocol for the overall method. We also identified additional human epidemiological studies for wildfire exposure. However, the database for evaluating specific cancer types remains inadequate for a systematic review.

## Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity to wood smoke provided by human epidemiology studies based on the [RoC listing criteria](#) (see Section 1.6)

### 1.1. Developing the Framework

The primary human cancer studies protocol describes methods for conducting literature searches and selecting and mapping the literature. We now include breast cancer in our final PECO [population, exposure, comparison group, outcome] (see Table 1-1) because a new study was identified in 2022, bringing the total to four studies in unique populations. These include two case-control studies conducted in low-and-middle income countries – Ethiopia (Hassen et al. 2022) and China (reported in two publications, Liu et al. 2021; Liu et al. 2020) – and a case-control study (White et al. 2014) and a cohort study (White and Sandler 2017) conducted in the United States.

Publication of other human cancer studies on wood smoke exposures did not identify any additional cancer sites for a systemic review and do not require any supplemental methods to the primary protocol.

**Table 1-1. Final PECO**

PECO element	Definition
<b>Population</b>	All (no restrictions)
<b>Exposure</b>	Use wood (or combination of wood and biomass <sup>a</sup> but not coal) for cooking/ heating
<b>Comparison</b>	No or lower exposure to wood for cooking/ heating and not using biomass or coal for cooking/ heating
<b>Outcome</b>	Lung, nasopharyngeal, esophageal cancer, <b>female breast cancer</b>

<sup>a</sup>Includes charcoal

### 1.2. Study evaluation of individual epidemiologic studies

The primary human cancer studies protocol presents guidance for evaluating study informativeness evaluation. This protocol addendum provides methods or information related to female breast cancer study assessment for outcome misclassification and confounding, which are cancer-type specific. Methods for assessing study sensitivity and the potential for biases related to selection and attrition, exposure measurement and misclassification, analysis remain unchanged.

#### 1.2.1. Outcome misclassification

Assessment of the potential for bias (i.e., risk of bias) due to measurement error or other outcome misclassification types considers (1) how well the study outcome represents the outcome of interest, (2) the accuracy of the outcome measurement methods, and (3) the potential for observation bias. The evaluation of follow-up length is usually considered in the assessment of study sensitivity.

## Relevant breast cancer statistics

The age-adjusted annual incidence of female breast cancer (per 100,000 women) in the United States in 2016–2022 is 126.9 and the mortality rate is 19.6 per 100,000 women per year. (U.S. SEER Statistics (<http://seer.cancer.gov/statfacts/html>)). The U.S. death rate is ~40% higher in Black women (27.6) compared to white women (19.7). Female breast cancer incidence rates per 100,000 women are much lower in the low- and middle-income countries where the other two studies were conducted (age-standardized to the world population, [Globocan 2020 projections](#): 39.1 in China and 41.5 in Ethiopia. (Note the U.S. incidence rate standardized to the world population is 90.3).

Survival rates for each cancer inform whether incidence or mortality data are best to use to avoid misclassification of cancer and potential bias in the estimates. Breast cancer survival is very high (~91%) (<https://seer.cancer.gov/statfacts/html/breast.html>) and high in China (82%), which suggests that incidence data is more informative since mortality analysis would miss cases with longer survival and later death (Zeng et al. 2018). (The Chinese case-control study of wood smoke cancer include both breast cancer incidence and mortality analyses. [Liu et al. 2021; Liu et al. 2020]) Survival rates in individuals and populations are most likely affected by socioeconomics because of access to and quality healthcare, affecting cancer screening and treatment, co-morbidities, and other related factors. Cancer mortality could be a better proxy for incidence in low-income countries if survival rates are low. We will search for country-specific survival data for studies published after this addendum.

## Questions and guidance

*Core question:* Is there a concern that the outcome measure does not reliably distinguish between the presence or absence of the cancer under study?

Outcome misclassification questions, guidance, and response options are the same as in Table 1.3 in the primary human cancer studies protocol.

### 1.2.2. Confounding bias

The evaluation of confounding is a multi-step process that involves consideration of both study methods and study findings. This section discusses (1) the potential confounders which would ideally be considered in studies of the four cancers and wood smoke exposure in both high-income and low-and middle-income countries, and (2) methods for evaluating how the authors assessed confounding in the study and/or provided information to inform the evaluation of confounding.

#### Potential confounders

Candidates for evaluation as potential confounders for breast cancer are shown in Table 1-2. Factors which have been established as known risk factors (e.g., identified from authoritative sources such as IARC, RoC, World Cancer Research Fund) for the cancer of interest are shown in Column 2; the factors likely to be related to wood smoke are considered critical potential confounders and shown in Column 3. Major potential confounders are defined as those factors which are likely to be associated with exposure and strongly associated with disease, are not in the causal pathway, and are not correlated with other risk factors. Because the relationship between a cancer risk factor (such as

smoking or alcohol consumption) and exposure (wood smoke) may vary by population, it may not be possible to identify a common set of confounders that should be considered in all studies; confounding will need to be evaluated in a study-specific manner. Also, there are likely to be population-specific risk factors (e.g., diet, household ventilation) associated with socioeconomic status (SES); controlling for SES may only partially control for these features. Finally, because data on the relationship between wood smoke and most potential confounders is lacking, we considered several exposures as potential confounders if it seemed reasonable that they could be associated with wood smoke exposure.

**Table 1-2. Potential confounders for wood smoke used in cooking and heating.**

Cancer site	Cancer risk factors	Potential confounders
<b>Breast</b>	<p><i>Reproductive factors:</i> later age at first full-term pregnancy, lower parity, breastfeeding (preventive)</p> <p><i>Diet, lifestyle, and pharmacologic factors:</i> alcohol consumption, tobacco smoke, obesity (complex pattern dependent on timing), oral contraceptive use, physical activity, SES</p>	<p><b>Wood smoke studies: high-income countries</b>  <i>Reproductive:</i> later age at first full-term pregnancy, lower parity, breastfeeding  <i>Diet, lifestyle factors:</i> alcohol consumption, obesity, physical activity, SES.</p> <p><b>Wood smoke studies: low- or middle-income countries</b>  <i>Reproductive factors:</i> later age at first full-term pregnancy, lower parity, breastfeeding  <i>Diet, lifestyle factors:</i> alcohol consumption, tobacco smoking, obesity, physical activity, SES</p>

Sources: (IARC 2022; WCRF 2018)

<sup>a</sup>Ideally, age, gender, SES, race/ethnicity should be considered in the analysis as effect modifiers.

## Questions and guidance

*Core question:* Is there a concern that either the methods are inadequate or there is inadequate information to evaluate potential confounding?

Confounding questions, guidance, and response options are the same as in Table 1.5 in the primary human cancer studies protocol.

### 1.2.3. Evidence Evaluation Integration

Methods are the same as in the primary human cancer studies protocol. We have limited ability to systematically evaluate key issues across breast cancer studies (e.g., using forest plots and/or text) because of the paucity of studies.

## References

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