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# Invited Perspective: Air Pollution and Breast Cancer Risk: Current State of the Evidence and Next Steps

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The scientific literature on outdoor air pollution and breast cancer risk has expanded dramatically in recent years. In their timely meta-analysis, Gabet et al. (2021) concluded that a 10-$\mu g/m^3$ increase in nitrogen dioxide ($NO_2$), a marker of exposure to traffic, is associated with a 3% higher risk of breast cancer. No overall associations with breast cancer were observed for particulate matter (PM) $\leq 2.5$ μm ($PM_{2.5}$) or $\leq 10$ μm ($PM_{10}$) in aerodynamic diameter.

Breast cancer is a multifactorial disease; even established risk factors, such as postmenopausal obesity and alcohol intake, have modest effects, with estimated risk ratios <2 (American Cancer Society 2019). For a 10-$\mu g/m^3$ increase in $PM_{2.5}$, studies show small but consistent ($\sim 10\%$) increases in risk for better-studied cardiorespiratory outcomes, including lung cancer (Hamra et al. 2014) and cardiovascular disease (Pranata et al. 2020). Therefore, modest associations for air pollution and breast cancer are not altogether surprising.

However, small effect sizes do not necessarily translate to a lack of public health importance—which is well demonstrated by Gabet et al. (2021). The authors used their meta-analytical relative risks, corrected for publication bias, to estimate the cases attributable to air pollution levels under various real-world counterfactual scenarios. The counterfactual scenarios considered included setting the air pollution concentrations to be in compliance with 2008 World Health Organization (WHO) guidelines, a nationwide 1-$\mu g/m^3$ decrease as well as a more ambitious scenario to not exceed the lowest concentrations in France (defined as the fifth percentile), to represent a plausible upper-bound of achievable reductions in air pollution levels. The resulting estimates of breast cancer cases and financial costs attributable to air pollution are only as strong as the underlying data. In addition to the comprehensive meta-analysis to summarize the literature and determine summary estimates, the authors used a nationwide, state-of-the art air pollution exposure model with fine spatial resolution and 10-y breast cancer incidence over the same time period to estimate attributable cases. The authors subsequently estimated both the annual tangible and intangible costs associated with the attributable cases to determine the corresponding financial burden. Compliance with the WHO guidelines alone would not be sufficient to decrease breast cancer incidence [0.01% reduction (95% confidence interval: 0.00, 0.01)]. However, decreasing $NO_2$ levels to the fifth percentile, their most ambitious scenario considered, would reduce breast cancer cases in France by approximately 3% and save over €800 million per year, similar to what has been previously estimated for female lung cancer (Kulhánová et al. 2018). Further, this is likely a conservative estimate given that regulations likely would simultaneously reduce multiple pollutants that may act independently or even synergistically to affect breast cancer risk.

Studies of air pollution and breast cancer have often been hampered by limited statistical power, a challenge exacerbated by the heterogenous etiology of breast cancer. It is well established that breast cancer risk factors and survival may vary by tumor subtype (Carey et al. 2006; Chen and Colditz 2007) and menopausal status (Trentham-Dietz et al. 2014), yet air pollution studies have rarely been well-powered to evaluate this etiologic heterogeneity. Meta-analyses such as the one presented here and pooling efforts are critical to better characterize risk in different tumor subtypes and in premenopausal women.

PM is a complex mixture that varies by geographic region due to varying exposure sources. Few epidemiologic studies of cancer have considered PM chemical components or mixtures (Andersen et al. 2017; White et al. 2019). In the Sister Study, we found that $PM_{2.5}$ component profiles significantly modified associations between $PM_{2.5}$ and breast cancer risk (White et al. 2019). Similarly, there was notable regional heterogeneity in associations between $PM_{2.5}$ and breast cancer in the Black Women's Health Study (White et al. 2021). The lack of association for exposure estimated based on total $PM_{2.5}$ concentrations observed in the meta-analysis by Gabet et al. (2021) may be due to the established heterogeneity in exposure. Efforts to understand how different $PM_{2.5}$ constituent mixtures and sources may influence breast cancer risk are critical to inform future public health interventions.

The conclusions from this meta-analysis are largely based on studies of White women. However, because of historical racial segregation, African American/Black women in the United States tend to live in areas of higher exposure to air and industrial pollution (Mikati et al. 2018; Morello-Frosch and Jesdale 2006; Perlin et al. 2001). In the Multiethnic Cohort Study, Cheng et al. (2020) observed that nitrogen oxide was more strongly related to breast cancer risk in African Americans compared with White women. Evaluating the varying sources of air pollution exposure in diverse populations and exploring potential interactions with social stressors that may enhance susceptibility is needed to fully assess the public health impact of reductions in air pollutant exposure levels.

Most studies have relied on air pollution exposure assessment at a single time point in adulthood. Given the long latency of breast cancer (Lynch and Smith 2005), more recent exposures may not be the most relevant. Evidence suggests that breast tissue is most vulnerable to carcinogenesis during windows of hypothesized biologic susceptibility, such as adolescence and pregnancy

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(Terry et al. 2019). Studies of early life exposure have been limited by the lack of available historical criteria air pollution exposure monitoring during these critical time periods (Bonner et al. 2005; Nie et al. 2007; Shmuel et al. 2017), but future studies will increasingly have the ability to address this challenge.

Gabet et al. (2021) have provided a comprehensive summary of the current evidence on air pollution and breast cancer and an analysis of the public health impact of a reduction in air pollution exposure levels. Future research that contributes to a better estimate of associations with breast cancer subtypes, characterizes air pollutant mixtures and their contributions to risk, explores racial/ethnic disparities, and considers the impact of air pollutants over the life course—particularly during early life—will have the potential to improve our understanding of the effect of air pollution on breast cancer risk.

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