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RESEARCH ARTICLE

Mathematical Modeling of PM2.5 Exposure, COX-2 Enzyme Expression, and Aspirin Intervention in Lung Cancer Risk

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ABSTRACT: Lung cancer remains one of the leading causes of cancer-related mortality worldwide. Epidemiological studies have established a significant correlation between exposure to fine particulate matter (PM2.5) and an increased risk of lung cancer. Notably, PM2.5 derived from wildfire smoke has been shown to exhibit greater toxicity than PM2.5 from other sources, due to its higher oxidative potential and pro-inflammatory composition. The COX-2 enzyme, a crucial mediator of inflammation, is known to be upregulated in response to PM2.5 exposure, promoting tumorigenesis. This study employs a mathematical modeling approach to describe COX-2 induction using a modified Michaelis-Menten equation, incorporating real-world clinical hazard ratios. Furthermore, the inhibitory effect of aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is modeled to determine its potential role in mitigating lung cancer risk. Monte Carlo simulations are conducted to evaluate variability in exposure-response relationships. Our results suggest a dose-dependent reduction in COX-2 levels with aspirin intake, which correlates with a significant decrease in estimated lung cancer risk. These findings provide a quantitative framework for understanding environmental risk mitigation and suggest potential pharmacological intervention strategies.

KEYWORDS: Computational Biology and Bioinformatics, Computational Biomodelling, Environmental Exposure, Monte Carlo Simulation, Lung Cancer.

Introduction

Recent increases in wildfire activity, driven by climate change and prolonged droughts, have raised serious concerns about their impact on public health. Wildfire smoke is a major source of ambient fine particulate matter (PM2.5) and is characterized by a higher concentration of carbonaceous particles, polycyclic aromatic hydrocarbons (PAHs), and toxic metals compared to PM2.5 from urban or industrial sources.[1] This unique chemical composition enhances its potential to induce oxidative stress and airway inflammation. Epidemiological studies have reported significantly higher rates of respiratory-related emergency room visits and hospital admissions during wildfire smoke episodes, especially among children and the elderly.[2,3] These findings suggest that wildfire-derived PM2.5 may pose a greater threat to respiratory health than PM2.5 from other sources, thereby underscoring the need to assess its potential role in long-term diseases such as lung cancer.

Lung cancer is a leading cause of cancer-related deaths, accounting for over 1.8 million deaths annually.[4] Among environmental risk factors, PM2.5 exposure has been identified as a major contributor to lung cancer development through oxidative stress, DNA damage, and chronic inflammation.[5,6] Fine particulate matter penetrates deep into lung tissues, activating pro-inflammatory signaling pathways, including COX-2, a key enzyme involved in inflammation and tumor progression.[7] Studies have shown that COX-2 is upregulated following PM2.5 exposure, linking air pollution to inflammation-driven carcinogenesis.[8] Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is known for its COX-2 inhibitory effects, which may provide protective benefits against pollution-induced lung cancer.[9] Several large-scale epidemiological studies suggest a dose-dependent reduction in lung cancer risk with regular aspirin use.[10,11] However, the precise mechanisms by which aspirin mitigates this risk, particularly in the context of PM2.5-induced inflammation, remain unclear.

This study demonstrates COX-2 as a key factor in PM2.5-induced inflammation, yet PM2.5 also contributes to lung cancer through various biological mechanisms such as oxidative DNA damage, immune dysregulation, and epigenetic changes.[12–14] Studies have shown that fine particulates generate reactive oxygen species (ROS), which lead to DNA strand breaks and adduct formation.[15] These multiple mechanisms highlight that COX-2 is one of the multifactorial responses to air pollution.

This study develops a mathematical framework to model the interplay between PM2.5 exposure, COX-2 expression, and aspirin intervention. A modified Michaelis-Menten equation describes COX-2 induction in response to PM2.5, while a competitive inhibition model quantifies aspirin's effect on COX-2 suppression. Additionally, a hazard ratio-based model estimates lung cancer risk, incorporating the effects of aspirin-mediated COX-2 inhibition. Monte Carlo simulations are performed to analyze probabilistic risk distributions, accounting for real-world variability. By integrating epidemiological data, mechanistic modeling, and pharmacological intervention, this research aims to enhance understanding of lung cancer risk mitigation strategies in high-pollution environments. The findings provide a quantitative basis for aspirin's potential as a chemopreventive agent, guiding future clinical and public health recommendations.

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Methods

COX-2 Expression Model:

The expression of COX-2 in response to PM2.5 exposure was modeled using a Michaelis-Menten-like equation to describe enzyme kinetics with environmental stimuli. The equation is as follows:

$$COX2(PM) = \frac{V_{max} \times [PM]}{K_m + [PM]} \quad (1)$$

Where V_{max} (μg/m^3/s) represents the maximum COX-2 induction, K_m (μg/m^3) is the half-maximal PM2.5 concentration, and $[PM]$ (μg/m^3) denotes the PM2.5 concentration. This equation (1) in this COX-2 model indicates that COX-2 expression increases with rising PM2.5 levels but approaches saturation at higher concentrations.

Aspirin Inhibition Model:

Aspirin inhibits COX-2 activity via competitive inhibition, modifying the standard Michaelis-Menten equation as follows:

$$COX2_{inh}(PM, A) = \frac{V_{max} \times [PM]}{\left(K_m \times \left(1 + \frac{[A]}{K_i}\right)\right) + [PM]} \quad (2)$$

Here, $[A]$ (mg/day) represents the aspirin dose, and K_i (mg/day) is the inhibition constant of aspirin. Our analysis on aspirin as a competitive inhibitor, as in equation (2), demonstrates that increasing aspirin doses lead to a reduction in COX-2 expression, with higher doses yielding more pronounced inhibition.

The K_i value was approximated using published competitive inhibition constants for COX-2. Gierse *et al*. reported K_i values of approximately 11–15 μM for NSAIDs.[16] Although aspirin-specific K_i values are not widely available, using this range allows a biologically plausible estimate in our model. Patrono *et al*. also informed the general concept of aspirin's COX inhibition, but did not report a specific K_i.[17]

Lung Cancer Risk Model:

To estimate lung cancer risk, we incorporated a hazard ratio (HR) framework, where the risk scales exponentially with COX-2 expression. The equation used is:

$$Risk_{lung}(PM, A) = Risk_{base} \times \left(HR_{PM2.5}\right)^{\frac{COX2_{inh}(PM, A)}{V_{max}}} \quad (3)$$

where $Risk_{base}$ is the baseline lung cancer risk, and $HR_{PM2.5}$ is the hazard ratio per 5 μg/m^3 increase in PM2.5 exposure. Equation (3) in this cancer risk model predicts that higher PM2.5 concentrations elevate lung cancer risk, while aspirin-mediated COX-2 inhibition reduces this risk.

Monte Carlo Simulation:

To account for variability in PM2.5 exposure and aspirin dosage, we conducted a Monte Carlo simulation with 10,000 iterations. PM2.5 concentrations were randomly sampled from a uniform distribution (5-50 μg/m^3), and aspirin doses were randomly selected from a set of common clinical doses (0, 50, 100, 150, and 300 mg). The resulting lung cancer risk was computed for each scenario to generate a distribution of risk estimates. The PM2.5 range (5–50 μg/m^3) was chosen to show how people are really exposed to it. In many OECD cities, the values at the lower end of this range are similar to the levels found in urban areas. Concentrations above 35 μg/m^3 are common during wildfires or times of high pollution in places like California, Beijing, and New Delhi.[18,19] This distribution includes both normal and extreme exposure conditions that are important for public health policy.

Results and Discussion

COX-2 Expression in Response to PM2.5 Exposure:

To quantify the relationship between PM2.5 concentration and COX-2 enzyme expression, we utilized a Michaelis-Menten-inspired equation to model the induction of COX-2.

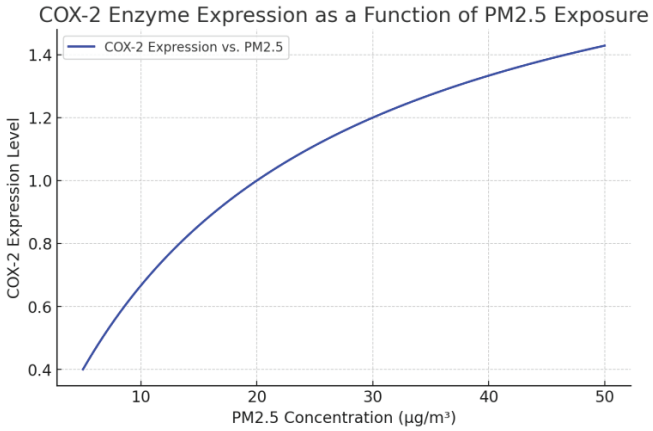

Figure 1: Graph showing the simulated COX-2 expression in response to the increased PM2.5 concentration, using the Michaelis-Menten-like equation. This curve shows a sharp increase in the COX-2 expression at lower PM2.5 levels, indicating increased susceptibility to inflammation, followed by a high-flat phase at higher concentrations, reflecting maximal enzyme induction and suggesting cellular saturation in inflammatory signal transmission. The modelling approach is consistent with the results of the lung toxicology experiment.

Figure 1 demonstrates that COX-2 expression follows a saturation curve in response to increasing PM2.5 exposure. At low PM2.5 concentrations, COX-2 expression increases rapidly, indicating a high sensitivity of inflammatory pathways to even minimal particulate matter exposure. However, at higher PM2.5 levels, COX-2 expression plateaus, suggesting a saturation effect, where the enzyme reaches its maximum induction capacity due to limited cellular response mechanisms. This phenomenon aligns with experimental findings in pulmonary inflammatory studies, where chronic exposure to high pollution levels does not further elevate COX-2 expression beyond a threshold.[7,8]

Impact of Aspirin on COX-2 Expression and Lung Cancer Risk:

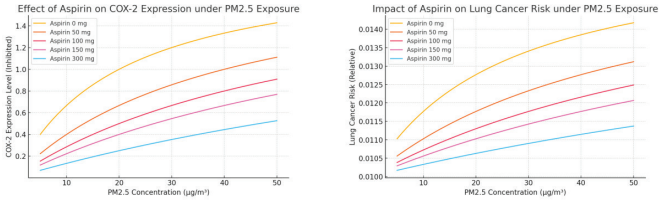

Figure 2: **(a)** Line graph demonstrating the inhibitory effect of aspirin on the COX-2 expression, simulated using the competitive inhibitory extension of the Michaelis-Menten framework. Increasing the dose of aspirin (0-300 mg/day) progressively reduces COX-2 level, with a notable inhibitory effect observed in the 50-150 mg range. **(b)** Exponential curves representing simulated lung cancer risk as a function of PM2.5 concentration, with varying aspirin content (0, 50, 100, 150, 300 mg). Without aspirin, the risk of lung cancer increases rapidly with increasing PM2.5 levels, corresponding to the risk-based epidemiological model. As the aspirin content increases, the risk curves gradually decrease, reflecting suppression of COX-2 expression and reduced inflammatory response. Together, these results suggest that modulating inflammatory pathways using aspirin can significantly change the environmental cancer risk profile.

Aspirin, a well-known COX-2 inhibitor, was examined for its role in mitigating lung cancer risk by suppressing inflammation induced by PM2.5 exposure. Figure 2(a) demonstrated that COX-2 expression is significantly reduced with increasing aspirin dosage, particularly in the range of 50–150 mg, beyond which diminishing returns were observed at 300 mg. This suppression of COX-2 aligns with established biochemical findings that NSAIDs, such as aspirin, can downregulate inflammatory pathways involved in carcinogenesis.[9,11]

Building on these findings, Figure 2(b) modeled lung cancer risk as a function of PM2.5 exposure while incorporating aspirin-mediated COX-2 inhibition. Without aspirin, lung cancer risk increases exponentially with PM2.5 concentration, reflecting real-world epidemiological hazard ratios.[20] However, aspirin intake effectively reduces this risk in a dose-dependent manner, with 50–150 mg providing substantial protective effects. At higher doses (300 mg), the additional reduction in risk is minimal, reaffirming the saturation effect seen in COX-2 suppression.

Specifically, the model estimates that increased aspirin intake from 0 mg to 150 mg/day leads to an approximate 27% reduction in relative lung cancer risk at a PM2.5 concentration of 30 μg/m^3, reflecting the nonlinear suppression of COX-2 activity.

Monte Carlo Simulated Lung Cancer Risk Distribution:

Given individual variations in PM2.5 exposure, genetic susceptibility, and aspirin metabolism, a Monte Carlo simulation was conducted to model lung cancer risk across 10,000 simulated cases.

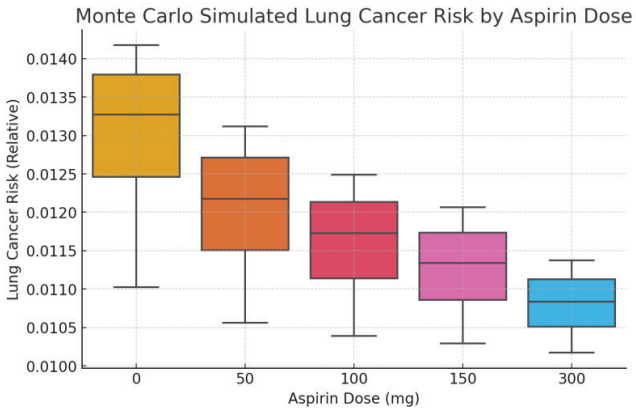

Figure 3: Box plot summarizing the probabilistic distribution of lung cancer risk estimates derived from 10,000 Monte Carlo simulations integrating randomly sampled PM2.5 concentrations (5–50 μg/m^3) and aspirin doses (0–300 mg). Each box represents median values, interquartile ranges, and distribution tails for each aspirin group. The results demonstrate that aspirin reduces both the central tendency and variability of predicted lung cancer risk. This figure illustrates population-level heterogeneity and highlights the value of probabilistic modeling in environmental health risk assessment.

Figure 3 presents the distribution of lung cancer risk across various aspirin dosages, derived from 10,000 Monte Carlo simulations. The box plot reveals the median, interquartile range (IQR), and overall distribution of risk estimates. The median predicted risk for the 0 mg group was approximately 1.25 times higher than that of the 150 mg group, confirming the protective trend observed in deterministic modeling. The interquartile range also narrowed with increasing aspirin dosage. This result suggests a reduction in the variability of risk among individuals.

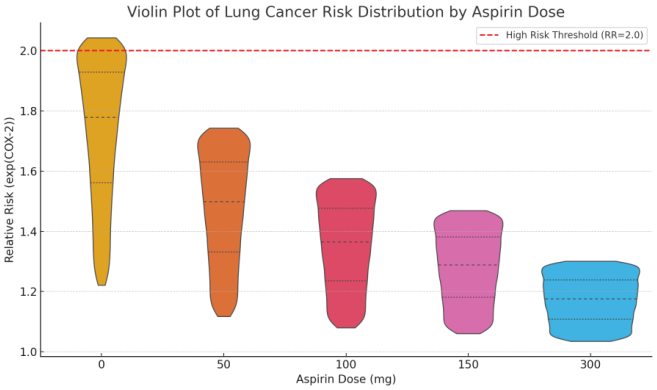

Figure 4: Violin plot showing the distribution of simulated lung cancer relative risk (RR) across 10,000 individuals per aspirin dose group. Width represents probability density. A red dashed line marks the high-risk threshold (RR = 2.0). Aspirin intake at 50 mg or more markedly reduces the density of high-risk outcomes, with little further improvement at higher doses.

The full probability density of lung cancer risk is visualized using a violin plot to enhance the interpretability of risk distribution across different aspirin dosages (Figure 4). This plot captures not only the interquartile range and medians of simulated risk but also the distribution shape for each dosage group. Without aspirin (0 mg), a sizable portion of the population exhibits relative risks (RR) greater than 2.0, as indicated by the red dashed threshold line. In contrast, the 50 mg aspirin

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group shows a significant leftward shift in the entire risk distribution, with the high-risk tail effectively eliminated. This distributional collapse remains consistent across higher doses (100–300 mg), reinforcing the saturation effect of COX-2 inhibition and highlighting 50 mg as a potential threshold for chemopreventive efficacy. The violin plot thus complements the box plot in emphasizing the population-level impact of low-dose aspirin in high-exposure scenarios.

Inflammation Dynamics Under Wildfire-Derived PM2.5:

PM2.5 derived from wildfires is recognized by its high oxidative potential and inflammatory effects. This model indicates a nonlinear relationship between PM2.5 exposure and COX-2 expression, exhibiting saturation kinetics at high concentrations. This association is consistent with previous research in cellular and animal studies demonstrating that PM2.5 induces COX-2 through NF-κB and MAPK signaling pathways.[21,22] Such responses have been observed in cultured lung epithelial cells and animal models, where COX-2 transcription is rapidly upregulated in response to particulate matter in the air. However, human *in vivo* data remain limited. While PM2.5 exposure is known to increase inflammatory cytokines in epidemiologic studies,[23] few studies have quantified COX-2 expression directly in human lung tissue after ambient exposure.[22,24,25] The modeled saturation effect likely reflects biological factors, such as transcriptional feedback or limited enzyme translation capacity, but requires empirical validation in exposed populations.

Modeling Lung Cancer Probability:

The COX-2-based risk model was constructed to reflect known epidemiological associations between PM2.5 and lung cancer. Numerous cohort studies have reported that each 10 μg/m3 increment in long-term PM2.5 exposure is associated with hazard ratios (HRs) ranging from 1.1 to 1.3, which link to a 10–20% increase in lung cancer mortality.[5,26,27] By assuming an HR of approximately 1.05–1.10 per 5 μg/m3, the model generated risk estimates that are broadly consistent with population-level observations, and also aligns with Figure 2(b). Importantly, the model deviates from standard log-linear assumptions by incorporating a saturation constraint derived from inflammatory regulation. This biologically informed curvature predicts attenuated risk increase at higher PM2.5 levels, a feature relevant for high-exposure environments such as wildfires or industrial environments. Under typical urban conditions, where long-term exposure rarely exceeds 50 μg/m3, the model converges with conventional linear risk estimations.

COX-2 as a Mechanistic Driver in Pollution-Associated Carcinogenesis:

COX-2 is identified as a key mediator of inflammation-driven carcinogenesis. The overexpression of this factor in lung cancer, especially in non-small-cell lung carcinoma (NSCLC), has been associated with increased proliferation, angiogenesis, and immune evasion.7 Numerous retrospective studies have highlighted increased tumor COX-2 expression as an indicator of adverse prognosis, with HRs ranging from 1.4 to 1.6 for high-expression compared to low-expression cohorts.[24,28] Although these findings are based on tumor tissue, they support the inclusion of COX-2 as a mechanistic indicator in our model. No prospective studies have evaluated whether elevated COX-2 levels in healthy persons predict future lung cancer incidence, hence constraining the accuracy with which this inflammatory axis can be used for individual risk assessment.

Aspirin as a Dose-Dependent Modulator of Inflammatory Risk:

Incorporating aspirin into the model via a competitive inhibition mechanism revealed its capacity to reduce COX-2 expression and, subsequently, the risk of lung cancer. Simulations indicated substantial COX-2 inhibition at dosages of 50-150 mg/day, with negligible further impact over 300 mg. This outcome aligns with pharmacological studies demonstrating optimal enzyme acetylation at minimal dosages.[29] Observational studies corroborate this, indicating that long-term aspirin users exhibit a reduced risk of lung cancer (relative risks of 0.85-0.90) in meta-analyses.[11,30] However, the model fails to consider individual variations in aspirin metabolism and bleeding-related implications. These criteria are essential for the practical application of chemoprevention methods and must be incorporated into future personalized models.

Our model highlights the potential of aspirin in reducing the risk of lung cancer linked to COX-2, yet it fails to address the drug's acknowledged clinical risks, notably gastrointestinal bleeding and hemorrhagic stroke.[17,31] The negative consequences, especially common among older individuals and those with additional health issues, restrict the widespread use of aspirin as a preventive measure. Future models must meticulously evaluate the benefits of mitigating inflammation against the potential adverse effects, especially when recommending extended or high-dose therapies.

Population-Level Variation Captured Through Monte Carlo Simulation:

Our application of Monte Carlo simulation aligns with established environmental risk assessment methodologies, which frequently utilize probabilistic models to estimate exposure and disease risk in heterogeneous populations. Prior studies, including those examining PAH-related lung cancer risk and PM2.5 exposure among children, demonstrate the utility of Monte Carlo frameworks in capturing real-world variability in pollutant concentrations, physiological parameters, and behavioral factors. In our study, 10,000 iterations integrating variable PM2.5 levels and aspirin dosages produced risk distributions with realistically broad interquartile ranges. Importantly, the findings indicate that aspirin's protective effect is most pronounced in high-exposure simulations, reinforcing the value of probabilistic approaches for identifying population subgroups most likely to benefit from targeted interventions.

■ Conclusion

This study offers an empirical method for evaluating lung cancer risk linked to PM2.5 exposure, mediated by COX-2 inflammatory signaling and influenced by aspirin intervention.

The model incorporates Michaelis-Menten kinetics, competitive inhibition models, and hazard ratios to explain the mechanisms by which environmental exposures may induce cancer and how pharmacological intervention could reduce that risk. The Monte Carlo simulation method effectively simulates individual heterogeneity in exposure and response, thereby improving the translational potential of targeted chemoprevention in high-exposure populations.

Our findings highlight the potential of aspirin to serve as a dose-dependent modulator of inflammation-related cancer risk, especially in environments of acute or chronic exposure to particulate matter. Although these findings originate in biological and epidemiological data, their application in clinical or public health settings requires additional validation. The paradigm reduces intricate carcinogenic pathways to a singular mediator and presumes a uniform pharmacologic response, disregarding individual characteristics such as genetics, consistency, and side effects.

Despite these obstacles, the model provides a reasonable foundation for the integration of environmental toxicology, biomolecular modeling, and public health risk assessment. Further research must integrate multi-pathway mechanisms, co-exposures, and empirical biomarker data to increase precision in forecasting and preventing environmental cancer risk.

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