Exposure to wildfire-related PM$_{2.5}$ and site-specific cancer mortality in Brazil from 2010 to 2016: A retrospective study

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Abstract

Long-term exposure to fine particles ≤2.5μm in diameter (PM$_{2.5}$) has been linked to cancer mortality. However, the effect of wildfire-related PM$_{2.5}$ exposure on cancer mortality risk is unknown. This study evaluates the association between wildfire-related PM$_{2.5}$ and site-specific cancer mortality in Brazil, from 2010 to 2016.

Methods and findings

Nationwide cancer death records were collected during 2010–2016 from the Brazilian Mortality Information System. Death records were linked with municipal-level wildfire- and non-wildfire-related PM$_{2.5}$ concentrations, at a resolution of 2.0° latitude by 2.5° longitude. We applied a variant difference-in-differences approach with quasi-Poisson regression, adjusting for seasonal temperature and gross domestic product (GDP) per capita. Relative risks (RRs) and 95% confidence intervals (CIs) for the exposure for specific cancer sites were estimated. Attributable fractions and cancer deaths were also calculated. In total, 1,332,526 adult cancer deaths (age ≥ 20 years), from 5,565 Brazilian municipalities, covering 136 million adults were included. The mean annual wildfire-related PM$_{2.5}$ concentration was 2.38μg/m$^3$, and the annual non-wildfire-related PM$_{2.5}$ concentration was 8.20μg/m$^3$. The RR for mortality from all cancers was 1.02 (95% CI 1.01–1.03, p < 0.001) per 1-μg/m$^3$ increase of wildfire-related PM$_{2.5}$ concentration, which was higher than the RR per 1-μg/m$^3$ increase of non-wildfire-related PM$_{2.5}$ (1.01 [95% CI 1.00–1.01], p = 0.007, with p for difference = 0.003). Wildfire-related PM$_{2.5}$ was associated with mortality from cancers of the nasopharynx (1.10 [95% CI 1.04–1.16], p = 0.002), esophagus (1.05 [95% CI 1.01–1.08], p = 0.012), stomach (1.03 [95% CI 1.01–1.06], p = 0.017), colon/rectum (1.08 [95% CI 1.05–1.10], p = 0.002), and lung (1.08 [95% CI 1.04–1.12], p = 0.002).
1.11, \( p < 0.001 \)), larynx (1.06 [95% CI 1.02–1.11], \( p = 0.003 \)), skin (1.06 [95% CI 1.00–1.12], \( p = 0.003 \)), breast (1.04 [95% CI 1.01–1.06], \( p = 0.007 \)), prostate (1.03 [95% CI 1.01–1.06], \( p = 0.019 \)), and testis (1.10 [95% CI 1.03–1.17], \( p = 0.002 \)). For all cancers combined, the attributable deaths were 37 per 100,000 population and ranged from 18/100,000 in the Northeast Region of Brazil to 71/100,000 in the Central-West Region. Study limitations included a potential lack of assessment of the joint effects of gaseous pollutants, an inability to capture the migration of residents, and an inability to adjust for some potential confounders.

Conclusions

Exposure to wildfire-related PM\(_{2.5}\) can increase the risks of cancer mortality for many cancer sites, and the effect for wildfire-related PM\(_{2.5}\) was higher than for PM\(_{2.5}\) from non-wildfire sources.

Author summary

Why was this study done?

- Cancer is a leading cause of death worldwide, and cancer-related deaths are projected to increase in the future in all countries, including Brazil.
- Given the increasing frequency and duration of wildfires in recent decades, the effects of wildfires on health need to be better understood.
- The association between wildfire PM\(_{2.5}\) and site-specific cancer mortality remains unclear.

What did the researchers do and find?

- We conducted a retrospective study using data from the Mortality Information System in Brazil to assess whether wildfire-related PM\(_{2.5}\) exposure was associated with mortality from cancer for common cancer sites in adults.
- Municipality-level wildfire- and non-wildfire-related PM\(_{2.5}\) concentrations were estimated and linked with the mortality data.
- We found that wildfire-related PM\(_{2.5}\) exposure was associated with cancer mortality for various common cancer sites in adults in Brazil, and higher effects were observed for wildfire-related PM\(_{2.5}\) than for non-wildfire sources of PM\(_{2.5}\).

What do these findings mean?

- Our findings suggest a high wildfire-related PM\(_{2.5}\) attributable cancer burden, among adults in Brazil.
- The potentially higher risk of wildfire-related PM\(_{2.5}\) compared with non-wildfire-related PM\(_{2.5}\) for all cancers combined suggests that the wildfire control and systemic
prevention strategies are warranted, to reduce cancer mortality risk in Brazil. This could be a health co-benefit of measures to preserve the Amazon rainforest and limit climate change.

Introduction

Wildfires have become more frequent under climate change in recent years and pose a serious threat to human health. Even those living many kilometers away from wildfires are exposed to their smoke; thus, the health impacts of wildfires on the general population are a concern. Wildfires emit high concentrations of air pollutants and hazardous substances, including fine particles ≤2.5 μm in diameter (PM$_{2.5}$), which are regarded as the fire tracer in epidemiological studies.

It has been estimated that 0.62% of all-cause deaths are annually attributable to the acute impacts of wildfire-related PM$_{2.5}$ exposure globally [1]. Apart from death, increased risks of morbidity from respiratory diseases, cardiovascular diseases, low birth weight and preterm birth, and influenza were observed after acute short-term wildfire smoke exposure [2]. Only a few studies have reported the long-term effect of wildfire-related PM$_{2.5}$ (e.g., on general health and lung capacity) [3–6]. Currently, there are research gaps regarding the potential health impacts of long-term wildfire smoke exposure, including on the risk of cancer.

Occupational studies investigating the risk of cancer in firefighters found that firefighters who experienced a high degree of wildfire smoke exposure had higher risks of cancer compared to firefighters exposed to limited wildfire smoke [7–9]. Wildfire-related particles were suggested to have smaller sizes and to contain more oxidative and proinflammatory components than urban sources of particles [2,10]. Thus, wildfire-related PM$_{2.5}$ exposure could also increase cancer mortality in the general population, and the effect may be higher than for non-wildfire PM$_{2.5}$ sources.

The majority of the Amazon rainforest, which represents over half of the planet’s rainforests, is contained within Brazil [11]. The current unprecedented scale of wildfires means many Brazilian people are exposed to fire smoke. Given that toxic smoke from wildfires travels long distances with wind, the assessment of the health effects of wildfires should not be limited to firefighters. If the association between wildfire-related PM$_{2.5}$ and cancer mortality is higher than that for non-wildfire PM$_{2.5}$, cancer could be an important consideration when making public health allocation strategies, especially in Brazil. Assessment of the impact of exposure to wildfire-related PM$_{2.5}$ upon mortality from all types of cancer would also inform public health measures to improve cancer survival.

To address this important issue, in this study, we analyze the associations between wildfire-related PM$_{2.5}$ and cancer-specific mortality, using national mortality data spanning 2010–2016 in Brazil. This study also compares the impacts of non-wildfire-related and wildfire-related PM$_{2.5}$ on cancer mortality. Finally, we estimate regional cancer death counts attributable to wildfire-related PM$_{2.5}$.

Methods

This study is reported as per the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement (S1 RECORD Checklist).
Protocol

This research was conducted using data from the Brazil Mortality Information System. Our study did not employ a prospective protocol. Analyses were first planned and performed in August 2021. During peer review, we added a figure of sensitivity analysis and a table comparing the effect on cancer mortality and drowning (as the negative control). Changes to the paper were also made at the request of peer reviewers.

Study population

Individual death records from 1 January 2010 to 31 December 2016 were collected from the Brazil Mortality Information System (Sistema de Informação sobre Mortalidade) [12]. Complete records from 5,565 municipalities, covering about 99.98% of the Brazilian population distributed in the 5 regions of Brazil, were included in the analyses. Municipalities with missing mortality data and records with missing age or sex were excluded from the analyses. Each death record included information on municipality, age, sex, date, and primary cause of death, coded according to the International Statistical Classification of Diseases and Related Health Problems—10th Revision (ICD-10, https://icd.who.int/browse10/2019/en). Cancer deaths were totaled for every municipality-year and grouped as follows: oral (C00–C10, C12–C14), nasopharynx (C11), esophagus (C15), stomach (C16), colon/rectum (C18–C21), liver (C22), gallbladder (C23–C24), pancreas (C25), larynx (C32), lung (C33–C34), bone (C40–C41), skin (C43), breast (C50), cervix (C51), uterus (C54–C55), ovary (C56), prostate (C61), testis (C62), kidney (C64–C66), bladder (C67), brain (C70–C72), lymphoma (C81–C85), and leukemia (C91–C95). The death counts were also divided by sex and age groups (male versus female; aged 20–59 versus 60+ years). Child and adolescent cancers are not the same as adult cancers, with different types, treatment, and survival [13,14]; thus, only cancer deaths in individuals aged ≥20 years were included in the analyses.

Pollution exposure

Daily all-source PM$_{2.5}$ and wildfire-related PM$_{2.5}$ were estimated during the study period; the details of model development and validation have been described in our previous work [1,15,16]. In summary, fire-induced change in PM$_{2.5}$ was predicted by the chemical transport model GEOS-Chem (version 12.0.0) as the difference in PM$_{2.5}$ from simulations with and without fire emissions. The anthropogenic emissions from 5 fire sources (boreal forest fires; tropical forest fires; savanna, grassland, and shrubland fires; temperate forest fires; agricultural waste burning) were from the EDGAR v4.2 inventory (http://edgar.jrc.ec.europa.eu/). The all-source PM$_{2.5}$ was then downscaled from the original resolution of 2.0° latitude × 2.5° longitude to a higher resolution of 0.25° × 0.25° using a random forest model, taking into account the impacts of meteorology on PM$_{2.5}$ in the fine grid cells. The downscaled all-source PM$_{2.5}$ from GEOS-Chem was validated against ground-level PM$_{2.5}$ monitored at 6,882 global sites, with a high coefficient of determination of up to 0.865 [1]. Then wildfire-related PM$_{2.5}$ was derived as the product of all-source PM$_{2.5}$ and the wildfire-to-all ratio calculated by the GEOS-Chem model. Annual mean non-wildfire- and wildfire-related PM$_{2.5}$ were calculated from daily non-wildfire PM$_{2.5}$ and wildfire-related PM$_{2.5}$ during 2000–2016. The official geographical boundaries of municipalities were downloaded from the website of the Brazilian Institute of Geography and Statistics (BIGS; https://www.ibge.gov.br/pt/inicio.html).

Other covariates

Daily mean temperatures were calculated from hourly temperature records from the European Centre for Medium-Range Weather Forecasts Reanalysis v5 (ERA5) dataset, with a 0.25° ×
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Statistical analysis: PM2.5–cancer mortality association

A variant difference-in-differences (DID) approach with quasi-Poisson regression was applied to examine the associations between exposure and all cancers and site-specific cancer mortality. The essence of the variant DID design is that the difference in temporal concentrations (wildfire- and non-wildfire-related PM2.5 in this study) is related to the difference in cancer mortality rates in each location during the study period [20]. Factors that keep stable during the study time and time trends in confounders that changed similarly across locations are controlled. Confounders that correlate with the wildfire- or non-wildfire-related PM2.5 concentrations and that change differently across regions by time should be adjusted in the model. The parameters of the variables are defined based on previous studies [21–23]. Temperature has been demonstrated to be associated with cancer mortality and thus is fitted in the main model [24,25]. Socioeconomic factors are represented by GDP per capita. Cancer-specific mortality associations were evaluated using the following model:

$$
\ln[E(Y_{st})] = \beta_0 + \beta_1 I_s + \beta_2 I_t + \beta_5 PM_{2.5,s,t} + \ln(Pop_{s,t}) + \beta_4 Temp_{summer,t} + \beta_6 Temp_{winter,t} + \beta_5 SD(Temp_{summer,t}) + \beta_6 SD(Temp_{winter,t}) + \beta_8 GDP_{per\,capita,t}
$$

where $Y_{st}$ represents the number of cases in municipality $s$, year $t$; $I_s$ is a dummy variable for municipality $s$; $I_t$ is a dummy variable for year $t$; $PM_{2.5,s,t}$ is the average wildfire- or non-wildfire-related PM2.5 in municipality $s$, year $t$; $\beta$ is the intercept or slope for the linear terms; $\ln(Pop_{s,t})$ is an offset term representing the natural log of the population in municipality $s$, year $t$; and Temp values are the means of summer and winter temperatures and their standard deviations (SDs).

We also performed subgroup analyses by age group (20–59 years versus 60 years or above) and sex. We used fixed-effects meta-analyses to compare the effect estimates between sex and age groups. All results are expressed as relative risks (RRs) and 95% confidence intervals (95% CIs) per 1-μg/m³ increase in annual average PM2.5 concentration. Several sensitivity analyses were performed—adding gas pollutants (CO, NO₂, O₃, SO₂), Normalized Difference Vegetation Index (NDVI), and nighttime light (NTL); modeling the summer and winter temperatures using natural cubic splines with 2 or 3 degrees of freedom; and removing GDP per capita from the main model—to check the robustness of the main findings.

R software (version 3.4.3; https://www.r-project.org/) was used to perform all data analyses. The “gnm” package was used to perform the conditional Poisson regression model. The “mvmeta” package was used to compare the subgroup differences. Statistical significance was defined as a 2-sided $p$-value $< 0.05$.

This study was approved by the Monash University Human Research Ethics Committee. The Brazilian Ministry of Health did not require ethics approval or informed consent for secondary analysis of aggregated anonymized data from the Mortality Information System.
Results

A total of 1,332,526 adult cancer death records from 5,565 municipalities, with municipality areas ranging from 3.56 to 159,533 km$^2$, covering almost the total population of Brazil from 2010 to 2016 were included in the main analyses. Cancer death counts from common cancer sites are presented in S1 Table. Of all records included, death counts varied from 0 to 123,571 within municipalities. Mean annual wildfire-related PM$_{2.5}$ was 2.38 μg/m$^3$ (ranging from 0.60 to 12.49 μg/m$^3$), with regional variability (Table 1). The distribution of wildfire-related PM$_{2.5}$ showed a radial pattern from municipalities in the Central-West Region and surrounding areas (Fig 1). The proportion of wildfire-related PM$_{2.5}$ of all-source PM$_{2.5}$ is shown in S1 Fig. High total PM$_{2.5}$ concentration in the North Region was observed, which may be associated with volcanic SO$_2$, lightning NOx, biogenic soil NO, ocean emissions, biogenic emissions, very short-lived iodine and bromine species, and decaying plants (S2 Fig).

Table 1. Descriptive characteristics of study participants and summary statistics for the 5,565 municipalities in Brazil.

| Characteristic                  | Number of participants | Mean (SD) | Median | Minimum | Maximum |
|--------------------------------|------------------------|-----------|--------|---------|---------|
| **Health data**                |                        |           |        |         |         |
| Cancer deaths (persons)        | 1,332,526              | 239 (2,350) | 29     | 0       | 123,571 |
| Age (years)                    |                        |           |        |         |         |
| 20–59                          | 420,792                | 7 (1,586)  | 76     | 0       | 39,375  |
| ≥60                            | 911,734                | 164 (767)  | 22     | 0       | 84,196  |
| Sex (persons)                  |                        |           |        |         |         |
| Males                          | 709,535                | 128 (1,163)| 17     | 0       | 61,533  |
| Females                        | 622,887                | 112 (1,189)| 12     | 0       | 62,038  |
| **Demographic data**           |                        |           |        |         |         |
| Population size (persons)      | 199,997,499            | 35,938 (212,436)| 11,306| 0       | 11,779,640 |
| Adult population size (persons)| 136,303,472            | 24,493 (152,255)| 7,490 | 0       | 8,457,673 |
| Age (years)                    |                        |           |        |         |         |
| 20–59                          | 112,977,597            | 20,301 (124,834)| 6,097 | 460     | 6,932,700 |
| ≥60                            | 23,325,874             | 4,192 (27,744)| 1,392 | 89      | 1,524,974 |
| Sex (persons)                  |                        |           |        |         |         |
| Males                          | 65,496,608             | 11,769 (70,120)| 3,816 | 306     | 3,902,467 |
| Females                        | 70,806,864             | 12,724 (82,151)| 3,704 | 274     | 4,555,206 |
| **Environmental data**         |                        |           |        |         |         |
| Wildfire PM$_{2.5}$ (μg/m$^3$) | —                      | 2.38 (1.62)| 1.94  | 0.60    | 12.49   |
| lag1$^a$                       | —                      | 2.26 (1.48)| 1.85  | 0.58    | 11.08   |
| lag0–1$^b$                     | —                      | 2.32 (1.55)| 1.89  | 0.59    | 11.79   |
| Non-wildfire PM$_{2.5}$ (μg/m$^3$) | —                    | 8.20 (1.50)| 7.89  | 4.16    | 17.11   |
| lag1$^a$                       | —                      | 8.22 (1.48)| 7.92  | 4.16    | 16.86   |
| lag0–1$^b$                     | —                      |           |        |         |         |
| Mean summer temperature (˚C)   | —                      | 25.27 (1.86)| 25.47 | 18.23   | 29.92   |
| SD of summer temperature (˚C)  | —                      | 1.45 (0.35)| 1.48  | 0.41    | 2.63    |
| Mean winter temperature (˚C)   | —                      | 21.33 (4.47)| 21.64 | 10.55   | 30.28   |
| SD of winter temperature (˚C)  | —                      | 1.96 (1.21)| 1.57  | 0.37    | 4.85    |
| **Socioeconomic data**         |                        |           |        |         |         |
| GDP per capita (USD)           | —                      | 4,333 (4,636.40)| 3,249 | 807     | 146,701 |

$^a$lag1 refers to 1 year prior to the current year.

$^b$lag0–1 refers to 2-year average (current year and 1 year prior to the current year) concentration.

GDP, gross domestic product; SD, standard deviation; USD, US dollars.

https://doi.org/10.1371/journal.pmed.1004103.t001
The associations between a 1-μg/m³ increase of wildfire-related PM$_{2.5}$ concentration and cancer mortality risks for single lag years and moving average lag years are shown in S3 Fig. Significant associations were observed in the current year and 1 year before the death for all cancers combined. Thus 2-year moving average concentration was used in later analyses. The
relationships between wildfire-related PM\(_{2.5}\) and total cancer mortality modeled by natural cubic splines with 1–4 degrees of freedom were similar, and linear analysis had the lowest QBIC (Quasi-Bayesian Information Criteria), indicating linear associations between wildfire-related PM\(_{2.5}\) and total cancer mortality (S4 Fig). Compared with non-wildfire PM\(_{2.5}\), people were more vulnerable to wildfire-related PM\(_{2.5}\) (Fig 2).

The RR for mortality for all cancers combined per 1-\(\mu\)g/m\(^3\) increase of wildfire-related PM\(_{2.5}\) concentration was 1.02 (95% CI 1.01–1.03, \(p<0.001\)). Cancer mortality was higher for wildfire-related PM\(_{2.5}\) than for other sources of PM\(_{2.5}\) (1.01 [95% CI 1.00–1.01], \(p=0.007\), \(p\) for difference = 0.003). Wildfire-related PM\(_{2.5}\) was associated with mortality from cancers of the nasopharynx (1.10 [95% CI 1.04–1.16], \(p=0.002\)), esophagus (1.05 [95% CI 1.01–1.08], \(p=0.012\)), stomach (1.03 [95% CI 1.01–1.06], \(p=0.017\)), colon/rectum (1.08 [95% CI 1.05–1.11], \(p<0.001\)), larynx (1.06 [95% CI 1.02–1.11], \(p=0.003\)), breast (1.04 [95% CI 1.01–1.06], \(p=0.007\)), prostate (1.03 [95% CI 1.01–1.06], \(p=0.019\)), and testis (1.10 [95% CI 1.03–1.17], \(p=0.002\)) (Fig 3). However, no significant association with lung cancer mortality was observed (1.00 [95% CI 0.98–1.01], \(p=0.503\)). RRs associated with wildfire-related PM\(_{2.5}\) were greater than RRs for non-wildfire PM\(_{2.5}\) for colorectal (1.03 [95% CI 1.02–1.04], \(p=0.001\)) and testis...
(1.10 [95% CI 1.03–1.17], p < 0.001) cancer mortality. Though no significant association was observed between cervical cancer and wildfire-related PM$_{2.5}$, adverse effects (1.03 [95% CI 1.01–1.04], p = 0.001) were found for non-wildfire PM$_{2.5}$ (S5 Fig).

To further examine vulnerable cancer sites and population subgroups, stratified analyses for mortality from potentially affected cancers by age and sex are shown in Fig 4. There was no significant difference for all cancers combined between males (1.02 [95% CI 1.01–1.04], p < 0.001) and females (1.02 [95% CI 1.00–1.03], p = 0.011; p for difference = 0.337) or between

| Cancer Sites          | RR (95% CI)     | p-value |
|-----------------------|-----------------|---------|
| Total                 | 1.02 (1.01 to 1.03) | <0.001  |
| Oral                  | 1.01 (0.98 to 1.05) | 0.525   |
| Nasopharynx           | 1.10 (1.04 to 1.16) | 0.002   |
| Oesophagus            | 1.05 (1.01 to 1.08) | 0.012   |
| Stomach               | 1.03 (1.01 to 1.06) | 0.017   |
| Colon rectum          | 1.08 (1.05 to 1.11) | <0.001  |
| Liver                 | 1.01 (0.98 to 1.04) | 0.411   |
| Gallbladder           | 0.99 (0.96 to 1.03) | 0.782   |
| Pancreas              | 1.01 (0.98 to 1.05) | 0.439   |
| Larynx                | 1.06 (1.02 to 1.11) | 0.003   |
| Lung                  | 1.00 (0.98 to 1.02) | 0.913   |
| Bone                  | 1.05 (0.99 to 1.10) | 0.093   |
| Skin                  | 1.06 (1.00 to 1.12) | 0.033   |
| Breast                | 1.04 (1.01 to 1.06) | 0.007   |
| Cervix                | 0.99 (0.97 to 1.02) | 0.638   |
| Uterus                | 0.99 (0.95 to 1.03) | 0.690   |
| Ovary                 | 1.03 (0.99 to 1.07) | 0.107   |
| Prostate              | 1.03 (1.01 to 1.06) | 0.019   |
| Testis                | 1.10 (1.03 to 1.17) | 0.002   |
| Kidney                | 1.00 (0.96 to 1.04) | 0.882   |
| Bladder               | 1.02 (0.98 to 1.06) | 0.440   |
| Brain                 | 1.00 (0.97 to 1.03) | 0.875   |
| Lymphoma              | 0.99 (0.97 to 1.02) | 0.665   |
| Leukaemia             | 1.00 (0.97 to 1.03) | 0.846   |

Fig 3. Estimated RRs and 95% CIs for the association between a 1-μg/m$^3$ increase in 2-year average (lag0–1) wildfire-related PM$_{2.5}$ and all-cancer and site-specific cancer mortality, from 2010–2016. The vertical dashed line represents the reference line for RR = 1, helping to compare the effect estimates with the null hypothesis; the error bars represent 95% CIs. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI, confidence interval; RR, relative risk.
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| Cancer Sites       | RR (95% CI)       | p-value  | p-value for difference |
|--------------------|-------------------|----------|------------------------|
| Total              | 1.02 (1.01 to 1.04) | <0.001   | 0.337                  |
| Nasopharynx        | 1.02 (1.00 to 1.03) | 0.011    |                        |
| Oesophagus         | 1.02 (1.00 to 1.03) | 0.024    | 0.325                  |
| Stomach            | 1.03 (1.01 to 1.04) | <0.001   |                        |
| Colon rectum       | 1.06 (1.00 to 1.12) | 0.057    | 0.011                  |
| Larynx             | 1.19 (1.11 to 1.28) | <0.001   |                        |
| Colon rectum       | 1.09 (1.03 to 1.16) | 0.004    | 0.786                  |
| Oesophagus         | 1.11 (1.03 to 1.18) | 0.004    |                        |
| Stomach            | 1.04 (1.00 to 1.08) | 0.039    | 0.468                  |
| Colon rectum       | 1.07 (1.01 to 1.13) | 0.021    |                        |
| Larynx             | 1.02 (0.97 to 1.07) | 0.493    | 0.164                  |
| Colon rectum       | 1.06 (1.02 to 1.11) | 0.004    |                        |
| Larynx             | 1.04 (1.00 to 1.07) | 0.224    | 0.715                  |
| Colon rectum       | 1.03 (0.99 to 1.07) | 0.168    |                        |
| Larynx             | 1.02 (0.98 to 1.06) | 0.318    | 0.437                  |
| Colon rectum       | 1.04 (1.01 to 1.07) | 0.016    |                        |
| Larynx             | 1.08 (1.04 to 1.11) | <0.001   | 0.742                  |
| Colon rectum       | 1.08 (1.05 to 1.12) | <0.001   |                        |
| Larynx             | 1.12 (1.08 to 1.16) | <0.001   | 0.017                  |
| Colon rectum       | 1.06 (1.03 to 1.09) | <0.001   |                        |
| Larynx             | 1.08 (1.03 to 1.12) | 0.001    | 0.117                  |
| Colon rectum       | 1.01 (0.94 to 1.08) | 0.771    |                        |
| Larynx             | 1.05 (1.00 to 1.11) | 0.058    | 0.696                  |
| Colon rectum       | 1.07 (1.02 to 1.12) | 0.006    |                        |
| Larynx             | 1.06 (1.00 to 1.13) | 0.049    | 0.828                  |
| Colon rectum       | 1.02 (0.96 to 1.09) | 0.510    |                        |
| Larynx             | 1.00 (0.94 to 1.06) | 0.964    | 0.046                  |
| Colon rectum       | 1.09 (1.02 to 1.16) | 0.006    |                        |
| Larynx             | 1.13 (1.07 to 1.19) | <0.001   | 0.380                  |
| Colon rectum       | 0.95 (0.89 to 1.02) | 0.152    |                        |
| Larynx             | 1.23 (1.16 to 1.31) | <0.001   | < 0.001                |
| Colon rectum       | 0.98 (0.92 to 1.04) | 0.481    |                        |
| Larynx             | 1.12 (1.03 to 1.20) | 0.005    | 0.063                  |
| Colon rectum       | 1.03 (1.01 to 1.06) | 0.013    |                        |
| Larynx             | 1.03 (1.00 to 1.06) | 0.083    | 0.382                  |
| Colon rectum       | 1.05 (1.01 to 1.09) | 0.008    |                        |
| Larynx             | 1.03 (1.01 to 1.06) | 0.014    |                        |
| Colon rectum       | 1.12 (1.06 to 1.19) | <0.001   | 0.006                  |
| Larynx             | 1.03 (1.00 to 1.06) | 0.031    |                        |
| Colon rectum       | 1.10 (1.04 to 1.17) | 0.002    |                        |

Relative risk for every 1 µg/m³ increase

[Table and graph showing relative risk for different cancer sites and age groups]
Discussion

We did a national analysis of the association between wildfire-related PM$_{2.5}$ exposure and cancer mortality. We found that wildfire-related PM$_{2.5}$ was significantly associated with an increased risk of all-cause cancer death in Brazil during 2010–2016. Increased risks were detected for cancers of the nasopharynx, esophagus, stomach, colon/rectum, larynx, skin, breast, prostate, and testis. Notably, we found that people may be more vulnerable to wildfire smoke than non-wildfire PM$_{2.5}$ sources, especially for esophageal, colorectal, and testicular cancer. To our best knowledge, this study is the first to specifically focus on associations between wildfire-related PM$_{2.5}$ and site-specific cancer mortality. The disease burden attributable to wildfire may be higher than previous estimates based on respiratory and cardiovascular diseases.

Cancer mortality is an outcome reflecting both the incidence of cancer and survival after diagnosis [26]. The association between wildfire-related PM$_{2.5}$ and cancer mortality may be explained by increased cancer incidence and shortened survival. PM$_{2.5}$ is classified by the...
International Agency for Research on Cancer (IARC) as a Group 1 carcinogen for sufficient evidence in increasing lung cancer risk [27]. Assuming

Wildfire particles are smaller than those from urban sources, and particles reaching miles away may have greater oxidative potential [41,42]. These characteristics of wildfire particles pose a significant health risk to individuals. The health impact of short-term exposure to

Table 2. Cancer deaths and attributable cancer deaths associated with 2-year average wildfire-related PM$_{2.5}$ exposure by region, age, sex, and year during 2010–2016.

| Factor | Number of cancer deaths | Cancer mortality/10$^6$ | Attributable cancer deaths 95% CI | Attributable cancer deaths/10$^6$ 95% CI |
|--------|-------------------------|-------------------------|-----------------------------------|----------------------------------------|
| Total  | 1,332,526               | 977.62                  | 50,621 (28,212–72,822)             | 37.14 (20.70–53.43)                    |
| Region |                         |                        |                                   |                                        |
| Central-West | 83,147                 | 819.13                  | 7,229 (4,029–10,399)               | 71.21 (39.69–102.45)                   |
| Northeast | 281,089                 | 781.27                  | 6,566 (3,659–9,446)               | 18.25 (10.17–26.25)                    |
| North | 60,475                  | 596.03                  | 3,743 (2,086–5,384)               | 36.89 (20.56–53.06)                    |
| Southeast | 646,683                 | 1,082.00                | 22,725 (12,665–32,692)             | 38.02 (21.19–54.7)                     |
| South | 261,132                 | 1,288.86                | 10,358 (5,773–14,901)             | 51.12 (28.49–73.35)                    |
| Age (years) |                         |                        |                                   |                                        |
| 20–59 | 420,792                 | 53.21                   | 12,381 (1,635–22,978)             | 10.96 (1.45–20.34)                     |
| 60+ | 911,734                 | 558.38                  | 41,350 (23,198–29,304)             | 177.27 (99.45–254.24)                  |
| Sex |                         |                        |                                   |                                        |
| Males | 709,535                 | 154.76                  | 32,549 (16,968–47,946)             | 49.70 (25.91–73.20)                    |
| Females | 622,887                | 125.67                  | 18,074 (4,210–31,767)             | 25.53 (2.95–44.86)                     |
| Year |                         |                        |                                   |                                        |
| 2010 | 172,715                 | 133.32                  | 6,361 (3,545–9,150)               | 4.91 (2.74–7.06)                       |
| 2011 | 177,971                 | 134.98                  | 6,902 (3,847–9,930)               | 5.23 (2.92–7.53)                       |
| 2012 | 184,680                 | 137.71                  | 6,467 (3,604–9,303)               | 4.82 (2.69–6.94)                       |
| 2013 | 190,192                 | 139.53                  | 6,491 (3,617–9,338)               | 4.76 (2.65–6.85)                       |
| 2014 | 195,432                 | 141.07                  | 6,906 (3,849–9,935)               | 4.98 (2.78–7.17)                       |
| 2015 | 203,071                 | 144.26                  | 8,785 (4,896–12,638)              | 6.24 (3.48–8.98)                       |
| 2016 | 208,465                 | 145.77                  | 8,709 (4,854–12,529)              | 6.09 (3.39–8.76)                       |
wildfire smoke has been well documented for all-cause mortality [1,43]. In comparison with the short-term effects of wildfire smoke, far fewer studies have included longer term health impacts, and no study to our knowledge has shown an association between wildfire particles and cancer. Some studies have reported an association between all-source PM$_{2.5}$ and cancer risks [44]. Our results show a higher risk for wildfire-related PM$_{2.5}$ than for PM$_{2.5}$ from non-wildfire source, for deaths from all cancers combined. Furthermore, we might expect that cancer at different sites would show different responses to wildfire-related PM$_{2.5}$ exposure.

In addition to the short-term effect, other effects of wildfire smoke exposure on cancer risk are still unknown in the general population, but higher cancer risks were observed among wildfire firefighters who were most exposed to wildfire smoke. The American Cancer Society (ACS) Cancer Prevention Study II demonstrated that wildland firefighters have an increased risk of lung cancer mortality [45]. Studies from Australia showed possible increased risks of colorectal and prostate cancers in paid male landscape firefighters, colorectal and kidney cancer in male firefighters, and all malignancies in female landscape firefighters [46–48]. However, no increased cancer mortality risks were observed, which may be due to the “healthy volunteer” effect [49–54]. Consistent with previous studies, lung cancer was not observed to have a higher mortality risk associated with wildfire-related PM$_{2.5}$ exposure, while statistically significant associations were observed in female and older populations with non-wildfire PM$_{2.5}$ in the current study [46–54]. However, our previous study conducted in the same population and over a similar study period showed significant associations between all-source PM$_{2.5}$ and lung cancer mortality for all subgroups (both sexes and age groups) [55]. The increased risk of lung cancer mortality may be explained by non-wildfire sources of PM$_{2.5}$ exposure, such as industry and transportation emissions, but not wildfires. Further studies on different sources of PM$_{2.5}$ and histological subtype-specific estimation are warranted.

Another kind of exposure similar to wildfire smoke is the emission from biomass burning. The literature suggests that indoor biomass burning is associated with lung cancer risk [56,57]. Robust evidence has been provided that biomass smoke from household cooking and heating is also associated with higher risks of gastrointestinal cancers [58–60]. Furthermore, indoor wood-burning stoves were suggested to be associated with a modestly increased risk of breast cancer in the Sister Study from the US [61]. An increased risk of hypopharyngeal cancer was also observed among lifelong users of wood in a case–control study from India [62]. Most studies were not able to assess the effect of biomass burning separately, as participants using fossil fuels included biomass and coal as cooking and heating fuels. However, in vitro studies have demonstrated that particles emitted by wood fires have mutagenic and endocrine-disrupting capacity, providing biological support for the possible role of wildfires in the pathogenesis of hormone-sensitive cancers [63,64].

Although both firefighter smoke exposure and indoor biomass burning pollution may not be directly comparable with wildfire-related PM$_{2.5}$ exposure in the general population, this literature sheds some light on cancer-specific risks. The current analysis establishes a higher risk for cancer, which means better control of wildfires is essential for cancer prevention in Brazil. In addition, individual-, community-, and national-level strategies should be considered to minimize fire exposure. However, the effectiveness of personal actions such as relocation, staying indoors, or wearing masks is still controversial [2]. The investigation of wildfire prediction models applied to Brazil is ongoing [65]. Warning systems for extremely hot weather
implemented in many countries may also provide a warning for increased wildfire risk [66]. Systemic strategies and guidance are warranted.

Major strengths of this study include that it is the first study to estimate the association between wildfire-related PM$_{2.5}$ and cancer-specific mortality, to our best knowledge. Also, this study is based on national death records, and the large sample size allowed the estimation of associations representative for the total Brazilian population. Lastly, the variant difference-in-differences approach could adjust for most of the unmeasured confounders stable during the study time and those that changed similarly across regions.

Some study limitations should also be recognized. First, we considered only PM$_{2.5}$ exposure in the analyses, and potential joint effects of gaseous pollutants were not estimated. Our estimation of wildfire-related PM$_{2.5}$ could not capture the complex mixture of environmental pollutants released during wildfires, and thus further studies are needed to refine the exposure metrics. Additionally, some confounders related to wildfires could not be adjusted for in the model due to data unavailability, including data on firefighting foam composition. For example, associations between firefighting chemicals and cancer at various cancer sites have been observed in previous studies: Firefighting foam containing per- and polyfluoroalkyl substances was suggested to be related to increased risk of breast cancer, bladder cancer, etc. [67]. Second, PM$_{2.5}$ concentrations were estimated at a global scale, and regional validation was not available due to limited ground-level monitors in Brazil. Third, municipality-level exposures were used in the analyses because individual exposure data were not available. The use of aggregated data may lead to some exposure misclassification, including the inability to capture the migration of residents between municipalities. However, potential effects of migration may be limited, as more than 96% of adults had an uninterrupted time of residence in a municipality for at least 2 years according, according to the 2010 census results published by BÍGS [68]. Finally, the use of registry data, rather than individual survey data, may have led to some misclassification of residential address and main cause of death, which may lead to bias in the association estimations. Some potentially changing confounders that correlated with both PM$_{2.5}$ exposure and cancer mortality were ignored in the analyses, due to the limited availability of individual lifestyle data. Further, the data used in this study did not allow an assessment of competing risks, as only the primary cause of death was recorded. Cancer patients who died from other causes (e.g., heart attack) could not be included. Also, our use of 2-year average PM$_{2.5}$ concentration as the exposure may be not appropriate for cancers with a longer survival time. Overall, further cohort studies are warranted to give a more accurate risk estimate.

In summary, this study provides the first quantitative estimate of the association between wildfire-related PM$_{2.5}$ and cancer-specific mortality across Brazil. The potentially higher risk of wildfire-related PM$_{2.5}$ compared with non-wildfire-related PM$_{2.5}$ for all cancers combined suggests that the wildfire control and systemic prevention strategies are warranted to reduce cancer mortality risk in Brazil. This could be a health co-benefit of measures to preserve the Amazon rainforest and limit climate change.

**Supporting information**

S1 RECORD Checklist. The RECORD statement checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

(DOCX)

S1 Data. Example data for analysis.

(CSV)
S1 Fig. The proportion of wildfire-related PM$_{2.5}$ of all-source PM$_{2.5}$ concentration during 2010–2016. The base map of this figure was downloaded from the Brazilian Institute of Geography and Statistics (https://www.ibge.gov.br/en/geosciences/territorial-organization/territorial-meshes/18890-municipal-mesh.html?edicao=30154&tt=downloads); the base map was free and open-access.

S2 Fig. Annual concentration of source-specific PM$_{2.5}$ in Brazil for the year 2017. The base map of this figure was downloaded from the Brazilian Institute of Geography and Statistics (https://www.ibge.gov.br/en/geosciences/territorial-organization/territorial-meshes/18890-municipal-mesh.html?edicao=30154&tt=downloads); the base map was free and open-access. Gridded fractional source contribution results in Brazil were extracted from [69].

S3 Fig. Estimated RRs (95% CIs) for the association between a 1-μg/m$^3$ increase in single lag0–2 and moving average wildfire-related PM$_{2.5}$ exposure and cancer mortality from 2010–2016. The horizontal dashed line represents the reference line for RR = 1, helping to compare the effect estimates with the null hypothesis; the vertical error bars represent 95% CIs. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI, confidence interval; RR, relative risk.

S4 Fig. Estimated response relationship between wildfire-related PM$_{2.5}$ and total cancer mortality, modeled by natural cubic splines with 1–4 degrees of freedom. The solid lines represent the RR, and the shaded areas represent the 95% CI. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI, confidence interval; RR, relative risk.

S5 Fig. Estimated RRs and 95% CIs for the association between a 1-μg/m$^3$ increase in 2-year average (lag0–1) wildfire-related PM$_{2.5}$ and non-wildfire-related PM$_{2.5}$ and mortality from all cancers and site-specific cancers from 2010–2016. The vertical dashed line represents the reference line for RR = 1, helping to compare the effect estimates with the null hypothesis; the error bars represent 95% CIs. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI, confidence interval; RR, relative risk.

S6 Fig. Estimated RRs (95% CIs) for the associations between a 1-μg/m$^3$ increase in 2-year average (lag0–1) wildfire-related PM$_{2.5}$ and mortality from all cancers and site-specific cancers from 2010–2016, by sex and age. The horizontal dashed line represents the reference line for RR = 1, helping to compare the effect estimates with the null hypothesis; the vertical error bars represent 95% CIs. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI,
S7 Fig. Comparison of the estimated RRs (95% CIs) for the association between a 1-μg/m³ increase in 2-year average (lag0–1) wildfire- and non-wildfire-related PM₂.₅ and lung cancer mortality from 2010–2016, by sex and age. The horizontal dashed line represents the reference line for RR = 1, helping to compare the effect estimates with the null hypothesis; the vertical error bars represent 95% CIs. The model, by its design, controlled for factors that were stable across the study period or had similar trend across geographical locations, and also adjusted for spatial-temporal factors including seasonal temperature and GDP per capita. CI, confidence interval; RR, relative risk.

S1 Table. Cancer death counts for common cancer sites by age and sex during 2010–2016 in Brazil.

S2 Table. Cancer deaths and attributable cancer deaths associated with the 2-year average wildfire-related PM₂.₅ exposure of each state in Brazil during 2010–2016.

S3 Table. Results of sensitivity analyses changing covariates and degrees of freedom of temperature for total cancer deaths.

S4 Table. Results of sensitivity analyses for total cancer and negative control mortality.

Acknowledgments

The authors thank the Brazilian Ministry of Health for providing death data.

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References

1. Chen G, Guo Y, Yue X, Tong S, Gasparini A, Bell ML, et al. Mortality risk attributable to wildfire-related PM2.5 pollution: a global time series study in 749 locations. Lancet Planet Health. 2021; 5(9):e579–87. https://doi.org/10.1016/S2542-5196(21)00200-X PMID: 34508679

2. Xu R, Yu P, Abramson MJ, Johnston FH, Samet JM, Bell ML, et al. Wildfires, global climate change, and human health. N Engl J Med. 2020; 383(22):2173–81. https://doi.org/10.1056/NEJMsr2028985 PMID: 33034960

3. Kim Y, Knowles S, Manley J, Radoias V. Long-run health consequences of air pollution: evidence from Indonesia’s forest fires of 1997. Econ Hum Biol. 2017; 26:186–98. https://doi.org/10.1016/j.ehb.2017.03.006 PMID: 28460366

4. Johnston FH, Henderson SB, Chen Y, Randerson JT, Marlier M, Defries RS, et al. Estimated global mortality attributable to smoke from landscape fires. Environ Health Perspect. 2012; 120(5):695–701. https://doi.org/10.1289/ehp.1104422 PMID: 22456494

5. Cascio WE. Wildland fire smoke and human health. Sci Total Environ. 2018; 624:586–95. https://doi.org/10.1016/j.scitotenv.2017.12.086 PMID: 29272827

6. Chen H, Samet JM, Bromberg PA, Tong H. Cardiovascular health impacts of wildfire smoke exposure. Part Fibre Toxicol. 2021; 18(1):2. https://doi.org/10.1186/s12989-020-00394-8 PMID: 33413506

7. Jallilian H, Ziaei M, Weiderpass E, Rueegg CS, Khosravi Y, Kjaerheim K. Cancer incidence and mortality among firefighters. Int J Cancer. 2019; 145(10):2639–46. https://doi.org/10.1002/ijc.32199 PMID: 30737784

8. Soteriades ES, Kim J, Christophi CA, Kales SN. Cancer incidence and mortality in firefighters: a state-of-the-art review and meta-analysis. Asian Pac J Cancer Prev. 2019; 20(11):3221–31. https://doi.org/10.31557/APJCP.2019.20.11.3221 PMID: 31759344

9. Casjens S, Bruning T, Taeger D. Cancer risks of firefighters: a systematic review and meta-analysis of secular trends and region-specific differences. Int Arch Occup Environ Health. 2020; 93(7):839–52. https://doi.org/10.1007/s00420-020-01539-0 PMID: 32306177

10. Dong TTT, Hinwood AL, Callan AC, Zosky G, Stock WD. In vitro assessment of the toxicity of bushfire emissions: a review. Sci Total Environ. 2017; 603–4:268–78. https://doi.org/10.1016/j.scitotenv.2017.06.062 PMID: 28628818

11. Montibeller B, Knoch A, Virro H, Mander U, Uuemaa E. Increasing fragmentation of forest cover in Brazil’s Legal Amazon from 2001 to 2017. Sci Rep. 2020; 10(1):5803. https://doi.org/10.1038/s41598-020-62591-x PMID: 32242044

12. Morais RMD Costa AL. Uma avaliação do Sistema de Informações sobre Mortalidade. Saúde em Debate. 2017; 41(SPE):101–17. https://doi.org/10.1590/0103-11042017s09

13. Stiller C. Epidemiology of cancer in adolescents. Med Pediatr Oncol. 2002; 39(3):149–55. https://doi.org/10.1002/mpo.10142 PMID: 12210442

14. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010; 36(4):277–85. https://doi.org/10.1016/j.ctrv.2010.02.003 PMID: 20231056

15. Ye T, Guo Y, Chen G, Yue X, Xu R, Coêlho MdSZS, et al. Risk and burden of hospital admissions associated with wildfire-related PM2.5 in Brazil, 2000–15: a nationwide time-series study. Lancet Planet Health. 2021; 5(9):e599–607. https://doi.org/10.1016/S2542-5196(21)00173-X PMID: 34508681

16. Yue X, Unger N. Fire air pollution reduces global terrestrial productivity. Nat Commun. 2018; 9(1):5413. https://doi.org/10.1038/s41467-018-07924-4 PMID: 30575760

17. Burkart KG, Brauer M, Aravkin AY, Godwin WW, Hay SI, He J, et al. Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: a two-part modelling approach applied to the Global Burden of Disease Study. Lancet. 2021; 398(10031):685–97. https://doi.org/10.1016/S0140-6736(21)01700-1 PMID: 34419204

18. Xu R, Zhao Q, Coelho M, Saldíva PHN, Abramson MJ, Li S, et al. Socioeconomic level and associations between heat exposure and all-cause and cause-specific hospitalization in 1,814 Brazilian cities: a
nationwide case crossover study. PLoS Med. 2020; 17(10):e1003369. https://doi.org/10.1371/journal.pmed.1003369 PMID: 33031393

19. Xu R, Zhao Q, Coelho MSZS, Saldíva PHN, Abramson MJ, Li S, et al. Socioeconomic inequality in vulnerability to all-cause and cause-specific hospitalisation associated with temperature variability: a time-series study in 1814 Brazilian cities. Lancet Planet Health. 2020; 4(12):e666–76. https://doi.org/10.1016/S2542-5196(20)30251-5 PMID: 33278374

20. Wang Y, Kloo G, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. Estimating causal effects of long-term PM2.5 exposure on mortality in New Jersey. Environ Health Perspect. 2016; 124(8):1182–8. https://doi.org/10.1289/ehp.1409671 PMID: 27082965

21. Yu W, Guo Y, Shi L, Li S. The association between long-term exposure to low-level PM2.5 and mortality in the state of Queensland, Australia: a modelling study with the difference-in-differences approach. PLoS Med. 2020; 17(6):e1003141. https://doi.org/10.1371/journal.pmed.1003141 PMID: 32555635

22. Renzi M, Forastiere F, Schwartz J, Davoli M, Michelozzi P, Stafoggia M. Long-term PM10 exposure and cause-specific mortality in the Latium Region (Italy): a difference-in-differences approach. Environ Health Perspect. 2019; 127(6):67004. https://doi.org/10.1289/EHP3759 PMID: 31166133

23. Schwartz J, Wei Y, Yitshak-Sade M, Di Q, Dominici F, Zanobetti A. A national difference in differences analysis of the effect of PM2.5 on annual death rates. Environ Res. 2020; 194:110649. https://doi.org/10.1016/j.envres.2020.110649 PMID: 33385394

24. Sharma A, Sharma T, Panwar MS, Sharma D, Bundel R, Hamilton RT, et al. Colder environments are associated with a greater cancer incidence in the female population of the United States. Tumour Biol. 2017; 39(10):1010428317724784. https://doi.org/10.1177/1010428317724784 PMID: 29022494

25. Lehrer S, Rosenzweig KE. Cold climate is a risk factor for thyroid cancer. Clin Thyroidol. 2014; 26(10):273–6. https://doi.org/10.1089/cdt.2014.26.273-276 PMID: 25558467

26. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA. 2000; 283(22):2975–7. https://doi.org/10.1001/jama.283.22.2975 PMID: 10865276

27. International Agency for Research on Cancer. List of classifications: agents classified by the IARC monographs, volumes 1–129. Lyon: International Agency for Research on Cancer; 2021 [cited 2021 Sep 27]. Available from: https://monographs.iarc.who.int/list-of-classifications.

28. Rolston KV. Infections in cancer patients with solid tumors: a review. Infect Dis Ther. 2017; 6(1):69–83. https://doi.org/10.1007/s40121-017-0146-1 PMID: 28160269

29. Glencross DA, Ho TR, Camina N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. Free Radic Biol Med. 2020; 151:56–68. https://doi.org/10.1016/j.freeradbiomed.2020.01.179 PMID: 32007522

30. Hu H, Dailey AB, Kan H, Xu X. The effect of atmospheric particulate matter on survival of breast cancer among US females. Breast Cancer Res Treat. 2013; 139(1):217–26. https://doi.org/10.1007/s10549-013-2527-9 PMID: 23592372

31. Deng H, Eckel SP, Liu L, Lurmann FW, Cockburn MG, Gilliland FD. Particulate matter air pollution and liver cancer survival. Int J Cancer. 2017; 141(4):744–9. https://doi.org/10.1002/ijc.30779 PMID: 28589567

32. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420(6917):861–7. https://doi.org/10.1038/nature01322 PMID: 12490959

33. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer. 2016; 16(1):20–33. https://doi.org/10.1038/nrc.2015.2 PMID: 26678314

34. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med. 2010; 49(11):1603–16. https://doi.org/10.1016/j.freeradbiomed.2010.09.006 PMID: 20840865

35. Gill JG, Piskounova E, Morrison SJ. Cancer, oxidative stress, and metastasis. Cold Spring Harb Symp Quant Biol. 2016; 81:163–75. https://doi.org/10.1101/sqsb.2016.81.030791 PMID: 28082378

36. Klaunig JE. Oxidative stress and cancer. Curr Pharm Des. 2018; 24(40):4771–8. https://doi.org/10.2174/1381612820566190215121712 PMID: 3076733

37. Beamish LA, Osornio-Vargas AR, Wine E. Air pollution: an environmental factor contributing to intestinal disease. J Crohns Colitis. 2011; 5(4):279–86. https://doi.org/10.1016/j.crohns.2011.02.017 PMID: 21683297

38. Salgueiro-González N, López de Alda MJ, Muniategui-Lorenzo S, Prada-Rodríguez D, Barceló D. Analysis and occurrence of endocrine-disrupting chemicals in airborne particles. Trac Trends Analyt Chem. 2015; 66:45–52. https://doi.org/10.1016/j.trac.2014.11.006

39. Ou JY, Hanson HA, Ramsay JM, Kaddas HK, Pope CA 3rd, Leiser CL, et al. Fine particulate matter air pollution and mortality among pediatric, adolescent, and young adult cancer patients. Cancer Epidemiol
40. De Toni L, Sabovic I, Cosci I, Ghezzi M, Foresta C, Garolla A. Testicular cancer: genes, environment, hormones. Front Endocrinol (Lausanne). 2019; 10:408. https://doi.org/10.3389/fendo.2019.00408 PMID: 31338064

41. Makkonen U, Hellen H, Anttila P, Ferm M. Size distribution and chemical composition of airborne particles in south-eastern Finland during different seasons and wildfire episodes in 2006. Sci Total Environ. 2010; 408(3):644–51. https://doi.org/10.1016/j.scitotenv.2009.10.050 PMID: 19903567

42. Verma V, Polidori A, Schauer JJ, Shafer MM, Cassee FR, Sioutas C. Physicochemical and toxicological profiles of particulate matter in Los Angeles during the October 2007 southern California wildfires. Environ Sci Technol. 2009; 43(3):954–60. https://doi.org/10.1021/es8021667 PMID: 19245042

43. Reid CE, Brauer M, Johnston FH, Jerrett M, Balmes JR, Elliott CT. Critical review of health impacts of wildfire smoke exposure. Environ Health Perspect. 2016; 124(9):1334–43. https://doi.org/10.1289/ehp.1409277 PMID: 27082891

44. Yu P, Guo S, Xu R, Ye T, Li S, Sim MR, et al. Cohort studies of long-term exposure to outdoor particulate matter and risks of cancer: a systematic review and meta-analysis. Innovation (Camb). 2021; 2(3):100143. https://doi.org/10.1016/j.xinn.2021.100143 PMID: 34557780

45. Navarro KM, Kleinman MT, Mackay CE, Reinhardt TE, Balmes JR, Bryoles GA, et al. Wildland firefighter smoke exposure and risk of lung cancer and cardiovascular disease mortality. Environ Res. 2019; 173:462–8. https://doi.org/10.1016/j.envres.2019.03.060 PMID: 30981117

46. Glass DC, Pircher S, Del Monaco A, Hoorn SV, Sim MR. Mortality and cancer incidence in a cohort of male paid Australian firefighters. Occup Environ Med. 2016; 73(11):761–71. https://doi.org/10.1136/oemed-2015-103467 PMID: 27456156

47. Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR. Mortality and cancer incidence among male volunteer Australian firefighters. Occup Environ Med. 2017; 74(9):628–38. https://doi.org/10.1136/oemed-2016-104088 PMID: 28391245

48. Glass DC, Del Monaco A, Pircher S, Vander Hoorn S, Sim MR. Mortality and cancer incidence among female Australian firefighters. Occup Environ Med. 2019; 76(4):215–21. https://doi.org/10.1136/oemed-2018-105336 PMID: 25708859

49. Zhao G, Erazo B, Ronda E, Brocal F, Regidor E. Mortality among firefighters in Spain: 10 years of follow-up. Ann Work Expo Health. 2020; 64(6):614–21. https://doi.org/10.1093/annweh/wxaa036 PMID: 32253442

50. Bates MN. Registry-based case-control study of cancer in California firefighters. Am J Ind Med. 2007; 50(5):339–44. https://doi.org/10.1002/ajim.20446 PMID: 17427202

51. Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaelle C, Simone MP, et al. French firefighter mortality: analysis over a 30-year period. Am J Ind Med. 2015; 58(4):437–43. https://doi.org/10.1002/ajim.22434 PMID: 25708859

52. Kullberg C, Andersson T, Gustavsson P, Selander J, Tornling G, Gustavsson A, et al. Cancer incidence in Stockholm firefighters 1958–2012: an updated cohort study. Int Arch Occup Environ Health. 2018; 91(3):285–91. https://doi.org/10.1007/s00420-017-1276-1 PMID: 29164319

53. Bigert C, Martinson JI, Gustavsson P, Sparer P. Cancer incidence among Swedish firefighters: an extended follow-up of the NOCCA study. Int Arch Occup Environ Health. 2020; 93(2):197–204. https://doi.org/10.1007/s00420-019-01472-x PMID: 31463517

54. Petersen KKS, Pedersen JE, Pedersen JS, Nielsen NE, Hansen J. Long-term follow-up for cancer incidence in a cohort of Danish firefighters. Occup Environ Med. 2018; 75(4):263–9. https://doi.org/10.1136/oemed-2017-104660 PMID: 29058844

55. Yu P, Xu R, Li S, Coelho MSZS, Saldiva PHN, Sim MR, et al. Associations between long-term exposure to PM2.5 and site-specific cancer mortality: a nationwide study in Brazil between 2010 and 2018. Environ Pollut. 2022; 302:119070. https://doi.org/10.1016/j.envpol.2022.119070 PMID: 35231538

56. Bruce N, Dherani M, Liu R, Hosgood HD 3rd, Sapkota A, Smith KR, et al. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax. 2015; 70(5):433–41. https://doi.org/10.1136/thoraxjnl-2014-206625 PMID: 25758120

57. Kurmi OP, Arya PH, Lam KB, Sorahan T, Ayres JG. Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis. Eur Respir J. 2012; 40(5):1228–37. https://doi.org/10.1183/09031936.00099511 PMID: 22653775

58. Sheikh M, Poustchi H, Pourshams A, Khoshtin M, Gharavi A, Zahedi M, et al. Household fuel use and the risk of gastrointestinal cancers: the Golestan Cohort Study. Environ Health Perspect. 2020; 128(6):67002. https://doi.org/10.1289/EHP9507 PMID: 32609005
59. Mota OM, Curado MP, Oliveira JC, Martins E, Cardoso DM. Risk factors for esophageal cancer in a low-incidence area of Brazil. Sao Paulo Med J. 2013; 131(1):27–34. https://doi.org/10.1590/s1516-31802013000100005 PMID: 23538592

60. Kayamba V, Heimburger DC, Morgan DR, Atadzhanov M, Kelly P. Exposure to biomass smoke as a risk factor for oesophageal and gastric cancer in low-income populations: a systematic review. Malawi Med J. 2017; 29(2):212–7. https://doi.org/10.4314/mmj.v29i2.25 PMID: 28955435

61. White AJ, Sandler DP. Indoor wood-burning stove and fireplace use and breast cancer in a prospective cohort study. Environ Health Perspect. 2017; 125(7):077011. https://doi.org/10.1289/EHP827 PMID: 28728136

62. Sapkota A, Gajalakshmi V, Jetly DH, Roychowdhury S, Dikshit RP, Brennan P, et al. Indoor air pollution from solid fuels and risk of hypopharyngeal/laryngeal and lung cancers: a multicentric case-control study from India. Int J Epidemiol.2008; 37(2):321–8. https://doi.org/10.1093/ije/dym261 PMID: 18234740

63. Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the links between endocrine disruptors and neurodevelopment. Endocrinology. 2015; 156(6):1941–51. https://doi.org/10.1210/en.2014-1734 PMID: 25714811

64. de Oliveira Alves N, Vessoni AT, Quinet A, Fortunato RS, Kajitani GS, Peixoto MS, et al. Biomass burning in the Amazon region causes DNA damage and cell death in human lung cells. Sci Rep. 2017; 7(1):10937. https://doi.org/10.1038/s41598-017-11024-3 PMID: 28883446

65. Silva IDB, Valle ME, Barros LC, Meyer JFCA. A wildfire warning system applied to the state of Acre in the Brazilian Amazon. Appl Soft Comput. 2020; 89:106075. https://doi.org/10.1016/j.asoc.2020.106075

66. Toloo GS, Fitzgerald G, Atken P, Verrall K, Tong S. Are heat warning systems effective? Environ Health. 2013; 12:27. https://doi.org/10.1186/1476-069X-12-27 PMID: 23561265

67. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res. 2021; 194:110690. https://doi.org/10.1016/j.envres.2020.110690 PMID: 33385391

68. Instituto Brasileiro de Geografia e Estatística. Censo demográfico 2010: nupcialidade, fecundidade e migração. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística; 2012.

69. McDuffie E, Martin R, Yin H, Brauer M. Global burden of disease from major air pollution sources (GBD MAPS): a global approach. Boston: Health Effects Institute; 2021.