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Breast Cancer Risk in Association with Atmospheric Pollution Exposure: A Meta-Analysis of Effect Estimates Followed by a Health Impact Assessment

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Background: The epidemiological literature of associations between atmospheric pollutant exposure and breast cancer incidence has recently strongly evolved.

Objectives: We aimed to perform *a*) a meta-analysis of studies considering this relationship, correcting for publication bias and taking menopausal status and cancer hormone responsiveness into account; and *b*) for the pollutants most likely to affect breast cancer, an assessment of the corresponding number of attributable cases in France and of the related economic costs.

Methods: We conducted a literature review and random-effects meta-analyses of epidemiological studies examining the association of fine particulate matter with aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), particulate matter with aerodynamic diameter less than or equal to 10 μm (PM_{10}), and NO_2 long-term exposure with breast cancer incidence; additional analyses were stratified on menopausal status and on tumor hormone responsiveness status. The resulting dose–response functions were combined with modeled atmospheric pollutant exposures in 2013 for France, cancer treatments costs, lost productivity, and years of life lost, to estimate the number of breast cancers attributable to atmospheric pollution and related economic costs in France.

Results: The review identified 32, 27, and 36 effect estimates for $PM_{2.5}$, PM_{10}, and NO_2, respectively. The meta-analytical relative risk estimates of breast cancer corrected for publication bias were 1.006 [95% confidence interval (CI): 0.941, 1.076], 1.047 (95% CI: 0.984, 1.113), and 1.023 (95% CI: 1.005, 1.041), respectively. NO_2 estimated effects appeared higher in premenopausal than in postmenopausal women and higher for hormone responsive positive (ER+/PR+) than negative (ER–/PR–) breast cancers. Assuming a causal effect of NO_2, we estimated that 1,677 (95% CI: 374, 2,914) new breast cancer cases were attributable to NO_2 annually in France, or 3.15% (95% CI: 0.70, 5.48) of the incident cases. The corresponding tangible and intangible costs were estimated to be €825 million (low, high: 570, 1,080) per year.

Conclusion: These findings suggest that decreasing long-term NO_2 exposure or correlated air pollutant exposures could lower breast cancer risk. https://doi.org/10.1289/EHP8419

Introduction

With more than 2 million incident cases worldwide in 2018 (corresponding to an age-standardized incidence rate of 46 per 100,000 person-years), breast cancer is the second most frequent cancer after lung cancer worldwide, the first in the European Union and the United States, and the first in women worldwide (Bray et al. 2018). About 630,000 women died from breast cancer in the world in 2018 (Bray et al. 2018). In France, in 2017 nearly 60,000 women were diagnosed with breast cancer, which killed about 12,000 women (INCa 2018). Breast cancer heritability is estimated to be about 5%–10% (Apostolou and Fostira 2013), which leaves much room for nongenetic influences. Besides genetic factors and family history of breast cancer, the main established risk factors for breast cancer in women include age, menstrual and reproductive history, breastfeeding, physical activity, alcohol intake, and hormone use (Key et al. 2001). An effect of chemical environmental factors was also suggested (Gray et al. 2017; Rodgers et al. 2018), such as that of exposures to endocrine disrupting compounds, and in particular to bisphenol A, or to xenoestrogens (Pastor-Barriuso et al. 2016); other environmental exposures reported as possibly associated with breast cancer include dioxins (Gray et al. 2017; Rodgers et al. 2018) and air pollution (White et al. 2018).

Air pollution is a ubiquitous complex mixture of solid and liquid particles and gases. Particulate matter (PM) and nitrogen oxides (NO_x), including nitrogen dioxide (NO_2), are prominent primary components of atmospheric pollution. PM is commonly characterized by size, distinguishing those with an aerodynamical diameter below 10 μm (PM_{10}) and those with an aerodynamical diameter below 2.5 μm ($PM_{2.5}$). The former can be inhaled, whereas the latter, which are included in the PM_{10} fraction, can reach the lung alveola and for their smallest fraction enter the blood circulation. PM can come from heating sources, road traffic, industry, and agriculture, or it can be of natural origin. The International Agency for Research on Cancer (IARC) classified outdoor air pollution and diesel exhaust as Group 1 carcinogens, and more specifically PM as a lung carcinogen (Benbrahim-Tallaa et al. 2012; Loomis et al. 2013). PM is a mixture that can include carcinogenic chemicals such as benzo[*a*]pyrene (BaP) and other polycyclic aromatic hydrocarbons (PAHs) (Ravindra et al. 2001). A major source of NO_x and NO_2 is fossil fuel combustion, mainly from combustion engine vehicles, and stationary power generation; as such, NO_x and NO_2 are considered traffic tracers and, more generally, tracers of fossil fuels use. Thus, although its intrinsic carcinogenicity is not clearly established (Huynh et al. 2015; Yaghjyan et al. 2017), NO_2 represents a marker of exposure to diesel exhaust, which contains many carcinogenic components such as PM, PAHs, and benzene. Atmospheric pollutants also exhibit estrogenic activity (Wenger et al. 2009), which is of importance, given the implication of the estrogenic pathway in breast cancer etiology (Pastor-Barriuso et al. 2016).

Epidemiological studies have recently started examining the relationship between air pollution exposure and breast cancer, almost all studies having been published in the last 3 y. Several

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positive associations between PM and breast cancer have been reported (Datzmann et al. 2018; Hwang et al. 2020; White et al. 2019a). For instance, based on health insurance individual data, Datzmann et al. (2018) assessed that breast cancer incidence increased by 19% [95% confidence interval (CI): 9, 31] per 10-$\mu g/m^3$ increase in PM_{10} exposure in Saxony. However, most prospective studies reported null associations with PM (Andersen et al. 2017a; Bai et al. 2020; Cheng et al. 2020; Hart et al. 2016; Villeneuve et al. 2018). For NO_2, most studies reported statistically nonsignificant associations with breast cancer, often with trends corresponding to a positive relation (Andersen et al. 2017a; Cheng et al. 2020; Goldberg et al. 2017; Hystad et al. 2015). For example, the pooled European Study of Cohorts for Air Pollution Effects (ESCAPE) conducted among more than 70,000 postmenopausal women reported a hazard rate (HR) of 1.02 (95% CI: 0.98, 1.07) for a 10-$\mu g/m^3$ increase in NO_2 exposure (Andersen et al. 2017b). Significantly increased relative risks were also reported (Bai et al. 2020; Crouse et al. 2010; Datzmann et al. 2018; Hwang et al. 2020; White et al. 2019a), e.g., by 5% (95% CI: 1, 10) per 10-$\mu g/m^3$ increase in NO_2 exposure in the North American Sister Study prospective cohort (White et al. 2019a). Overall, drawing firm conclusions from an individual consideration of these studies is difficult because of the limited power of many of them and the potential for publication bias. Both of these issues can in principle to some extent be overcome by meta-analyses.

In addition to several qualitative reviews on the topic (Rodgers et al. 2018; Sahay et al. 2019; White et al. 2018), some meta-analyses previously summarized the relationship between air pollution exposure and breast cancer risk (Guo et al. 2021; Keramatinia et al. 2016; Kim et al. 2020; Zhang et al. 2019). Zhang et al. (2019), Kim et al. (2020), and Guo et al. (2021) reported meta-analytical relative risks (RR) of 1.02 (95% CI: 0.93, 1.11), 0.96 (95% CI: 0.87, 1.07), and 1.04 (95% CI: 0.98, 1.10) by 10-$\mu g/m^3$ increase in $PM_{2.5}$, respectively, and of 1.05 (95% CI: 0.98, 1.12), 1.05 (95% CI: 0.97, 1.14), and 1.03 (95% CI: 0.98, 1.09) by 10-$\mu g/m^3$ increase in PM_{10}, respectively. Concerning nitrogen oxides, Keramatinia et al. (2016) reported a significant correlation between breast cancer incidence rates and NO_2 or NO_x exposure, whereas Kim et al. (2020) reported a meta-analytical RR of 1.05 (95% CI: 0.99, 1.11) by 10-$\mu g/m^3$ increase in NO_2. However, these meta-analyses did not encompass the latest evidence or missed some relevant studies, and only Guo et al. (2021) considered potential for publication bias for PM.

Furthermore, the relationship of exposure to PM or NO_2 to breast cancer was suggested to vary by menopausal status. For example, Goldberg et al. (2019) observed that breast cancer relative risk was higher in premenopausal than postmenopausal women: in the Canadian National Breast Screening Study (CNBSS) prospective cohort, breast cancer RRs were 1.09 (95% CI: 1.00, 1.20) in premenopausal women and 1.00 (95% CI: 0.97, 1.03) in postmenopausal women, for a 10-$\mu g/m^3$ increase in NO_2 levels. Possible effect measure modification according to menopausal status have also been reported for other populations (Andersen et al. 2017a; Hart et al. 2016; Hystad et al. 2015; Villeneuve et al. 2018; White et al. 2019a). Furthermore, the relationship of air pollution exposure to the development of specific breast cancer subtypes, such as hormone responsive positive (ER+/PR+) and negative (ER–/PR–), was broached in recent studies (Cheng et al. 2020; Goldberg et al. 2017; Hart et al. 2016; Lemarchand et al. 2021; White et al. 2019a). To our knowledge, issues concerning menopausal status and hormonal receptor subtypes have not been considered in previous meta-analyses.

If air pollution exposure caused breast cancer, the corresponding health burden could be high, given the widespread exposure (Brauer et al. 2016). According to a French senate valuation carried out as part of the Clean Air for Europe (CAFE) Program, the national cost related to air pollution would amount up to 100 billion Euros a year (French Senate 2015). Possible impacts on breast cancer were not considered in these cost estimates.

Considering mixed results and the need to update meta-analyses with the most recent studies, to correct for publication bias, and to consider the recent hypothesis regarding hormone responsive tumors, we conducted an exhaustive literature-based meta-analysis of the relationship between ambient $PM_{2.5}$, PM_{10}, and NO_2 long-term exposure and breast cancer onset, considering menopausal and hormone responsiveness tumor status. We used the resulting dose–response functions to estimate the annual number of incident breast cancer cases attributable to atmospheric pollution exposure in France, and the related economic costs.

Material and Methods

Meta-Analysis

We characterized the dose–response functions between $PM_{2.5}$, PM_{10}, and NO_2 long-term exposure and breast cancer incidence through a literature-based meta-analysis corrected for publication bias.

Literature review. We searched for all epidemiological human studies providing quantitative estimates of the association between breast cancer incidence and exposure to individual air pollutants such as $PM_{2.5}$, PM_{10}, or NO_2. To do so, in January 2021, two of us conducted in parallel a literature search in the PubMed database without any restriction for publication time using the following query:

(air pollution [title/abstract] OR particulate* [title/abstract] OR nitrogen oxide* [title/abstract] OR nitrogen dioxide [title/abstract]) AND ((neoplasms/epidemiology [MeSH] AND breast [all fields]) OR (breast neoplasms/epidemiology [MeSH]) OR (cancer [title/abstract] AND breast [title/abstract])).

The articles retrieved by the literature search were first screened by title and abstract to determine those not relevant for full-text review (e.g., off-topic studies, nonhuman studies, comments, nonresearch articles, etc.). Full-text review allowed us to reject studies providing no quantitative estimates (e.g., literature reviews), studies dealing only with aggregated health data (e.g., ecological studies), studies of breast cancer–related outcomes other than incidence (e.g., mortality, mammographic density, etc.), and studies not providing a quantitative assessment of one of the three air pollutants considered (e.g., proxies as "traffic proximity" etc.), as well as studies providing unusable estimates and duplicates. We additionally included any study related to the topic that we identified (by reviewing references cited in screened papers) and that met our selection criteria but missed the keyword search criteria. We also included one study recently led in the French Breast Cancer: Epidemiological Study on the Environment in Côte d'Or and Ille-et-Vilaine (CECILE) case–control study (Lemarchand et al. 2021) as part of the same research project than the present meta-analysis.

When several effect estimates of a relationship related to a specific pollutant were available for a given study population, we always retained the dose response corresponding to a linear coding of exposure estimated in the main study population group in the model adjusted for the largest number of (relevant) potential confounders. In some studies simultaneously relying on several approaches to assess pollution exposures [such as satellite observations, air monitoring station measurements, land use regression (LUR) modeling, etc.], we selected the estimates based on the LUR model.

Main meta-analyses. Prior to meta-analysis, which was performed using Stata (version 15.1; Stata Corp.), all effect estimates were expressed per 10-$\mu g/m^3$ increase on average pollutant exposure; NO_2 levels in parts per billion (ppb) were converted in micrograms per cubic meter, applying a ratio of 1.88. For each pollutant, we used a bootstrapped DerSimonian-Laird (BDL) random-effects meta-analysis model (bootstrapping set to 10,000 repetitions) on the selected publications using the Metaan Stata module (Kontopantelis and Reeves 2009). When a study did not provide a global effect estimate in "all women" (i.e., irrespective of menopausal status), we included in the main meta-analysis (not stratified on menopausal status) the effect estimates reported separately in postmenopausal, and, if available, premenopausal women, to reflect the global effect expected in "all women."

Heterogeneity between the studies included in meta-analyses was tested by Cochrane's heterogeneity Q test; a leave-out-one meta-analysis was conducted to identify the studies contributing the most to the heterogeneity. We used funnel plots (Metafunnel Stata module) and Egger's tests for small-study effects (Metabias Stata module) to evidence publication bias. When such bias was detected, we used trim-and-fill analyses with random-effects (Metatrim Stata module) to derive meta-analytical RRs corrected for publication bias. Trim-and-fill analysis recalculates a meta-analytical estimate after adding the minimal number of hypothetical studies necessary to observe a perfectly symmetrical funnel plot; imputed studies are of inverse RRs and of same standard errors as those of studies included in the primary meta-analysis, ordering studies by effect estimate.

We also performed BDL random-effects meta-analyses specific to menopausal status (premenopausal or postmenopausal women) and to hormonal receptor subtype (ER+/PR+ or ER−/PR−).

Sensitivity meta-analyses. We performed sensitivity analyses to examine the impact on the estimated meta-analytical RRs (not corrected for publication bias) of the between-study heterogeneity (by excluding the study most contributing to heterogeneity), the study design (by selecting prospective cohorts only), the study area (European only or North American only), and the adjustment factors in the models used in the meta-analysis (by restricting to estimates adjusted *a*) for the main reproductive factors, namely age at menarche, age at the first full-term pregnancy, and parity; or *b*) for socioeconomic context at the area level). We also studied the impact of analytic decisions, such as the inclusion of effect estimates reported in postmenopausal women only in the main meta-analyses (by selecting effect estimates reported in "all women" only), the inclusion of both effect estimates reported separately in postmenopausal and premenopausal women in absence of global effect estimate (by excluding the individual effect estimate reported in premenopausal women), and the inclusion of a yet unpublished study (by excluding it). We also assessed the impact of the approaches used to characterize air pollution exposure in source studies, restricting meta-analyses to studies estimating exposure based on the detailed home addresses (i.e., excluding studies in which air pollutant levels were assessed at the postal code scale), on collection of residential history (i.e., excluding studies in which air pollutant levels were assessed ignoring changes of home address during the exposure window), or on modeling approaches (LUR, dispersion or chemistry-transport models) as well as focusing on studies whose recruitment started after 1999, because PM monitoring networks were generally less developed before 2000.

Health Impact Assessment

To assess the impact (number of attributable cancer cases) of the pollutants with the most likely effects on breast cancer incidence on the population living in France, we coupled the meta-analytical dose–response functions with air pollutant exposure.

Atmospheric pollution exposure assessment. Exposure to $PM_{2.5}$, PM_{10}, and NO_2 was assessed coupling modeled pollutant concentration in France with information on population density in each geographical unit using QGIS (version 3.10.4; OSGeo Foundation).

Pollutant concentrations were provided by the national air pollutant dispersion model developed by Ineris, at the 1-square kilometer spatial resolution, with a daily temporal resolution. As previously described (Benmerad et al. 2017a), this model was developed through kriging of the European mesoscale CHIMERE chemistry transport model data (Menut et al. 2013) using the measurements from the French air quality monitoring station network; a further leave-one-out cross-validation allowed to verify the very good correlation between the model's estimates and measurements from monitoring stations (Benmerad et al. 2017b). Pollution data were available over the whole metropolitan France (i.e., continental France and Corsica; see Table S1 and Figure S1). For the present study, the annual mean of $PM_{2.5}$, PM_{10}, and NO_2 daily concentrations per 1-km^2 model unit was computed for 2013, the most recent year covered by this model.

Population density data according to gender and 15-y age groups were obtained for the year 2013 from the National Institute of Statistics and Economic Studies (Insee 2016b) at the Housing Block Regrouped for Statistical Information (IRIS) level. IRIS is the smallest geographical census units in France (similar to U.S. Census block groups); each IRIS represents a homogeneous neighborhood of about 2,000 inhabitants on average (Insee 2016a). Each 1-km^2 exposure model grid was linked to one or more IRIS units, and IRIS population numbers and characteristics were distributed among model grids according to the proportion of each IRIS area included in a given grid.

Attributable cases assessment. The number of attributable breast cancer cases in metropolitan France was assessed through a counterfactual approach using Stata 15.1. The annual average number of incident breast cancer cases (ICD10: C50) was provided by the French National Cancer Institute for each French *département* over the 2007–2016 period (INCa 2019b). Next, incident cases were distributed across 1-km^2 model units proportionally to the population density of women by age. Because the age distribution of incident cases was only available at the national scale (INCa 2019a), we assumed that age-specific incidence rates in each *département* was equal to the age-specific national rates.

We estimated the difference in the number of cancer cases (Δ_{NCC}) between the 2007–2016 period and the counterfactual situation, as:

$$\Delta_{NCC} = \sum_i NCC_{0i}\left[1 - \exp\left(-\Delta pol_i \times \frac{ln(RR)}{10}\right)\right]$$

where NCC_{0i} is the baseline yearly average number of incident breast cancers in each 1-km^2 air pollutant model unit i, Δpol_i is the difference in pollutant levels between the baseline (pollutant levels in 2013) and the counterfactual situation in each 1-km^2 model unit i, and RR is the meta-analytical relative risk associated with a 10-$\mu g/m^3$ increase in air pollutant concentrations established in the meta-analysis. For limiting the error on the estimate of the attributable case number, we used only the most reliable effect estimates, to wit the meta-analytical relative risk corrected for publication bias.

We considered the following counterfactual situations: *a*) "Compliance with the World Health Organization (WHO) guideline," in which pollutant concentrations above the current WHO

guideline value would be brought down to this value (i.e., 10, 20, and 40 $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, and NO_2, respectively); *b*) "Low pollution level," in which pollutant concentrations would not exceed the fifth percentile of concentrations at the French territory scale (i.e., 12.0, 17.2, and 6.3 $\mu g/m^3$ for $PM_{2.5}$, PM_{10}, and NO_2 in 2013, respectively); *c*) "Low pollution level within the same urbanization degree areas," in which pollutant concentrations would not exceed the fifth percentile of concentrations within areas of the same degree of urbanization (for instance, 12.3 $\mu g/m^3$ for NO_2 in 2013 in "Cities," see Table S1) and finally; *d*) "Pollutant concentration levels 1 $\mu g/m^3$ lower than baseline," in which pollutant level in each 1-km^2 model unit would be decreased by 1 $\mu g/m^3$.

The degree of urbanization was assessed with the degree of urbanization (DEGURBA) index, provided at the municipality scale (Eurostat; latest update: 2011). Briefly, the DEGURBA index gathers municipalities in three groups characterized as follows (see Figure S1): "Cities" with at least 50% of the population living in urban centers; "Rural areas" with at least 50% of the population living in rural zones; "Towns and suburbs" gathering all municipalities not belonging to one of the first two groups (European Commission 2019).

Related economic costs. We conducted a literature review to identify epidemiological and economic data sources specific to breast cancer. Favoring the latest French economic available studies, these data sources were used to adapt a methodology previously developed to assess the economic costs related to lung cancer cases attributable to air pollution (Morelli et al. 2019). We valued tangible costs, which include direct medical costs paid by the health insurance system and indirect costs due to loss of productive work supported by the society, as well as intangible costs, which are a monetary value encompassing all nonfinancial aspects of the illness such as grief and loss of quality of life borne by the patient and his or her family. All costs are expressed in 2019 Euros (Insee 2020b).

For direct tangible costs, according to a French recent medicoeconomic study (Cortaredona and Ventelou 2017) and to breast cancer survival rates (INCa 2019c), the average value of the total treatment cost for breast cancer was estimated to €48,110 per case with a range of (±) €4,116 (see Table S2). For indirect tangible costs, we relied on the case–control study on breast cancer in working women by Drolet et al. (2005) and assumed 6 months of work lost for nonretired women; with the average age of breast cancer diagnosis (61.8 y) (INCa 2017) being close to retirement age in France, we considered the average indirect tangible costs per case to be halved. The Improving Knowledge and Communication for Decision Making on Air Pollution and Health in Europe (Aphekom) project valued a workday at €98.50 ± 33% and, through a literature review of contingent valuations, allowed to estimate the value of a life-year (VOLY) to €102,748 ± 33% (Chanel 2011). Considering the women's life expectancies at age 60 (Insee 2020a), which is approximatively the average age of breast cancer diagnosis (INCa 2017), and the survival rates at 1, 3, 5, and 10 y (INCa 2019c), as well as assuming a total lethality of 20% (based on 80% of survival at 10 y) and assuming full cancer remission for women who survive for 10 y, we estimated that breast cancer patients would lose on average 4.2 y of life (see Table S2). Intangible costs per breast cancer case were then estimated by multiplying this loss by the VOLY. Cost estimates are provided with low–high intervals, which are based, regarding direct tangible costs, on the 95% CI of the treatment cost estimates for breast cancer (Cortaredona and Ventelou 2017), and, regarding indirect tangible costs and intangible, on the uncertainty range obtained by adding or subtracting 33% to the value of a workday and to the VOLY, respectively (Chanel 2011).

Results

Literature Review

We initially retrieved 203 articles through PubMed database search (see Figure S2). After screening titles and abstracts, 63 were considered relevant for full-text review. Among these, we excluded 50 studies that did not meet our selection criteria: 11 studies not providing quantitative estimates, 7 studies based on aggregated health data (i.e., ecological studies not allowing proper adjustment for confounders), 18 studies considering breast cancer-related outcomes other than incidence, and 14 studies in which air pollution exposure to $PM_{2.5}$, PM_{10}, or NO_2 has not been estimated specifically. We additionally excluded one study for which exposure could not be converted in micrograms per cubic meters (Huo et al. 2013). Because White et al. (2019a) updated associations previously reported by Reding et al. (2015) in the same population, we disregarded the study by Reding et al. In addition, we included one study that was cited in articles that we reviewed and that met our selection criteria but missed the keyword search criteria (Villeneuve et al. 2018), as well as the recent study led by Lemarchand et al. (2021). In total, 13 publications were used for the meta-analysis (Andersen et al. 2017b, 2017a; Bai et al. 2020; Cheng et al. 2020; Crouse et al. 2010; Datzmann et al. 2018; Goldberg et al. 2017, 2019; Hart et al. 2016; Hystad et al. 2015; Lemarchand et al. 2021; Villeneuve et al. 2018; White et al. 2019a), in which 32, 27, and 36 effect estimates between breast cancer incidence and long-term exposure to $PM_{2.5}$, PM_{10}, or NO_2 were reported, respectively (Tables 1–3; Table S3 and Figure S2). Specifically, 7, 6, and 7 risk estimates were reported in "all women," 12, 10, and 17 in postmenopausal women, and 5, 3, and 4 in premenopausal women for $PM_{2.5}$, PM_{10}, or NO_2, respectively; in addition, 4 effect estimates for ER+/PR+ and ER–/PR– subtypes were identified for each pollutant. Studies were mostly based on modeling data (LUR, dispersion model, or chemistry-transport model; Tables 1–3). All studies were conducted in "all women" (i.e., irrespective of menopausal status) or postmenopausal women, from European or North American populations, including a total of nearly 4 million women.

Dose–Response Functions

The meta-analytical RR of breast cancer was 1.014 (95% CI: 0.929, 1.106) for a 10-$\mu g/m^3$ increase in exposure to $PM_{2.5}$ without correction for publication bias (Figure 1). The two studies that contributed most to this estimate were ONPHEC and CNBSS (47.8% of the total weight). Between-study heterogeneity was moderate in the main meta-analysis ($I^2 = 37.4$, Cochrane's test $p = 0.13$; Table 4); when excluding VHM&PP, the study contributing most to this heterogeneity (SA1; Figure S3), the between-study heterogeneity became low and the meta-analytical relative risk was 1.017 (95% CI: 0.970, 1.067; Table 4). The Funnel plot indicated a possible publication bias (Figure 2; Table S4) and the addition of three unobserved associations through a trim-and-fill analysis resulted in a corrected meta-analytical RR close to the null (RRc: 1.006; 95% CI: 0.941, 1.076 by 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure; Table 4). Meta-analytical RRs were relatively stable in sensitivity analyses related to study design (SA2), adjustment for socioeconomic context (SA6), analytic decisions (SA7-8), and RRs varied sensibly when stratifying on the population (SA3–SA4, with stronger effect estimates in Europe, in which sample size was low, in comparison with that of the United States) and in sensitivity analyses related to adjustment for reproductive factors (SA5) and to exposure characterization (SA9–SA12; Table 4). The association for $PM_{2.5}$ was positive in premenopausal women (1.110; 95% CI: 0.976, 1.263,

Table 1. Epidemiological studies dealing with the exposure to particulate matter with an aerodynamic diameter below 2.5 μm ($PM_{2.5}$) and the risk of breast cancer.

Study						Participants			Exposure		
Name	Reference	Design	Country	Enrollment	Follow-up period (y)	Mean age (y)	Cases	Overall	Assessment method	Residential history[d]	Mean ± SD (μg/m^3)
CEANS[a]	Andersen et al. (2017b)	Cohort	Sweden	1992–2002	9.5	59.8	226	5,997	LUR	No	7.3 ± 1.3
CECILE	Lemarchand et al. (2021)	Case–control	France	2005–2007	NC	55.3	1,165	2,436	DM	10 y	13.6 ± 1.3
CNBSS	Villeneuve et al. (2018)	Cohort	Canada	1980–1985	25	NA	6,427	89,247	Satellite	No	9.5
DCH	Andersen et al. (2017b)	Cohort	Denmark	1993–1997	15	57.7	1,054	15,835	LUR	No	11.3 ± 0.8
DNC	Andersen et al. (2017a)	Cohort	Denmark	1993 or 1999	16	52.9	1,145	22,877	CTM	3 y	19.7
EPIC-NL[b]	Andersen et al. (2017b)	Cohort	Netherlands	1993–1997	11.5	58.6	542	12,837	LUR	No	16.8 ± 0.5
EPIC-Oxford	Andersen et al. (2017b)	Cohort	United Kingdom	1993–2001	13.2	59.7	319	7,299	LUR	No	9.6 ± 1.0
EPIC-Turin	Andersen et al. (2017b)	Cohort	Italy	1993–1998	12.8	55.2	76	1,950	LUR	No	30.2 ± 1.6
HUBRO	Andersen et al. (2017b)	Cohort	Norway	2000–2001	8.6	57.2	68	1,931	LUR	No	8.9 ± 1.4
MEC	Cheng et al. (2020)	Cohort	United States	1993–1996	14.7	NA	2,726	57,589	AQMS	15 y	NA
NHSII	Hart et al. (2016)	Cohort	United States	1989	19	47	3,416	115,921	AQMS	4 y	NA
ONPHEC	Bai et al. (2020)	Cohort[c]	Canada	2001–2015	15	53.7	91,146	2,564,340	Satellite[c]	3 y	10.8
Sister Study	White et al. (2019a)	Cohort	United States	2003–2009	8.4	55.6	2,820	47,433	LUR	No	NA
VHM&PP	Andersen et al. (2017b)	Cohort	Austria	1985–2005	16.4	65.1	628	13,387	LUR	No	13.6 ± 1.2
Overall	—	—	—	—	—	—	111,758	2,959,079	—	—	10.9[e]

Note: AQMS, air quality monitoring system (permanent monitoring stations); CEANS, Cardiovascular Effects of Air pollution and Noise in Stockholm; CECILE, Breast cancer: epidemiological study on the environment in Côte d'Or and Ille-et-Vilaine; CNBSS, Canadian National Breast Screening Study; CTM, chemistry-transport model; DCH, Diet, Cancer and Health; DM, dispersion model; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; LUR, land-use regression; MEC, Multiethnic Cohort; NA, not available; NC, not concerned; NHSII, Nurses' Health Study II cohort; ONPHEC, Ontario Population Health and Environment Cohort; SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Prevention Program

[a]Pool of four cohorts from Stockholm analyzed as one: Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 Years Old/IMPROVE study (60YO/IMPROVE), and Stockholm Diabetes Prevention Program (SDPP).

[b]Pool of two Dutch cohorts analyzed as one: EPIC-Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN) and EPIC-Prospect.

[c]Cohort based on health insurance database; exposure of participants was assessed at the postal code scale.

[d]I.e., exposure assessment based on participants' residential history (with the number of years considered) or without collection of changes in home addresses ("No").

[e]Mean of air pollution exposure weighted by the number of participants in each study, when available.

Table 2. Epidemiological studies dealing with the exposure to particulate matter with an aerodynamic diameter below 10 μm (PM_{10}) and the risk of breast cancer.

Study						Participants			Exposure		
Name	Reference	Design	Country	Enrollment	Follow-up period (y)	Mean age (y)	Cases	Overall	Assessment method	Residential history[d]	Mean ± SD (μg/m^3)
AOK PLUS	Datzmann et al. (2018)	Cohort[c]	Germany	2007–2014	5	68.8	9,577	1,021,032	LUR[c]	No	20.9
CEANS[a]	Andersen et al. (2017b)	Cohort	Sweden	1992–2002	9.5	59.8	226	5,997	LUR	No	15.1 ± 4.3
CECILE	Lemarchand et al. (2021)	Case–control	France	2005–2007	NC	55.3	1,165	2,436	DM	10 y	21.6 ± 1.6
DCH	Andersen et al. (2017b)	Cohort	Denmark	1993–1997	15	57.7	1,054	15,835	LUR	No	17.2 ± 1.9
DNC	Andersen et al. (2017a)	Cohort	Denmark	1993 or 1999	16	52.9	1,145	22,877	CTM	3 y	23.5
EPIC-NL[b]	Andersen et al. (2017b)	Cohort	Netherlands	1993–1997	11.5	58.6	542	12,837	LUR	No	25.3 ± 1.2
EPIC-Oxford	Andersen et al. (2017b)	Cohort	United Kingdom	1993–2001	13.2	59.7	319	7,299	LUR	No	15.9 ± 2.0
EPIC-Turin	Andersen et al. (2017b)	Cohort	Italy	1993–1998	12.8	55.2	76	1,950	LUR	No	46.6 ± 4.1
HUBRO	Andersen et al. (2017b)	Cohort	Norway	2000–2001	8.6	57.2	68	1,931	LUR	No	13.4 ± 3.1
MEC	Cheng et al. (2020)	Cohort	United States	1993–1996	14.7	NA	2,729	57,589	AQMS	15 y	NA
NHSII	Hart et al. (2016)	Cohort	United States	1989	19	47	3,416	115,921	AQMS	4 y	NA
Sister Study	White et al. (2019a)	Cohort	United States	2003–2009	8.4	55.6	2,820	47,433	LUR	No	NA
VHM&PP	Andersen et al. (2017b)	Cohort	Austria	1985–2005	16.4	65.1	628	13,387	LUR	No	20.8 ± 2.4
Overall	—	—	—	—	—	—	23,765	1,326,524	—	—	20.9[e]

Note: AOK PLUS, Statutory health insurance database in Saxony; AQMS, air quality monitoring system (permanent monitoring stations); CEANS, Cardiovascular Effects of Air pollution and Noise in Stockholm; CECILE: Breast cancer: epidemiological study on the environment in Côte d'Or and Ille-et-Vilaine; CTM, chemistry-transport model; DCH, Diet, Cancer and Health; DM, dispersion model; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; LUR, land-use regression; MEC, Multiethnic Cohort; NA, not available; NC: not concerned; NHSII, Nurses' Health Study II cohort; SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Prevention Program.

[a]Pool of four cohorts from Stockholm analyzed as one: Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 Years Old/IMPROVE study (60YO/IMPROVE), and Stockholm Diabetes Prevention Program (SDPP).

[b]Pool of two Dutch cohorts analyzed as one: EPIC-Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN) and EPIC-Prospect.

[c]Cohort based on health insurance database; exposure of participants was assessed at the postal code scale.

[d]I.e., exposure assessment based on participants' residential history (with the number of years considered) or without collection of changes in home addresses ("No").

[e]Mean of air pollution exposure weighted by the number of participants in each study, when available.

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Table 3. Epidemiological studies dealing with the exposure to nitrogen dioxide (NO_2) and the incidence of breast cancer.

Study						Participants			Exposure		
Name	Reference	Design	Country	Enrollment	Follow-up period (y)	Mean age (y)	Cases	Overall	Assessment method	Residential history[d]	Mean ± SD (μg/m^3)
AOK PLUS	Datzmann et al. (2018)	Cohort[c]	Germany	2007–2014	5	68.8	9,577	1,021,032	LUR[c]	No	20.4
CCSPBCM1	Crouse et al. (2010)	Case–control	Canada	1996–997	NC	NA	383	799	LUR	No	23.9[e]
CCSPBCM2	Goldberg et al. (2017)	Case–control	Canada	2008–2011	NC	61.7	681	1,277	LUR	No	22.7 ± 5.1[e]
CEANS[a]	Andersen et al. (2017b)	Cohort	Sweden	1992–2002	9.5	59.8	226	5,997	LUR	No	11.8 ± 5.0
CECILE	Lemarchand et al. (2021)	Case–control	France	2005–2007	NC	55.3	1,165	2,436	DM	10 y	17.0 ± 7.0
CNBSS	Goldberg et al. (2019)	Cohort	Canada	1980–1985	25	NA	6,503	126,599	LUR	No	28.7 ± 12.0[e]
DCH	Andersen et al. (2017b)	Cohort	Denmark	1993–1997	15	57.7	1,054	15,835	LUR	No	16.5 ± 7.0
DNC	Andersen et al. (2017a)	Cohort	Denmark	1993 or 1999	16	52.9	1,145	22,877	CTM	3 y	12.5
EPIC-E3N	Andersen et al. (2017b)	Cohort	France	1993–1996	12.8	57.2	267	5,319	LUR	No	
EPIC-NL[b]	Andersen et al. (2017b)	Cohort	Netherlands	1993–1997	11.5	58.6	542	12,837	LUR	No	26.3 ± 5.0
EPIC-Oxford	Andersen et al. (2017b)	Cohort	United Kingdom	1993–2001	13.2	59.7	319	7,299	LUR	No	22.9 ± 7.0
EPIC-San Sebastian	Andersen et al. (2017b)	Cohort	Spain	1992–1995	12.3	55.3	57	1,776	LUR	No	24.1 ± 6.7
EPIC-Turin	Andersen et al. (2017b)	Cohort	Italy	1993–1998	12.8	55.2	76	1,950	LUR	No	53.0 ± 10.3
EPIC-Umeå	Andersen et al. (2017b)	Cohort	Sweden	1992–1996	13.5	54.4	175	3,762	LUR	No	5.4 ± 2.5
EPIC-Varese	Andersen et al. (2017b)	Cohort	Italy	1993–1997	11.0	56.6	201	4,727	LUR	No	44.2 ± 17.4
HUBRO	Andersen et al. (2017b)	Cohort	Norway	2000–2001	8.6	57.2	68	1,931	LUR	No	19.6 ± 7.2
MEC	Cheng et al. (2020)	Cohort	United States	1993–1996	14.7	NA	2,590	57,589	LUR	15 y	NA
NECSS	Hystad et al. (2015)	Case–control	Canada	1994–1997	NC	57.2	1,569	3,193	LUR	18 y	22.6[e]
ONPHEC	Bai et al. (2020)	Cohort[c]	Canada	2001–2015	15	53.7	91,146	2,564,340	LUR[c]	3 y	33.7[e]
Sister Study	White et al. (2019a)	Cohort	United States	2003–2009	8.4	55.6	2,817	47,433	LUR	No	NA
VHM&PP	Andersen et al. (2017b)	Cohort	Austria	1985–2005	16.4	65.1	628	13,387	LUR	No	20.4 ± 5.5
Overall	—	—	—	—	—	—	121,189	3,922,395	—	—	29.6[f]

Note: AOK PLUS, Statutory health insurance database in Saxony; CCSPBCM1, Case–control study for postmenopausal breast cancer in Montreal 1; CCSPBCM2, Case–control study for postmenopausal breast cancer in Montreal 2; CEANS, Cardiovascular Effects of Air pollution and Noise in Stockholm; CECILE, Breast cancer: epidemiological study on the environment in Côte d'Or and Ille-et-Vilaine; CNBSS, Canadian National Breast Screening Study; CTM, chemistry-transport model; DCH, Diet, Cancer and Health; DM, dispersion model; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; LUR, land-use regression; MEC, Multiethnic Cohort; NA, not available; NC, not concerned; NECSS, National Enhanced Cancer Surveillance System; ONPHEC, Ontario Population Health and Environment Cohort; SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Prevention Program.

[a]Pool of four cohorts from Stockholm analyzed as one: Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 Years Old/IMPROVE study (60YO/IMPROVE), and Stockholm Diabetes Prevention Program (SDPP).

[b]Pool of two Dutch cohorts analyzed as one: EPIC-Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN) and EPIC-Prospect.

[c]Cohort based on health insurance database; exposure of participants was assessed at the postal code scale.

[d]I.e., exposure assessment based on participants' residential history (with the number of years considered) or without collection of changes in home addresses ("No").

[e]NO_2 levels in ppb were converted in micrograms per cubic meter using the ratio: 1 ppb = 1.88 μg/m^3.

[f]Mean of air pollution exposure weighted by the number of participants in each study, when available.

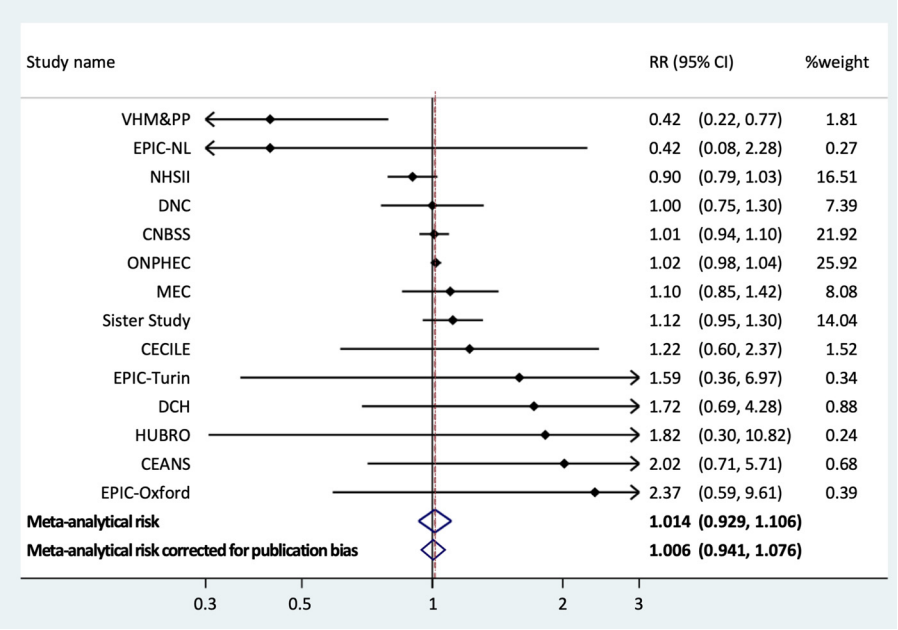

Figure 1. Random-effects meta-analytical relative risk of breast cancer incidence associated with a 10-μg/m^3 increase in exposure to particulate matter with an aerodynamic diameter below 2.5 μm ($PM_{2.5}$; $N_{cases} = 111{,}758$, $N_{participants} = 2{,}959{,}079$). Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; CECILE, Breast Cancer: Epidemiological Study on the Environment in Côte d'Or and Ille-et-Vilaine; CNBSS, Canadian National Breast Screening Study; DCH: Diet, Cancer and Health; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; MEC, Multiethnic Cohort; NHSII, Nurses' Health Study II cohort; ONPHEC, Ontario Population Health and Environment Cohort; VHM&PP, Vorarlberg Health Monitoring and Prevention Program.

based on five effect estimates) and protective in postmenopausal women (0.931; 95% CI: 0.770, 1.126; Table 4). RRs for ER+/PR+ and ER−/PR− tumors were 0.978 (95% CI: 0.862, 1.110 among 5,917 cases) and 0.967 (95% CI: 0.742, 1.259 among 1,336 cases) by 10-μg/m^3 increase in $PM_{2.5}$ exposure, respectively.

For PM_{10}, the meta-analytical RR of breast cancer was 1.058 (95% CI: 0.994, 1.126) for a 10-μg/m^3 increase in exposure levels (Figure 3). The two studies that contributed most to this estimate were the Sister Study and NHSII (45.6% of the total weight). Between-study heterogeneity was moderate in the main meta-analysis ($I^2 = 27.6$, $p = 0.14$; Table 5); when excluding AOK PLUS, the study contributing most to heterogeneity (SA1; Figure S3), the between-study heterogeneity became low and the meta-analytical RR decreased to 1.023 (95% CI: 0.975, 1.073; Table 5). The Funnel plot indicated a possible publication bias (Figure 2; Table S4) and the addition of three unobserved associations through a trim-and-fill analysis resulted in a corrected meta-analytical RR of 1.047 (95% CI: 0.984, 1.113) by 10-μg/m^3 increase in PM_{10} exposure (Table 5). The meta-analytical RRs for PM_{10} exposure remained similar in sensitivity analyses on analytic decisions (SA7–SA8) but varied sensibly in those on study design (SA2), study population (SA3–SA4), adjustment level (SA5–SA6), and exposure characterization (SA9–SA12; Table 5). Meta-analytical RRs appeared similar in premenopausal (0.992; 95% CI: 0.894, 1.100, based on three effect estimates) and postmenopausal women (1.013; 95% CI: 0.932, 1.102; Table 5); RRs for ER+/PR+ and ER−/PR− tumors were 1.012 (95% CI: 0.955, 1.072 among 5,917 cases) and 0.991 (95% CI: 0.807, 1.217 among 1,338 cases) by 10-μg/m^3 increase in PM_{10} exposure, respectively.

Concerning NO_2, the meta-analytical RR of breast cancer was 1.027 (95% CI: 1.009, 1.047) for a 10-μg/m^3 increase in exposure levels (Figure 4). The studies that contributed most were ONPHEC and CNBSS (42.5% of the total weight, when adding the independent weights of effect estimates in premenopausal and postmenopausal women from CNBSS). Between-study heterogeneity was moderate in the main meta-analysis ($I^2 = 24.0$, $p = 0.15$; Table 6); when excluding the study contributing most to heterogeneity (SA1), i.e., AOK PLUS (see Figure S3), the between-study heterogeneity became low, and the meta-analytical RR was 1.019 (95% CI: 1.003, 1.036; Table 6). Probable publication bias (asymmetrical funnel plot, Figure 2) and small-study effect (Egger's test $p = 0.018$, see Table S4) were suspected for NO_2; the addition of six unobserved associations through a trim-and-fill analysis resulted in a corrected meta-analytical RR slightly diminished (1.023; 95% CI: 1.005, 1.041, by 10-μg/m^3 increase in NO_2 exposure; Table 6). The meta-analytical association reported for NO_2 appeared relatively stable across sensitivity analyses on study design (SA2), study population (SA3–SA4), adjustment level (SA5–SA6), and analytic decisions (SA7–SA9) but somewhat varied in those on exposure characterization (SA10–SA12), with individual estimates ranging from 1.012 (95% CI: 0.991, 1.033) in studies with exposure assessment based on residential history to 1.055 (95% CI: 1.002, 1.112) in studies with recruitment starting in 2000 or later (Table 6). Lastly, the association for NO_2 appeared higher in premenopausal women (1.059, 95% CI: 0.985, 1.138, based on 4 effect estimates) than in postmenopausal women (1.019, 95% CI: 0.993, 1.046; Table 6); regarding hormone responsiveness, RRs were 1.045 (95% CI: 0.980, 1.114 among 4,460 cases) for ER+/PR+ tumors and 0.987 (95% CI: 0.885, 1.101) for ER−/PR− tumors, for each 10-μg/m^3 increase in NO_2 exposure.

Health and Economic Impact in France

The Metropolitan France study included 32.8 million women in 2013 (Insee 2016b). Almost half of the French population (45.3%) lived in "Cities," which encompass about 5% of the territory (IGN 2018) (see Table S1 and Figure S1). The annual

Table 4. Random-effects meta-analysis for the association between a 10-μg/m^3 increase in exposure to particulate matter with an aerodynamic diameter below 2.5 μm ($PM_{2.5}$) and breast cancer onset: main analyses, sensitivity analyses (SA, based on the main analysis not corrected for publication bias), and supplementary analyses according to the menopausal status or the hormonal receptor subtype.

Meta-analysis	*n* effect estimates	*n* cases	*n* participants	RR (95% CI)	I^2 (%)	Heterogeneity *p*-value[a]
Main analysis (not corrected for publication bias)[b]	14	111,758	2,959,079	1.014 (0.929, 1.106)	37.4	0.13
Main analysis (corrected for publication bias)[b]	17	112,371[c]	2,974,306[c]	1.006 (0.941, 1.076)	34.3	0.12
SA1. Leave-one-out meta-analysis[d]	13	111,130	2,945,692	1.017 (0.970, 1.067)	7.7	0.50
SA2. Restricted to prospective cohort studies	12	19,447	392,303	1.012 (0.883, 1.159)	42.2	0.072
SA3. Restricted to European populations	9	5,223	84,549	1.084 (0.730, 1.608)	42.4	0.084
SA4. Restricted to North American populations	5	106,535	2,874,530	1.012 (0.957, 1.070)	34.1	0.29
SA5. Restricted to studies with adjustment for main reproductive factors[e]	4	8,452	198,823	0.958 (0.856, 1.073)	3.3	0.47
SA6. Restricted to studies with adjustment for socioeconomic context[f]	12	109,448	2,933,766	1.013 (0.910, 1.128)	46.3	0.066
SA7. Restricted to effect estimates reported in "all women" only[g]	7	108,845	2,899,843	1.014 (0.970, 1.059)	12.8	0.52
SA8. Excluding CECILE case–control study (not published yet)	13	110,593	2,956,643	1.011 (0.922, 1.109)	41.8	0.096
SA9. Restricted to studies with exposure assessment based on precise home addresses[h]	13	20,612	394,739	1.017 (0.895, 1.155)	38.9	0.095
SA10. Restricted to studies with exposure assessment based on residential history[i]	5	99,598	2,763,163	1.000 (0.935, 1.070)	13.6	0.42
SA11. Restricted to studies with exposure assessment based on modeling data[j]	10	8,043	131,982	1.071 (0.798, 1.437)	41.9	0.11
SA12. Restricted to studies with recruitment starting in 2000 or later[k]	4	95,199	2,616,140	1.024 (0.990, 1.059)	0.2	0.61
In premenopausal women	5	4,078	NA[l]	1.110 (0.976, 1.263)	2.6	0.51
In postmenopausal women	12	13,021	NA[l]	0.931 (0.770, 1.126)	46.8	0.035
Hormone responsive positive (ER+/PR+)	4	5,917	NA[l]	0.978 (0.862, 1.110)	0.0	0.83
Hormone responsive negative (ER−/PR−)	4	1,336	NA[l]	0.967 (0.742, 1.259)	0.0	0.79

Note: Studies included in sensitivity analyses (SA): SA1: All but VHM&PP; SA2: CEANS, CNBSS, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, Sister Study, VHM&PP; SA3: CEANS, CECILE, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, VHM&PP; SA4: CNBSS, MEC, NHSII, ONPHEC, Sister Study; SA5: CECILE, DNC, MEC, NHSII; SA6: CEANS, CNBSS, DCH, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, ONPHEC, Sister Study, VHM&PP; SA7: CECILE, CNBSS, DNC, MEC, NHSII, ONPHEC, Sister Study; SA8: All but CECILE; SA9: CEANS, CECILE, CNBSS, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, Sister Study, VHM&PP; SA10: CECILE, DNC, MEC, NHSII, ONPHEC; SA11: CEANS, CECILE, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, Sister Study, VHM&PP; SA12: CECILE, HUBRO, ONPHEC, Sister Study; In premenopausal women: CECILE, CNBSS, DNC, NHSII, Sister Study; In postmenopausal women: CEANS, CECILE, CNBSS, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, NHSII, Sister Study, VHM&PP; On hormonal receptor subtypes: CECILE, MEC, NHSII, Sister Study. CI: confidence interval.

[a]Cochrane's heterogeneity Q test.

[b]Effect estimates reported in studies led in postmenopausal women only were included in the main meta-analysis in addition to the effect estimates reported in "all women" (i.e., irrespective of menopausal status).

[c]Effectives simulated by trim-and-fill analysis.

[d]I.e., excluding the study contributing the most to the between-study heterogeneity (see Figure S3).

[e]Age at menarche, age at the first full-term pregnancy, and parity.

[f]At the area level.

[g]I.e., irrespective of menopausal status.

[h]I.e., excluding studies in which air pollutant levels were assessed at the postal code scale.

[i]I.e., excluding studies in which air pollutant levels were assessed for a single home address.

[j]I.e., from land-use regression (LUR), dispersion model (DM), or chemistry-transport model (CTM).

[k]Because of stronger potential for exposure misclassification in studies recruiting subjects before 2000.

[l]Sample size could not be calculated due to missing information in source studies.

average of new breast cancer cases in women was 53,174 over the 2007–2016 period (INCa 2019b), corresponding to a crude incidence rate of 1,619 for 1 million person-years (see Table S1).

Air pollutants' concentrations were higher within urban areas, in northeastern France, in the Rhone Valley, and along the Mediterranean coast (Figure 5); exposure levels showed an increasing gradient with urbanization degree (see Table S1). The French nationwide yearly average exposure levels to $PM_{2.5}$, PM_{10}, and NO_2 were 14.5, 21.0, and 17.4 μg/m^3 in 2013, respectively; the corresponding means of air pollutant exposure over all studies included in the meta-analysis were 10.9, 20.9, and 29.6 μg/m^3, respectively (data available for 92.5%, 83.3%, and 97.3% of the total population of the meta-analysis, respectively; Tables 1–3). Although almost the entire French population (>99.9%) was exposed in 2013 to annual average levels of $PM_{2.5}$ not complying with the 10-μg/m^3 WHO guideline value, 42.5% of the population was exposed to levels of PM_{10} under the 20-μg/m^3 guideline value and almost all (98.3%) the population was exposed to levels of NO_2 complying with the 40-μg/m^3 WHO guideline value.

Because the confidence interval of the meta-analytical effect estimate corrected for publication bias for $PM_{2.5}$ tended to be centered around the null (RRc: 1.006; 95% CI: 0.941, 1.076 by 10-μg/m^3 increase), contrarily to that for the two other pollutants, the health impact assessment in France was conducted for PM_{10} and NO_2 only. To do so, we considered the meta-analytical RRs corrected for publication bias of 1.047 (95% CI: 0.984, 1.113) for PM_{10} and 1.023 (95% CI: 1.005, 1.041) for NO_2, for each 10-μg/m^3 increase.

Reaching the WHO guideline values for exposure to PM_{10} would result in an estimated reduction of 384 (95% CI: 0, 883) new breast cancer cases each year, which would correspond to 189 million Euros (M€; 130, 247) saved each year (Table 7). If PM_{10} average concentrations were as low as the fifth percentile of the concentrations modeled over the French territory, we estimated that 1,143 (95% CI: 0, 2,613) new breast cancer cases would be avoided each year, breast cancer incidence rate would be lower by 2.15% (95% CI: 0, 4.91), and annual economic savings would amount to €562 million (388, 736). Average PM_{10} levels as low as the lowest concentrations (fifth percentile) within areas of the same degree of urbanization would lead to an estimated reduction of 975 (95% CI: 0.0, 2,236) incident breast cancer cases each year, whereas a decrease by 1 μg/m^3 in PM_{10}

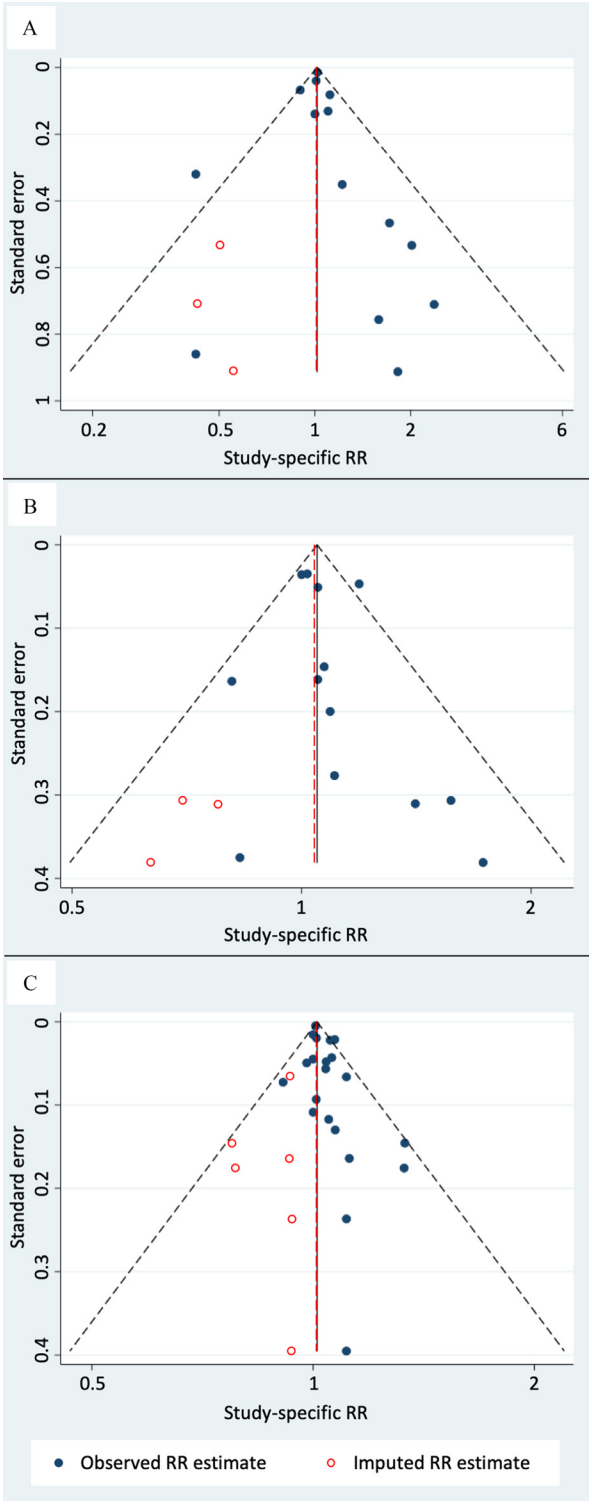

Figure 2. Funnel plots of the study-specific estimates of breast cancer relative risk associated with a 10-μg/m^3 increase in exposure to (A) particulate matter with an aerodynamic diameter below 2.5 μg/m^3 ($PM_{2.5}$), (B) particulate matter with an aerodynamic diameter below 10 μg/m^3 (PM_{10}), and (C) nitrogen dioxide (NO_2). Black solid dots: study-specific relative risk estimates identified by the literature review and included in the meta-analysis; red hollow dots: imputed relative risk estimates by trim-and-fill analysis necessary to observe a symmetrical funnel plot; vertical lines: meta-analytical relative risk estimates based on fixed-effects meta-analysis, before, in black solid line, and after, in red dotted line, trim-and-fill analysis (fixed-effects, that assume no between-study heterogeneity, are required to assess potential for publication bias).

levels would prevent 244 (95% CI: 0.0, 566) incident breast cancer cases each year. For NO_2, we estimated that three (95% CI: 1, 5) new breast cancer cases would be prevented each year if exposure levels complied with the WHO guideline values, which would correspond to €1.43 million (0.99, 1.87) of annual economic savings (Table 8). Average NO_2 levels as low as the lowest concentrations (fifth percentile) would lead to an estimated reduction by 1,677 (95% CI: 374, 2,914) new breast cancer cases each year, corresponding to a decrease by 3.15% (95% CI: 0.70, 5.48) in breast cancer incidence rate and annual savings of 825 M€ (570, 1,080). We also estimated that 1,331 (95% CI: 296, 2,319) new breast cancer cases would be avoided each year if NO_2 levels were as low as the lowest concentrations (fifth percentile) modeled within areas of the same degree of urbanization and that 121 (95% CI: 27, 213) new breast cancer cases would be prevented annually for a 1-μg/m^3 decrease in NO_2 levels.

Discussion

Main Findings

Breast cancer is the most frequent cancer in terms of incidence in many areas of the world. Its heritability of about 5%–10% (Apostolou and Fostira 2013) leaves room for a rather strong influence of nongenetic factors. Our quantitative synthesis, based on an extensive review of the literature, of the effect of air pollution long-term exposure on breast cancer risk, considered potential for publication bias. Our findings support a relationship between chronic exposure to air pollution, and specifically nitrogen dioxide, and breast cancer incidence. Although there was some evidence of publication bias for NO_2 (based on an asymmetrical funnel plot) and small study effects (Egger's test $p = 0.018$), the positive association was only slightly diminished after correction for publication bias. The meta-analytical relative risks associated with NO_2 were relatively stable across sensitivity analyses. In comparison, the meta-analytical relative risk associated with PM_{10} appeared less robust, on the basis of our sensitivity analysis. No clear association with breast cancer was observed for $PM_{2.5}$. Although based on few studies, associations of NO_2 levels with breast cancer risk appeared higher in premenopausal than in postmenopausal women, and for ER+/PR+ than ER–/PR– tumors. On the basis of these associations, we conducted what is, to the best of our knowledge, the first health and economic impact assessment on this issue, estimating that 1,677 (95% CI: 374, 2,914) new breast cancer cases could be prevented each year in France if NO_2 levels were as low as 6.3 μg/m^3, corresponding to fifth percentile of the concentrations over the French territory in 2013, which would entail annual tangible and intangible cost savings of €825 million (570, 1,080). We also estimated that decreasing PM_{10} levels down to the fifth percentile observed at the country level (i.e., 17.2 μg/m^3) could lead to avoiding 1,143 (95% CI: 0.0, 2,613) new breast cancer cases each year and to generate economic savings of €562 million (388, 736) per year. Given the spatial correlations between NO_2 and PM_{10} levels, these estimated impacts are likely not to be mutually independent and should not be added.

Estimated Effects of Air Pollution on Breast Cancer

We performed BDL random-effects models to estimate the relationship of air pollutants with breast cancer incidence. DerSimonian-Laird models (DerSimonian and Laird 1986), which are the most commonly used random-effects models in meta-analyses, do not make assumptions about the form of the distribution of either the within- or between-study effects, hence allowing between-study heterogeneity to contribute to the

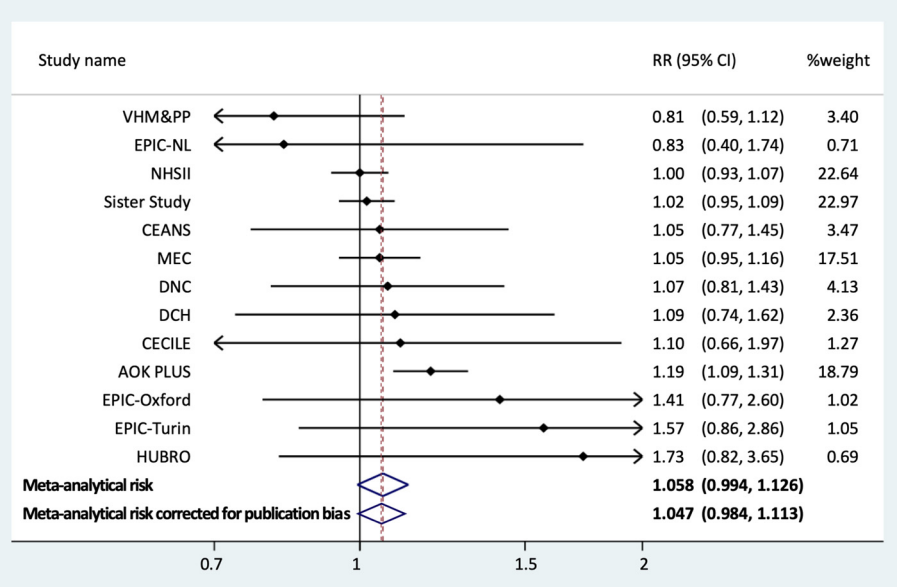

Figure 3. Random-effects meta-analytical relative risk of breast cancer incidence associated with a 10-μg/m^3 increase in exposure to particulate matter with an aerodynamic diameter below 10 μm (PM_{10}; $N_{cases} = 23{,}765$, $N_{participants} = 1{,}326{,}524$). Note: AOK PLUS, Statutory Health Insurance Database in Saxony; CEANS, Cardiovascular Effects of Air pollution and Noise in Stockholm; CECILE, Breast Cancer: Epidemiological Study on the Environment in Côte d'Or and Ille-et-Vilaine; DCH, Diet, Cancer and Health; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; MEC, Multiethnic Cohort; NHSII, Nurses' Health Study II cohort; VHM&PP, Vorarlberg Health Monitoring and Prevention Program.

variance. Additionally, by relying on nonparametric bootstrap, BDL models are recognized as performing better and providing better consolidated estimates than classical DerSimonian-Laird models (Kontopantelis and Reeves 2009).

Most of the effect estimates included in the meta-analyses were from studies of "all women" (Andersen et al. 2017b; Crouse et al. 2010; Goldberg et al. 2017) or mostly postmenopausal women (Cheng et al. 2020; Goldberg et al. 2019; Hystad et al. 2015; Lemarchand et al. 2021; Villeneuve et al. 2018); information on menopausal status was unavailable in the largest studies (representing 88.3%, 80.5%, and 92.6% of the participants of studies on $PM_{2.5}$, PM_{10}, and NO_2, respectively) (Bai et al. 2020; Datzmann et al. 2018; White et al. 2019a). To avoid discarding any study, we included in the main meta-analyses the relative risk estimates reported in "all women" (i.e., irrespective of menopausal status) as well as the relative risk estimates reported in studies including postmenopausal women only (see Table S3). Sensitivity meta-analyses showed that meta-estimates were little changed for all pollutants when restricting to estimates reported in "all women" only. To reflect the global effect expected in "all women" from CNBSS for NO_2, for lack of a global effect estimate in this study, we opted to include in the main meta-analysis both effect estimates reported separately in postmenopausal and premenopausal women. This analytical decision had minor effects on final estimates, given the similarity between meta-analytical RRs including or excluding the estimate reported in premenopausal women from CNBSS (1.027; 95% CI: 1.009, 1.047; and 1.025; 95% CI: 1.006, 1.043 by 10-μg/m^3 increase in NO_2 levels, respectively).

The studies were heterogenous in terms of characterization of air pollution exposure. Most of the studies on PM and all studies on NO_2 were based on modeling data, which generally provide a finer exposure characterization than air monitoring measurements. For $PM_{2.5}$ and PM_{10}, meta-analytical estimates were sensibly increased when restricting to studies relying on models (such as LUR models) to assess exposure, which is coherent with reliance on air quality monitoring networks only biasing estimates toward the null. Data sources could also be discussed for old studies, particularly for $PM_{2.5}$, for which large-scale monitoring was developed in 1990s. In that case, authors had to rely on PM_{10} measurements to reckon $PM_{2.5}$ concentrations, as in the U.S. Multiethnic Cohort study (Li et al. 2017), or back-extrapolate air pollutant concentrations from predictions of models developed for more recent periods, as in the ESCAPE project (Andersen et al. 2017b). Both approaches may introduce uncertainty in exposure assessment, as suggested by the increase in meta-analytical RRs when restricting to studies with recruitment starting in 2000 or later for all pollutants. Last, the fineness of the exposure assessment depends on the richness of information on participants' home addresses. Although some studies relied on participants' residential history over several years (Andersen et al. 2017a; Bai et al. 2020; Cheng et al. 2020; Hart et al. 2016; Hystad et al. 2015; Lemarchand et al. 2021), others assessed the air pollution exposure to a single home address (mostly recorded at recruitment or at breast cancer diagnosis); when excluding the latter studies, meta-analytical RRs were decreased for all pollutants. In two studies, exposure assessment was done on the basis of the ZIP code only (Bai et al. 2020; Datzmann et al. 2018); meta-analytical RRs were stable for $PM_{2.5}$ and NO_2, in comparison with a sensible attenuation toward the null for PM_{10} when excluding the latter studies. The number of considered studies varied strongly between sensitivity analyses related to exposure assessment, but overall, these analyses were in favor of the approach used to characterize air pollution exposure substantially influencing the measures of association with breast cancer risk.

Our study is suggestive of air pollution effect differing according to menopausal status, though few studies reported results in premenopausal women, which was expectable knowing that 70% of breast cancers occur after age 50 y (Bray et al. 2018). Because menopausal status is strongly related to age, a stronger relative risk in premenopausal women cannot easily be distinguished from air pollutant effects, which are stronger in early-onset as opposed to late-onset breast cancers. This effect would be compatible with attenuation bias (Hernán 2010). Alternatively, or in addition, a

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Table 5. Random-effects meta-analysis for the association between a 10-μg/m^3 increase in exposure to particulate matter with an aerodynamic diameter below 10 μm (PM_{10}) and breast cancer onset: main analyses, sensitivity analyses (SA, based on the main analysis not corrected for publication bias), and supplementary analyses according to the menopausal status or the hormonal receptor subtype.

Meta-analysis	*n* effect estimates	*n* cases	*n* participants	RR (95% CI)	I^2 (%)	Heterogeneity *p*-value[a]
Main analysis (not corrected for publication bias)[b]	13	23,765	1,326,524	1.058 (0.994, 1.126)	27.6	0.14
Main analysis (corrected for publication bias)[b]	16	24,228[c]	1,337,704[c]	1.047 (0.984, 1.113)	27.5	0.13
SA1. Leave-one-out meta-analysis[d]	12	14,188	305,492	1.023 (0.975, 1.073)	3.9	0.69
SA2. Restricted to prospective cohort studies	11	13,023	303,056	1.023 (0.971, 1.078)	7.6	0.61
SA3. Restricted to European populations	10	14,800	1,105,581	1.119 (0.998, 1.254)	14.9	0.43
SA4. Restricted to North American populations	3	8,965	220,943	1.017 (0.973, 1.062)	0.0	0.74
SA5. Restricted to studies with adjustment for main reproductive factors[e]	4	8,455	198,823	1.019 (0.964, 1.078)	0.0	0.84
SA6. Restricted to studies with adjustment for socioeconomic context[f]	10	11,878	280,179	1.023 (0.965, 1.085)	11.6	0.53
SA7. Restricted to effect estimates reported in "all women" only[g]	6	20,852	1,267,288	1.058 (0.990, 1.131)	48.1	0.079
SA8. Excluding CECILE case–control study (not published yet)	12	22,600	1,324,088	1.058 (0.991, 1.130)	33.0	0.10
SA9. Restricted to studies with exposure assessment based on precise home addresses[h]	12	14,188	305,492	1.023 (0.975, 1.073)	3.9	0.69
SA10. Restricted to studies with exposure assessment based on residential history[i]	4	8,455	198,823	1.019 (0.964, 1.078)	0.0	0.84
SA11. Restricted to studies with exposure assessment based on modeling data[j]	11	17,620	1,153,014	1.084 (0.987, 1.192)	24.0	0.15
SA12. Restricted to studies with recruitment starting in 2000 or late[k]	4	13,630	1,072,832	1.129 (0.929, 1.373)	49.2	0.033
In premenopausal women	3	2,849	NA[l]	0.992 (0.894, 1.100)	4.7	0.37
In postmenopausal women	10	6,692	NA[l]	1.013 (0.932, 1.102)	9.6	0.53
Hormone responsive positive (ER+/PR+)	4	5,917	NA[l]	1.012 (0.955, 1.072)	0.0	0.75
Hormone responsive negative (ER–/PR–)	4	1,338	NA[l]	0.991 (0.807, 1.217)	39.4	0.13

Note: Studies included in sensitivity analyses (SA): SA1: All but AOK PLUS; SA2: CEANS, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, Sister Study, VHM&PP; SA3: AOK PLUS, CEANS, CECILE, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, VHM&PP; SA4: MEC, NHSII, Sister Study; SA5: CECILE, DNC, MEC, NHSII; SA6: CEANS, DCH, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, Sister Study, VHM&PP; SA7: AOK PLUS, CECILE, DNC, MEC, NHSII, Sister Study; SA8: All but CECILE; SA9: CEANS, CECILE, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, MEC, NHSII, Sister Study, VHM&PP; SA10: CECILE, DNC, MEC, NHSII; SA11: AOK PLUS, CEANS, CECILE, DCH, DNC, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, Sister Study, VHM&PP; SA12: AOK PLUS, CECILE, HUBRO, Sister Study; In premenopausal women: CECILE, NHSII, Sister Study; In postmenopausal women: CEANS, CECILE, DCH, EPIC-NL, EPIC-Oxford, EPIC-Turin, HUBRO, NHSII, Sister Study, VHM&PP; On hormonal receptor subtypes: CECILE, MEC, NHSII, Sister Study. CI: confidence interval.
[a]Cochrane's heterogeneity Q test.
[b]Effect estimates reported in studies led in postmenopausal women only were included in the main meta-analysis in addition to the effect estimates reported in "all women" (i.e., irrespective of menopausal status).
[c]Effectives simulated by trim-and-fill analysis.
[d]I.e., excluding the study contributing the most to the between-study heterogeneity (Figure S3).
[e]Age at menarche, age at the first full-term pregnancy, and parity.
[f]At the area level.
[g]I.e., irrespective of menopausal status.
[h]I.e., excluding studies in which air pollutant levels were assessed at the postal code scale.
[i]I.e., excluding studies in which air pollutant levels were assessed for a single home address.
[j]I.e., from land-use regression (LUR), dispersion model (DM), or chemistry-transport model (CTM).
[k]Because of stronger potential for exposure misclassification in studies recruiting subjects before 2000.
[l]Sample size could not be calculated due to missing information in source studies.

role of breast cancer morphology or hormonal subtypes might be suggested to explain this difference in estimates by menopausal status. Indeed, menopausal status in breast cancer is likely to reflect different cancer morphology types and hormonal receptor subtypes, though patterns have not clearly been described (Akram et al. 2017). Thus, White et al. (2019a) reported stronger effect estimates for ductal carcinoma *in situ* (DCIS) than for invasive breast cancer for exposure to $PM_{2.5}$ (HR 1.15; 95% CI: 1.02, 1.30 vs. HR 1.02; 95% CI: 0.95, 1.08 per 3.6-μg/m^3 increase, respectively) and NO_2 (HR 1.23; 95% CI: 1.12, 1.36 vs. HR 1.01; 95% CI: 0.96, 1.07 per 5.8-ppb increase, respectively) in the Sister Study. This is, to our knowledge, the only study to have compared the effect of air pollution on breast cancer incidence according to the tumor morphology type. The relation between breast cancer and air pollution exposure was also possibly dependent on hormonal receptor subtypes in some studies (Cheng et al. 2020; Goldberg et al. 2017; Hart et al. 2016; Lemarchand et al. 2021; White et al. 2019a). Our meta-analyses did not suggest an effect of air pollution differing according to hormonal receptor subtype for PM; for NO_2, our results supported a higher RR for ER+/PR+ compared to ER–/PR– breast cancers, on the basis of few studies. This result is of interest, given that atmospheric pollutants have an estrogenic activity (Wenger et al. 2009). In a context of scarce evidence, further research is needed to better understand the interconnections between air pollution exposure, breast cancer morphology types, hormonal receptor subtypes, and menopausal status.

Our meta-analytical RR estimates were higher in European than in American populations, whatever the air pollutant. This finding could be related to residual confounding of the association of air pollution with breast cancer by socioeconomic factors. Indeed, population features, neighborhood deprivation, and air pollution levels are often interconnected, although directions of associations vary between areas (Kihal-Talantikite et al. 2018). Our meta-analytical RR estimates became closer to the null for PM_{10} and NO_2 when restricting to studies with adjustment for socioeconomic context (with the association still present for NO_2). This geographical pattern could be linked to the composition of the air pollution mixture; the risk of breast cancer associated with PM varied indeed across the United States in the Sister

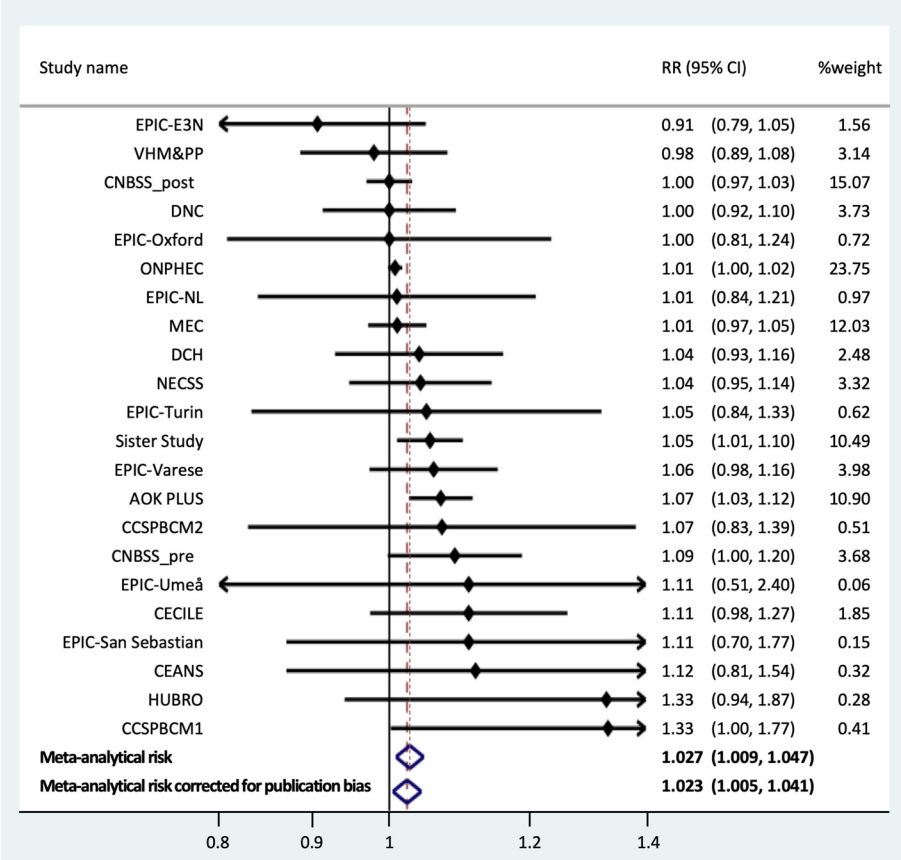

Figure 4. Random-effects meta-analytical relative risk of breast cancer incidence associated with a 10-μg/m^3 increase in exposure to nitrogen dioxide (NO_2; N_{cases} = 121,189, $N_{participants}$ = 3,922,395). Breast cancer relative risk estimates from CNBSS, reported separately in premenopausal women ("CNBSS_pre") and postmenopausal women ("CNBSS_post"). Note: AOK PLUS, Statutory Health Insurance Database in Saxony; CCSPBCM1, Case-control Study for Postmenopausal Breast Cancer in Montreal 1; CCSPBCM2, Case–control Study for Postmenopausal Breast Cancer in Montreal 2; CEANS, Cardiovascular Effects of Air pollution and Noise in Stockholm; CECILE, Breast Cancer: Epidemiological Study on the Environment in Côte d'Or and Ille-et-Vilaine; CNBSS, Canadian National Breast Screening Study; DCH, Diet, Cancer and Health; DNC, Danish Nurse Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; HUBRO, Oslo Health Study; MEC, Multiethnic Cohort; NECSS, National Enhanced Cancer Surveillance System; ONPHEC, Ontario Population Health and Environment Cohort; VHM&PP, Vorarlberg Health Monitoring and Prevention Program.

Study when considering geographic regions of distinct PM chemical component profiles (White et al. 2019a). Alternatively or in addition, it might reflect a possible vulnerability intrinsic of specific populations regarding air pollution exposure, as Cheng et al. (2020) suggested in the Multiethnic Cohort women stratifying on ethnicity (e.g., HR 1.08; 95% CI: 0.96, 1.22 in all women, HR 1.26; 95% CI: 1.01, 1.58 in African Americans, HR 1.42; 95% CI: 1.05, 1.91 in Japanese Americans, HR 0.99; 95% CI: 0.80, 1.24 in Latinos, and HR 0.92; 95% CI: 0.71, 1.20 in Whites per 50-ppb increase in NO_x after adjusting for neighborhood socioeconomic status). Thus, new studies dealing concomitantly with spatial variability in population features, socioeconomic level, and air pollution composition are needed to better characterize their specific roles in breast cancer onset.

Several studies provided qualitative syntheses of the recent evidence regarding the relationship of air pollution exposure to breast cancer risk (Rodgers et al. 2018; Sahay et al. 2019; White et al. 2018), as well as quantitative syntheses (Guo et al. 2021; Keramatinia et al. 2016; Kim et al. 2020; Zhang et al. 2019). Zhang et al. (2019) estimated that breast cancer mortality relative risk was 17% (95% CI: 5, 30) and 11% (95% CI: 2, 21) higher for a 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} exposure, respectively. Their estimates of the association for breast cancer incidence were 1.02 (95% CI: 0.93, 1.11) and 1.05 (95% CI: 0.98, 1.12) for a 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} exposure, respectively, whereas no estimate was reported for NO_2. Our study including four additional studies (Bai et al. 2020; Lemarchand et al. 2021; Villeneuve et al. 2018; White et al. 2019a) obtained similar results concerning PM in relation to breast cancer incidence. Guo et al. (2021) recently summarized the relationship of exposure to $PM_{2.5}$ and PM_{10} to breast cancer incidence and mortality, and reported similar effect estimates for incidence. Meta-analytical RRs were 1.20 (95% CI: 0.92, 1.48) and 1.07 (95% CI: 0.93, 1.20) by 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} exposure for mortality, respectively, and 1.04 (95% CI: 0.98, 1.10) and 1.03 (95% CI: 0.98, 1.09) for incidence, respectively. Although the authors explored the potential for publication bias, they did not detect any among the panel of included studies. Keramatinia et al. (2016) focused on NO_x and NO_2 exposure effects and reported a significant association with breast cancer incidence rate through a meta-analysis based on ecological studies published before mid-2014 (i.e., only 5 effect estimates, in comparison with 22 in our study), without correcting for publication bias. Most studies that examined the association between NO_2 exposure and breast cancer risk were published from 2017 onward. Finally, Kim et al. (2020) reported meta-analytical RRs for breast cancer of 0.96 (95% CI: 0.87, 1.07), 1.05 (95% CI: 0.97, 1.14), and 1.05 (95% CI: 0.99, 1.11) by 10-μg/m^3 increase in $PM_{2.5}$, PM_{10}, and NO_2, respectively. However, the latter study dealt with the relationship of air pollution to nonlung cancer in general and did not include

Table 6. Random-effects meta-analysis for the association between a 10-μg/m^3 increase in exposure to nitrogen dioxide (NO_2) and breast cancer onset: main analyses, sensitivity analyses (SA, based on the main analysis not corrected for publication bias), and supplementary analyses according to the menopausal status or the hormonal receptor subtype.

Meta-analysis	*n* effect estimates	*n* cases	*n* participants	RR (95% CI)	I^2 (%)	Heterogeneity *p*-value[a]
Main analysis (not corrected for publication bias)[b,c]	22	121,189	3,922,395	1.027 (1.009, 1.047)	24.0	0.15
Main analysis (corrected for publication bias)[b,c]	28	123,263[d]	3,939,096[d]	1.023 (1.005, 1.041)	23.0	0.14
SA1. Leave-one-out meta-analysis[e,c]	21	111,612	2,901,363	1.019 (1.003, 1.036)	12.1	0.41
SA2. Restricted to prospective cohort studies[e]	16	16,668	329,318	1.020 (1.000, 1.041)	4.9	0.56
SA3. Restricted to European populations	14	15,500	1,121,165	1.042 (1.009, 1.075)	5.1	0.62
SA4. Restricted to North American populations[e]	8	105,689	2,801,230	1.024 (0.999, 1.049)	46.3	0.11
SA5. Restricted to studies with adjustment for main reproductive factors[f]	5	7,150	87,372	1.020 (0.986, 1.055)	3.1	0.67
SA6. Restricted to studies with adjustment for socio-economic context[g,c]	18	109,035	2,870,731	1.019 (1.003, 1.036)	10.5	0.47
SA7. Restricted to effect estimates reported in "all women" only[h]	7	110,009	3,718,900	1.032 (1.005, 1.061)	54.9	0.035
SA8. Excluding the effect estimate reported in pre-menopausal women from CNBSS	21	120,537	3,884,185	1.025 (1.006, 1.043)	21.6	0.20
SA9. Excluding CECILE case–control study (not published yet)[e]	21	120,024	3,919,959	1.026 (1.007, 1.044)	23.0	0.17
SA10. Restricted to studies with exposure assessment based on precise home addresses[i,c]	20	20,466	337,023	1.026 (1.005, 1.047)	7.6	0.47
SA11. Restricted to studies with exposure assessment based on residential history[j]	5	97,615	2,650,435	1.012 (0.991, 1.033)	14.1	0.62
SA12. Restricted to studies which started since 2000[k]	6	105,454	3,638,449	1.055 (1.002, 1.112)	62.4	0.008
In premenopausal women	4	2,065	NA[l]	1.059 (0.985, 1.138)	15.4	0.38
In postmenopausal women	17	14,050	NA[l]	1.019 (0.993, 1.046)	5.0	0.63
Hormone responsive positive (ER+/PR+)	4	4,460	NA[l]	1.045 (0.980, 1.114)	15.9	0.40
Hormone responsive negative (ER–/PR–)	4	NA[l]	NA[l]	0.987 (0.885, 1.101)	19.6	0.28

Note: Studies included in sensitivity analyses (SA): SA1: All but AOK PLUS; SA2: CEANS, CNBSS, DCH, DNC, EPIC-E3N, EPIC-NL, EPIC-Oxford, EPIC-San Sebastian, EPIC-Turin, EPIC-Umeå, EPIC-Varese, HUBRO, MEC, Sister Study, VHM&PP; SA3: AOK PLUS, CEANS, CECILE, DCH, DNC, EPIC-E3N, EPIC-NL, EPIC-Oxford, EPIC-San Sebastian, EPIC-Turin, EPIC-Umeå, EPIC-Varese, HUBRO, VHM&PP; SA4: CCSPBCM1, CCSPBCM2, CNBSS, MEC, NECSS, ONPHEC, Sister Study; SA5: CCSPBCM2, CECILE, DNC, MEC, NECSS; SA6: CCSPBCM1, CCSPBCM2, CEANS, CNBSS, DCH, EPIC-NL, EPIC-Oxford, EPIC-San Sebastian, EPIC-Turin, EPIC-Umeå, EPIC-Varese, HUBRO, MEC, NECSS, ONPHEC, Sister Study, VHM&PP; SA7: AOK PLUS, CECILE, DNC, MEC, NECSS, ONPHEC, Sister Study; SA8: All studies without the effect estimate reported in premenopausal women from CNBSS; SA9: All but CECILE; SA10: CCSPBCM1, CCSPBCM2, CEANS, CECILE, CNBSS, DCH, DNC, EPIC-E3N, EPIC-NL, EPIC-Oxford, EPIC-San Sebastian, EPIC-Turin, EPIC-Umeå, EPIC-Varese, HUBRO, MEC, NECSS, Sister Study, VHM&PP; SA11: CECILE, DNC, MEC, NECSS, ONPHEC; SA12: AOK PLUS, CCSPBCM2, CECILE, HUBRO, ONPHEC, Sister Study; In premenopausal women: CECILE, CNBSS, NECSS, Sister Study; In postmenopausal women: CCSPBCM1, CCSPBCM2, CEANS, CECILE, CNBSS, DCH, EPIC-E3N, EPIC-NL, EPIC-Oxford, EPIC-San Sebastian, EPIC-Turin, EPIC-Umeå, EPIC-Varese, HUBRO, NECSS, Sister Study, VHM&PP; On hormonal receptor subtypes: CCSPBCM2, CECILE, MEC, Sister Study.

[a]Cochrane's heterogeneity Q test.

[b]Effect estimates reported in studies led in postmenopausal women only were included in the main meta-analysis in addition to the effect estimates reported in "all women" (i.e., irrespective of menopausal status).

[c]Because no global effect estimate was available in "all women" from CNBSS, both effect estimates reported separately in postmenopausal and premenopausal CNBSS women were included.

[d]Effectives simulated by trim-and-fill analysis.

[e]It means, excluding the study contributing the most to the between-study heterogeneity (Figure S3).

[f]Age at menarche, age at the first full-term pregnancy, and parity.

[g]At the area level.

[h]I.e., irrespective of menopausal status.

[i]I.e., excluding studies in which air pollutant levels were assessed at the postal code scale.

[j]I.e., excluding studies in which air pollutant levels were assessed for a single home address.

[k]Because of stronger potential for exposure misclassification in studies recruiting subjects before 2000.

[l]Sample size could not be calculated due to missing information in source studies.

several studies focusing on breast cancer (Bai et al. 2020; Cheng et al. 2020; Datzmann et al. 2018; Goldberg et al. 2019; Lemarchand et al. 2021; Villeneuve et al. 2018; White et al. 2019a). None of these previous quantitative syntheses conducted meta-analyses by menopausal status or hormonal receptor subtype.

Health and Economic Impact Assessment

Health impact assessment studies strongly depend on input parameters, namely dose–response functions, exposure data, and breast cancer incidence data, and on the considered counterfactual situations. We relied on meta-analytical relative risks corrected for publication bias, reflecting the whole evidence of the literature. We did not rely on meta-analytical RRs specific of European populations, for which our sensitivity analyses were in favor of stronger associations than in the rest of the world, which might have led to an underestimation of the health impact in France.

Our exposure data stemmed from a fine-scale (1-km^2 grid) air pollution dispersion model. The leave-one-out cross-validation of the daily model estimates showed very good fit with PM_{10} and NO_2 routine monitoring station measurements (median $r = 0.93$ and 0.90, respectively) (Benmerad et al. 2017b). To our knowledge, this air pollutant model is the nationwide model with the finest spatial and temporal resolutions currently available in France. This rather fine spatial resolution is a strength of the study, because relying on less fine models can lead to underestimating the health impact (Kulhánová et al. 2018; Morelli et al. 2016).

Breast cancer incidence was obtained for each of the 96 metropolitan French *départements* over the 2007–2016 period. Using a 10-y annual cancer incidence average including the study baseline (2013) allowed us to limit temporal fluctuations while matching the pollution exposure time. We relied on cancer cases' counts at mesoscale (i.e., regional scale) and cancer cases' distribution by age at national scale, which was the finest French nationwide data available. Local geographic variations in the distribution by age of breast cancer cases cannot be ruled out, with possible impacts on our estimates. Cancer registries providing breast cancer incidence data at the scale of cities also exist, but

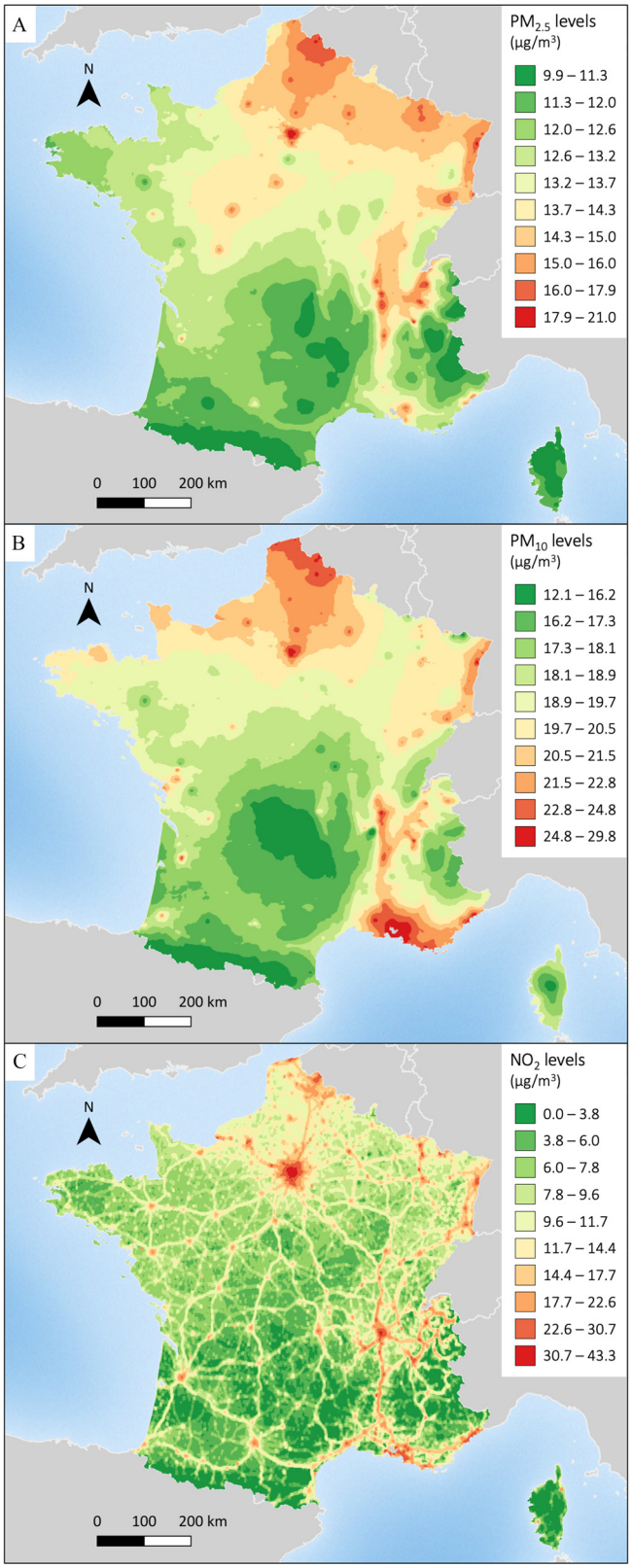

Figure 5. Annual average concentration levels of (A) particulate matter with an aerodynamic diameter below 2.5 µg/m^3 ($PM_{2.5}$), (B) particulate matter with an aerodynamic diameter below 10 µg/m^3 (PM_{10}), and (C) nitrogen dioxide (NO_2), in France, in 2013. Data at the 1-km^2 spatial resolution, from the national air pollution model developed by the French National Institute for Industrial Environment and Risks (Ineris) (Benmerad et al. 2017a).

they cover only 20 out of the 96 French *départements* and could therefore not be employed in this nationwide study.

We considered several counterfactual scenarios. WHO guideline values, set up in 2008 [European Union (Official Journal) 2008], represent targets that may have relevance for countries with high exposure levels. We considered other counterfactual situations such as air pollutant levels not exceeding the lowest concentrations within the French territory (a so-called minimum natural level) as well as a homogeneous decrease by 1 µg/m^3 all over the country. Such alternatives are relevant, respectively, for quantifying the global health impact of anthropogenic air pollution and for the assessment *ex ante* of the health benefits that could be drawn from public policies aiming to decrease air pollution exposure (Morelli et al. 2019).

When available, we favored French economic studies for valuing the annual tangible and intangible costs associated with breast cancer cases. Few studies quantified the medical costs related to breast cancer and the related sick-leave durations, which might limit the accuracy of tangible cost estimates. We relied on a Canadian study to estimate the sick-leave duration for breast cancer because we lacked data for France. Sick-leave duration is mostly a function of the disease itself, of treatments, and also of the health insurance system of the country. Additionally, we assumed that the average age at diagnosis (61.8 y) was equal to the retirement age in France (about 65 y). These analytical decisions could have introduced error in the estimation of indirect tangible costs. Nonetheless, the total cost estimates should be little affected, in view of the small part that indirect tangible costs represent among all costs; indeed, tangible costs encompassed about 12% of the total costs, of which about 85% were direct tangible costs. Considering the lack of recent data on breast cancer survival more than 10 y after diagnosis, we assumed no fatality after this time span. This assumption may lead to an underestimation of the average years of life loss per breast cancer case and hence of intangible costs.

Kulhánová et al. (2018) assessed that exposure to anthropogenic $PM_{2.5}$ would entail about 3,000 new lung cancer cases each year in France. As far as women are concerned, with nearly 1,700 new breast cancer cases yearly attributable to NO_2 or related compounds, the health impact of air pollution exposure on breast cancer would therefore be similar to that on lung cancer in women. Thus, our impact study emphasizes that breast cancer would deserve to be considered alongside lung cancer to fully appraise the burden of air pollution on cancer.

Biological Plausibility of the Relationship between Air Pollution and Breast Cancer

The $PM_{2.5}$ fraction contains mutagenic species (Valavanidis et al. 2008), many of which being produced by fossil fuel combustion. However, the meta-analysis that we conducted did not support an effect of $PM_{2.5}$ on breast cancer (which of course does not allow to discard such an effect), and the relation with PM_{10} varied sensibly in sensitivity analyses (except in those related to analytical decisions). The studies included in the meta-analyses only considered PM mass concentration. An increased risk of breast cancer was shown in a few studies that focused on chemical components constituting the air pollution mixture. Thus, Andersen et al. (2017b) associated breast cancer relative risk with PM_{10} elemental composition in nickel (HR 1.40; 95% CI: 1.00, 1.95, by 2-ng/m^3 increase, in 44,009 women) and vanadium (HR 1.39, 95% CI: 1.03, 1.87, by 3-ng/m^3 increase, in 51,937 women), two heavy metals mainly originating from oil-burning and industry (HR was 1.07; 95% CI: 0.89, 1.30, by 10-µg/m^3 increase in total PM_{10} concentration, in the 68,806 women included in this study). An estrogen-like effect has further

Table 7. Incident breast cancer cases yearly attributable to particulate matter with an aerodynamic diameter below 10 μm (PM_{10}) exposure in France and related economic costs (in millions of 2019 Euros), depending on the considered counterfactual situation.

	Attributable to PM_{10} exposure[b]			Related economic costs [€ (millions)]	
Counterfactual situation[a]	Count (95% CI)	Incidence[c] (95% CI)	% Baseline[d] (95% CI)	Cost component	Amount (Low, high)[e]
Compliance with the WHO guideline value	384 (0, 883)	11.7 (0, 26.9)	0.72% (0, 1.66)	All costs	189 (130, 247)
				Intangible costs	167 (112, 223)
				Direct tangible costs	18.5 (16.9, 20.0)
				Indirect tangible costs	3.41 (2.27, 4.55)
Low pollution level	1,143 (0, 2,613)	34.8 (0, 79.6)	2.15% (0, 4.91)	All costs	562 (388, 736)
				Intangible costs	497 (331, 662)
				Direct tangible costs	55.0 (50.3, 60.0)
				Indirect tangible costs	10.1 (6.75, 13.5)
Low pollution level within the same urbanization degree areas	975 (0, 2,236)	29.7 (0, 68.1)	1.83% (0, 4.21)	All costs	480 (331, 628)
				Intangible costs	424 (283, 565)
				Direct tangible costs	46.9 (42.9, 50.9)
				Indirect tangible costs	8.65 (5.76, 11.5)
Pollutant concentration levels 1 $\mu g/m^3$ lower than baseline	244 (0, 566)	7.42 (0, 17.2)	0.46% (0, 1.06)	All costs	120 (82.8, 157)
				Intangible costs	106 (70.6, 141)
				Direct tangible costs	11.7 (10.7, 12.7)
				Indirect tangible costs	2.16 (1.44, 2.88)

Note: Based on the meta-analytical relative risk corrected for publication bias of 1.047 (0.984, 1.113) by 10-$\mu g/m^3$ increase in PM_{10} exposure. Note: CI, confidence interval; DEGURBA, degree of urbanization; WHO, World Health Organization.
[a]Current WHO guideline value: 20 $\mu g/m^3$ for PM_{10}; "low pollution level": defined as the 5th percentile of concentrations at the French territory scale (i.e., 17.2 $\mu g/m^3$ for PM_{10} in 2013); "low pollution level within the same urbanization degree areas": defined as the 5th percentile of concentrations within areas of the same degree of urbanization (i.e., 18.5, 17.3, and 16.8 $\mu g/m^3$ for PM_{10} in 2013 in "Cities," "Towns and suburbs," and "Rural areas," respectively), according to the DEGURBA index provided for each municipality by the European statistical office of the European Commission (latest update: 2011; see Figure S1).
[b]In 2013, based on the modeled air pollutant concentration data.
[c]For 1 million person-years.
[d]Proportion (in %) of the baseline annual new breast cancer cases, based on the regional incidence data provided by the National Institute for Cancer (INCa) over the 2007–2016 period.
[e]Regarding intangible and indirect tangible costs, low–high intervals are based on the uncertainty range of ±33% applied to the value of a life-year (VOLY) and to the value of a workday in Aphekom project, respectively (Chanel 2011); regarding direct tangible costs, they are based on the 95% CI of the treatment cost estimates for breast cancer (Cortaredona and Ventelou 2017).

been suggested for some heavy metals, including nickel (Aquino et al. 2012). White et al. (2019b) reported in the Sister Study (n cases = 2,034) elevated relative risks of postmenopausal breast cancer for airborne metallic chemicals such as mercury, cadmium, and lead, with respective HR of 1.3 (95% CI: 1.1, 1.5), 1.1 (95% CI: 0.96, 1.3), and 1.1 (95% CI: 0.98, 1.3) when comparing the highest to the lowest exposure quintiles. Airborne cadmium concentrations were also positively associated with ER−/PR− breast cancer incidence (n cases = 245) in the never-smoking participants of the California Teachers Study (Liu et al. 2015).

Table 8. Incident breast cancer cases yearly attributable to nitrogen dioxide (NO_2) exposure in France and related economic costs (in millions of 2019 Euros), depending on the considered counterfactual situation.

	Attributable to NO_2 exposure[b]			Related economic costs [€ (millions)]	
Counterfactual situation[a]	Count (95% CI)	Incidence[c] (95% CI)	% Baseline[d] (95% CI)	Cost component	Amount (low, high)[e]
Compliance with the WHO guideline value	3 (1, 5)	0.09 (0.02, 0.16)	0.01% (0.00, 0.01)	All costs	1.43 (0.99, 1.87)
				Intangible costs	1.26 (0.84, 1.68)
				Direct tangible costs	0.14 (0.13, 0.15)
				Indirect tangible costs	0.03 (0.02, 0.03)
Low pollution level	1,677 (374, 2,914)	51.1 (11.4, 88.7)	3.15% (0.70, 5.48)	All costs	825 (570, 1,080)
				Intangible costs	729 (486, 972)
				Direct tangible costs	80.7 (73.8, 87.6)
				Indirect tangible costs	14.9 (9.91, 19.8)
Low pollution level within the same urbanization degree areas	1,331 (296, 2,319)	40.5 (9.01, 70.6)	2.50% (0.56, 4.36)	All costs	654 (452, 857)
				Intangible costs	579 (386, 771)
				Direct tangible costs	64.0 (58.5, 69.5)
				Indirect tangible costs	11.8 (7.86, 15.7)
Pollutant concentration levels 1 $\mu g/m^3$ lower than baseline	121 (27, 213)	3.68 (0.81, 6.49)	0.23% (0.05, 0.40)	All costs	59.4 (41.0, 77.7)
				Intangible costs	52.5 (35.0, 70.0)
				Direct tangible costs	5.81 (5.31, 6.31)
				Indirect tangible costs	1.07 (0.71, 1.43)

Note: Based on the meta-analytical relative risk corrected for publication bias of 1.023 (1.005, 1.041) by 10-$\mu g/m^3$ increase in NO_2 exposure. Note: CI, confidence interval; WHO, World Health Organization.
[a]Current WHO guideline value: 40 $\mu g/m^3$ for NO_2; "low pollution level": defined as the fifth percentile of concentrations at the French territory scale (i.e., 6.3 $\mu g/m^3$ for NO_2 in 2013); "low pollution level within the same urbanization degree areas": defined as the fifth percentile of concentrations within areas of the same degree of urbanization (i.e., 12.3, 8.9, and 4.7 $\mu g/m^3$ for NO_2 in 2013 in "Cities," "Towns and suburbs," and "Rural areas," respectively), according to the DEGURBA index provided for each municipality by the European statistical office of the European Commission (latest update: 2011; see Figure S1).
[b]In 2013, based on the modeled air pollutant concentration data.
[c]For 1 million person-years.
[d]Proportion (%) of the baseline annual new breast cancer cases, based on the regional incidence data provided by the National Institute for Cancer (INCa) over the 2007–2016 period.
[e]Regarding intangible and indirect tangible costs, low–high intervals are based on the uncertainty range of ±33% applied to the value of a life-year (VOLY) and to the value of a workday in Aphekom project, respectively (Chanel 2011); regarding direct tangible costs, they are based on the 95% CI of the treatment cost estimates for breast cancer (Cortaredona and Ventelou 2017).

Mammographic breast density, a strong risk factor for breast cancer, was also positively associated with airborne lead and cobalt, two metals present in vehicles exhaust (except in unleaded gas engines) and industrial steams (White et al. 2019c). Positive associations between nonmetallic airborne carcinogens (e.g., methylene chloride, styrene) and breast cancer incidence were also reported in the Sister Study (Niehoff et al. 2019). Last, the oxidative potential of PM (Daellenbach et al. 2020) could also be considered for future research in relation to breast cancer.

Although laboratory studies showed that nitrogen oxides in contact with organic compounds (even nonmutagenic compounds) and sunlight (Claxton et al. 2004) could lead to the formation in the air of secondary mutagenic nitrogen-containing compounds, the inherent carcinogenicity of nitrogen oxides has not been proven. The association of exposure to nitrogen oxides with mammographic breast density was only suggested (White et al. 2019c; Yaghjyan et al. 2017) and not consistently observed (DuPre et al. 2017; Huynh et al. 2015). Effects of air pollutants, including NO_2 or NO_x, on DNA methylation have also been suggested (Alfano et al. 2018), though the link between epigenome-wide DNA hypermethylation in prediagnostic blood samples and breast cancer risk appeared uncertain as Bodelon et al. (2019) recently showed through a meta-analysis of four prospective studies (meta-analytical RR 0.94; 95% CI: 0.85, 1.05). Knowing that NO_x and NO_2 are considered as the best road traffic tracers, that diesel exhaust has been classified as a whole as Group 1 carcinogen by IARC (Benbrahim-Tallaa et al. 2012), and that air pollutants have estrogenic activity (Wenger et al. 2009), NO_2 may represent a marker of exposure to components with plausible biological mechanisms, without being directly involved in the cancer pathophysiology.

It can be hypothesized that NO_2 is a better marker of exposure to specific PM species or heavy metals with carcinogenic or hormonal properties and found in vehicles exhaust than ambient total PM concentration levels as assessed by current studies. Tsai et al. (2015) showed that air concentrations in nickel or vanadium in $PM_{2.5}$ were more highly correlated to NO_2 or NO_x concentration levels than to total $PM_{2.5}$ concentration levels. Vehicle exhausts, in addition to tobacco smoke, are also a major source of benzene exposure in the general population. Benzene exposure was related to ER–/PR– breast tumors in the California Teachers Study cohort (Garcia et al. 2015). *In vivo* studies showed that benzene could induce mammary tumors in animals (Rudel et al. 2007). Finally, NO_2 may be a marker of exposure to PAH levels, of which major urban sources are residential heating with solid fuels and combustion engine vehicle exhaust (mainly diesel engines). Because Petralia et al. (1999) reported in an occupational setting that PAHs could be involved in breast cancer onset, several specific exposure windows appeared of higher concern: at menarche (Nie et al. 2007), at first pregnancy (Nie et al. 2007), and before age 36 (Labrèche et al. 2010). PAHs are lipophilic and thus can accumulate in the fat tissue of the breast, have estrogenic or antiestrogenic properties (Santodonato 1997), induce pro-cancerous and proinflammatory responses (Niu et al. 2017), induce mammary tumors in animals (Rudel et al. 2007), and can lead to the formation of PAH-DNA adducts (Gray et al. 2017; Rodgers et al. 2018). Benzo[*a*]pyrene was classified as Group 1 carcinogen to humans by IARC (Baan et al. 2009), and 3 and 11 other PAHs were classified as belonging to Group 2A (probably carcinogenic) or Group 2B (possibly carcinogenic), respectively.

In conclusion, this study provides an up-to-date quantitative synthesis of the literature regarding the relationship between long-term exposure to ambient $PM_{2.5}$, PM_{10}, and NO_2 and breast cancer onset. After correction for publication bias, we estimated that breast cancer incidence was increased by 2.3% (95% CI: 0.5, 4.1) for each 10-$\mu g/m^3$ increase in NO_2 exposure. Premenopausal women appeared more at risk than postmenopausal women, though estimates for premenopausal women were based on only four studies (n cases = 2,065) for NO_2, and effect estimates appeared stronger for the risk of tumors responsive to estrogen and progesterone (ER+/PR+, n cases = 4,460), compared with non-hormonally responsive tumors (ER–/PR–), on the basis of four studies for NO_2. Results concerning exposure to PM were less conclusive. On the basis of the dose–response functions established, we estimated that about 1,700 breast cancer cases could be attributable yearly to exposure to NO_2 or correlated air pollutants. We cannot claim that this association is a consequence of NO_2 exposure itself. Indeed, NO_2 may be a marker of exposure to traffic-related air pollutants with potential carcinogenic or hormonal properties, in particular heavy metals as well as aromatic hydrocarbons such as PAHs and benzene. Further studies are needed to better characterize the exposure of the general population to these pollutants and hence to bring better understanding of their role in breast cancer pathophysiology, particularly in premenopausal women and according to tumor morphology types and hormonal receptor subtypes, areas of research in which the evidence remains scarce. Our study emphasizes that breast cancer would deserve to be considered to fully appraise the burden of air pollution on women's health.

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