**Appendix 1.** **Description of the four-way decomposition approach in more detail**

The four-way decomposition approach is a regression-based method that deconstructs the excess relative risk for the total effect of smoking on bladder cancer (*ERRTE*) into four components. The *ERRTE* is defined on the ratio scale as the relative risk for the total effect of smoking on bladder cancer minus one (*ERRTE=RRTE-1*), and its components are the excess relative risks for the controlled direct effect (*ERRCDE*), the reference interaction (*ERRINTref*), the mediated interaction (*ERRINTmed*), and the pure indirect effect (*ERRPIE*).[1] These causal effects of smoking on bladder cancer risk capture all possible combinations of mediation and interaction, where mediation occurs when the exposure causes the mediator, and interaction occurs when the change in the mediator is necessary for the exposure to have an effect [1].

|  |  |  |
| --- | --- | --- |
| **Component of the *ERR*** | **Mediation** | **Interaction** |
| CDE | No | No |
| INTref | No | Yes |
| INTmed | Yes | Yes |
| PIE | Yes | No |

For a continuous mediator and binary outcome, the approach is based on the following logistic and linear regression models, where the linear regression model is fit only among controls to account for the case-control study design:

  (1)

 (2)

Using the coefficients from the regression models in equations 1 and 2, VanderWeele derived equations 3, 4, 5, and 6 for estimating the relevant causal effects as components of the *ERR*.

  (3)

  (4)

  (5)

  (6)

These four causal effects are calculated based on specific levels of the mediator and covariates. We set indicator variables for each category of race/ethnicity, education level, WHI study arm, and DNA extraction method equal to the proportions observed among controls. Similarly, we set age (65.46), follow-up time in days (5131.51), and year of enrollment (2.38) to their averages in controls. We restricted to non-smoking controls to calculate average M-values in the absence of smoking-related hypomethylation, and used an *m\** of 3.98 for cg05575921, 1.55 for cg03636183, and 3.84 for cg19859270. To calculate the proportion of *ERR*, each component of the *ERR* is divided by the total *ERR* (i.e. *ERRTE*). Confidence intervals and p-values were calculated for the component and proportion estimates based on the delta method.[1]

Within this framework, the *ERRCDE* captures the excess relative risk of bladder cancer attributable to the direct effect of smoking if there were no smoking-mediator interaction and the mediator was fixed to *m\**. The *ERRINTref* captures the excess relative risk of bladder cancer attributable to the change in the effect of smoking that would be observed only if smoking and the mediator occurred together when the mediator is fixed to *m\**. The *ERRINTmed* captures the excess relative risk of bladder cancer attributable both to the change in the effect of smoking that would be observed only if smoking and the mediator occurred together and to the changes in the mediator caused by smoking. The *ERRPIE* captures the excess relative risk of bladder cancer that would be observed if the changes in the mediator caused by smoking occurred in never smokers.

**Appendix 1: References**

[1] VanderWeele T. Explanation in Causal Inference: Methods for Mediation and Interaction. Oxford, New York: Oxford University Press; 2015.

**Appendix 2: Short list of WHI investigators**

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner

Women’s Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*For a list of all the investigators who have contributed to WHI science, please visit:* https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf