Breast Cancer Incidence in Relation to Long-Term Low-Level Exposure to Air Pollution in the ELAPSE Pooled Cohort

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ABSTRACT

Background: Established risk factors for breast cancer include genetic disposition, reproductive factors, hormone therapy, and lifestyle-related factors such as alcohol consumption, physical inactivity, smoking, and obesity. More recently a role of environmental exposures, including air pollution, has also been suggested. The aim of this study, was to investigate the relationship between long-term air pollution exposure and breast cancer incidence.

Methods: We conducted a pooled analysis among six European cohorts (n = 199,719) on the association between long-term residential levels of ambient nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$), black carbon (BC), and ozone in the warm season (O_3) and breast cancer incidence in women. The selected cohorts represented the lower range of air pollutant concentrations in Europe. We applied Cox proportional hazards models adjusting for potential confounders at the individual and area-level.

Results: During 3,592,885 person-years of follow-up, we observed a total of 9,659 incident breast cancer cases. The results of the fully adjusted linear analyses showed a HR (95% confidence interval) of 1.03 (1.00–1.06) per 10 $\mu g/m^3$ NO_2, 1.06 (1.01–1.11) per 5 $\mu g/m^3$ $PM_{2.5}$, 1.03 (0.99–1.06) per 0.5 10^{-5} m^{-1} BC, and 0.98 (0.94–1.01) per 10 $\mu g/m^3$ O_3. The effect estimates were most pronounced in the group of middle-aged women (50–54 years) and among never smokers.

Conclusions: The results were in support of an association between especially $PM_{2.5}$ and breast cancer.

Impact: The findings of this study suggest a role of exposure to NO_2, $PM_{2.5}$, and BC in development of breast cancer.

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Introduction

According to the most recent cancer statistics, female breast cancer has surpassed lung cancer and has become the most frequently diagnosed cancer worldwide and the leading cause of cancer-related deaths among women (1). The incidence of breast cancer varies considerably between transitioned and transitioning countries (55.9 vs. 29.7 cases per 100,000, respectively); however, with a rapid increase observed in many transitioning countries (1, 2).

Established risk factors for postmenopausal breast cancer include reproductive factors including parity and age at first birth, age at menarche, the use of hormone therapy (HT), a family history of breast cancer, and lifestyle factors such as alcohol consumption, smoking, physical inactivity, and obesity—mainly through an etiological pathway of sex-steroid hormones (3–5). Premenopausal breast cancers largely share these risk factors, however with a stronger genetic component (6). The regional variation in combination with a rise in incidence reflect changes in lifestyle-related risk factors in countries of growing economic development and industrialization, but may also point to a role of environmental exposures in the etiology of breast cancer.

Air pollution has been classified as a human carcinogen by the International Agency for Research on Cancer based on evidence of associations with lung cancer (7), and in recent years, several epidemiological studies have emerged focusing on a possible link between air pollutants and breast cancer. So far, the evidence is mixed. A newly published review and meta-analysis reported a HR of 1.02 [95% confidence interval (CI): 1.01–1.04] per 10 $\mu g/m^3$ increase in nitrogen dioxide (NO_2), which represents local fossil fuel combustion sources (e.g., major roads/motorized traffic), across estimates from the existing literature ($N = 18$) and a HR of 1.03 (95% CI, 0.99–1.06) per 10 $\mu g/m^3$ increase in particulate matter (PM) with aerodynamic diameters less than or equal to 2.5 μm ($PM_{2.5}$) – primarily reflecting air pollution transported over large distances (8). The estimates, however, were somewhat heterogenous across different study designs, geographical regions, menopausal status, and breast cancer subgroups. Two Canadian studies addressing air pollution effect estimates in relation to age showed higher risks of breast cancer in younger women (assumed premenopausal) in association with higher exposure to NO_2 and $PM_{2.5}$, but no association for older women (>50 years; refs. 9, 10). Also, findings from the Danish Nurse Cohort Study indicated an association between $PM_{2.5}$ exposure and premenopausal but not postmenopausal breast cancer (11). Findings from the large European Study of Cohorts for Air Pollution Effects (ESCAPE), which was based on 15 European cohorts across nine European countries, were suggestive of a higher hazard of postmenopausal breast cancer with higher exposure to $PM_{2.5}$ (12). The study also pointed toward possible effects of individual $PM_{2.5}$ constituents especially for nickel and vanadium. All reported estimates were, however, with a high level of statistical uncertainty. Studies regarding possible effects of ozone (O_3) are few, but so far not indicative of an association with breast cancer (13, 14).

In this study, we used data from the large Effects of Low-level Air Pollution: a Study in Europe (ELAPSE) which builds on the ESCAPE collaboration by pooling data across cohorts, to investigate the relationship between long-term air pollution exposure and breast cancer incidence. In contrast to the meta-analytic approach across individual cohort effect estimates applied in ESCAPE, we performed a pooled data analysis—thereby gaining statistical power and the ability to exploit the concentration-response function—with a more Europe-wide state-of-the-art hybrid model for exposure assessment and a longer follow-up period.

Materials and Methods

Study population

We used data from the following six out of nine cohorts included in the ELAPSE collaboration, which contained information on female breast cancer incidence and the most important potential confounders: Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) - which is the collective name of four sub-cohorts [Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; ref. 15); Stockholm Screening Across the Lifespan Twin study (SALT; ref. 16); The Stockholm cohort of 60-year-olds (Sixty; ref. 17); and the Stockholm Diabetes Prevention Programme (SDPP; ref. 18); the Danish Diet, Cancer and Health cohort (DCH; ref. 19); the Danish Nurse Cohort (DNC; ref. 20); the Dutch European Investigation into Cancer and Nutrition (EPIC-NL) - consisting of the two sub-cohorts EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (EPIC-MORGEN) and (EPIC-Prospect; ref. 21); the Etude Epidemiologique aupres de femmes de la Mutuelle Générale de l'Education Nationale (E3N or EPIC-France; ref. 22); and the Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP; ref. 23). Cohorts were recruited between 1985 and 2005 with a follow up until 2011 to 2015 and selected to include a large number of subjects residing at areas of low air pollution exposures, that is, below current air quality standards ($PM_{2.5}$ 25 $\mu g/m^3$, NO_2 40 $\mu g/m^3$ for the EU). Data from all cohorts were pooled and stored on a secure server in Utrecht University. Key covariates were identified from each cohort and harmonized. All six cohorts had information available at baseline on age, sex, smoking status, amount and duration of smoking in current smokers (E3N and VHM&PP only in classes), body mass index (BMI), employment status, and area-level socio-economic status (SES). With the exception of CEANS Sixty, CEANS SNAC-K and the VHM&PP, information on alcohol consumption, HT use, and nulliparity was also available.

We included all women who were free of cancer at baseline (with the exception of nonmelanoma skin cancer).

Exposure assessment

The model developed for air pollution exposure assessment and validation has been described in detail elsewhere (24, 25). In brief, Europe-wide hybrid land use regression (LUR) models were applied incorporating air pollution monitoring data, satellite observations, chemistry and transport model (CTM) estimates, land use, and road variables as predictors. To develop and evaluate models, we used 2010 AirBase routine monitoring data maintained by the European Environmental Agency for $PM_{2.5}$, NO_2 and O_3 (warm season) and ESCAPE monitoring data for black carbon (BC) (26). Year 2010 was the earliest year of a sufficiently wide coverage of $PM_{2.5}$ monitoring across Europe, and ESCAPE monitoring was performed in the period 2009 to 2010. For reasons of consistency, we used the 2010 period for NO_2 and O_3 for our main models as well. We applied models for 2010 (annual averages) to create surfaces (100 m × 100 m grids) and linked these to the baseline residential address of cohort members.

Outcome

The cohort participants were followed in national cancer registries, death certificates or medical records. One exception was the E3N cohort which applied self-reports from biannual questionnaires or death certificates, confirmed through pathologic reports and reviewed by an oncologist. We defined breast cancer according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code C50 or 9th Revision (ICD-9) code 174.

Statistical analysis

We applied Cox proportional hazards models with age as the underlying time scale, censoring each cohort member at time of first occurrence of any cancer other than breast cancer, date of death, emigration, loss to follow-up, or at the end of follow-up. NO_2, $PM_{2.5}$, BC, and O_3 were incorporated with a linear function and HRs for increments of 10 $\mu g/m^3$, 5 $\mu g/m^3$, 0.5 $10^{-5}m^{-1}$, and 10 $\mu g/m^3$, respectively, were reported. We included strata per individual (sub) cohort to account for baseline hazard heterogeneity across the cohorts and to relax the proportional hazards assumption.

We modelled the association between the air pollutants and breast cancer incidence in three models: (i) accounting for age (applied as the underlying time-scale), (sub) cohort ID (included as strata), and adjustment for year of enrolment in order to account for time-trends in exposure and outcome; (ii) further adjusted for individual-level factors marital status (married/cohabiting, divorced, single, widowed), employment status (yes vs. no), BMI (<18.5, 18.5–24, 25–29, and 30+ kg/m^2), smoking status (never, former, current), smoking duration (years of smoking) and smoking intensity (cigarettes/day) for current smokers; (iii) (main model) further adjusted for area-level mean income in 2001, as a proxy for SES, which was the most consistently available variable and year across cohorts. The spatial scale of an area varied from smaller neighborhoods and city districts (CEANS, EPIC-NL, E3N) to municipalities (DNS, DCH, and VHM&PP). We excluded participants with incomplete information on model 3 variables from all analyses.

Sensitivity analyses included: (i) analyzing the cohort in age groups. For this categorization, we used age at diagnosis and followed a time varying setting of the data, breaking follow-up time into three time windows: <50 years, 50 to 54 years, and 55+ years. We tested the heterogeneity in effects across the age groups by a meta-analytic approach using the Cochran Chi statistic and the I^2 statistic. We did not have information on menopausal status available in all cohorts. (ii) Investigating the impact of the potential confounders alcohol consumption (linear term), HT (ever use yes/no), and nulliparity (yes/no), by comparing estimates in identical subsets of cohorts with and without adjustment. These variables were not available in all cohorts. (iii) Addressing potential effect measure modification between the exposures and the covariates smoking status, BMI (three categories of <25, 25–29, and 30+ kg/m^2), and area-level socio-economic status (two-categories below and above the mean area-level income of 18,900 Euros) by including an interaction term in the model tested by the Wald test. (iv) We additionally explored alternative exposure definitions by (a) back-extrapolating to the baseline address for all cohort members and (b) time-varying air pollution exposure extrapolated across the address history from enrolment to end of follow-up in cohorts with the available information (excluding DNC and E3N). In the time-varying analyses, we specified a 1-year calendar time-period strata to handle time trends in air pollution and breast cancers. The extrapolation estimated concentrations from the Danish Eulerian Hemispheric Model (DEHM), which includes hourly values of a number of chemical species, averaged into monthly concentrations across Europe at 26 km × 26 km spatial resolution (27). We applied the trends predicted by the DEHM for all four pollutants to calculate annual average concentrations for all years from recruitment up to end of follow-up, allowing different spatial trends within Europe. Extrapolation was performed using the absolute difference and the ratio between the baseline period and 2010. Finally, to disentangle interdependencies and pollutant-specific impacts on breast cancer, we performed two-pollutant models to test the sensitivity of the estimates of one pollutant to inclusion of another and calculated a cumulative risk index (CRI) including all four pollutants assuming additive effects of the combined exposures on breast cancer risk (28):

$$\mathrm{CRI} = exp\left[\sum_{p=1}^{P} \hat{\beta}_p x_p\right] \equiv exp\left(\hat{\beta}' x\right)$$

where $\hat{\beta}' = (\hat{\beta}_1, \ldots \hat{\beta}_p)$ are the effect estimates of the log-HR for pollutant p ($P = 1,\ldots, P$) from the multi-pollutant model at concentration x_p. We also calculated the confidence interval using the variance-covariance matrix of the pollutant-specific estimates.

Table 1. Description of the included (sub)cohort studies.

	Total participants	Baseline period	End of follow-up	Baseline age (mean/SD) years	NO_2 (mean/SD)[a] $\mu g/m^3$	$PM_{2.5}$ (mean/SD)[a] $\mu g/m^3$	BC (mean/SD)[a] ($10^{-5}m^{-1}$)	O_3 (mean/SD)[a] $\mu g/m^3$	Breast cancers
CEANS Stockholm, Sweden									
SDPP	4,346	1992–1998	31–12–2011	47.3 (4.9)	16.0 (4.4)	7.7 (0.9)	0.6 (0.2)	77.3 (2.0)	179
SIXTY	1,831	1997–1999	31–12–2011	60 (0)	20.9 (6.0)	8.3 (0.9)	0.8 (0.2)	76.6 (2.5)	104
SALT	3,001	1998–2003	31–12–2011	58.0 (10.7)	21.5 (6.0)	8.4 (0.8)	0.8 (0.3)	76.5 (2.7)	131
SNAC-K	1,471	2001–2004	31–12–2011	73.6 (10.6)	27.3 (5.1)	8.6 (0.8)	1.1 (0.1)	75.1 (2.7)	30
DCH, Copenhagen/ Aarhus, Denmark	27,709	1993–1997	31–12–2015	56.7 (4.4)	28.3 (6.9)	13.2 (1.4)	1.4 (0.4)	77.3 (5.0)	2,077
DNC, Denmark									
DNC-1993	15,556	1993	31–12–2012	56.0 (8.3)	21.8 (8.0)	12.7 (1.5)	1.1 (0.4)	80.4 (4.0)	938
DNC-1999	7,430	1999	31–12–2012	47.9 (4.1)	25.8 (8.5)	13.8 (1.5)	1.3 (0.4)	80.6 (3.8)	288
EPIC-NL, Netherlands									
MORGEN	9,681	1993–1997	31–12–2012	42.3 (11.3)	34.6 (6.1)	18.0 (1.0)	1.7 (0.3)	73.4 (7.7)	312
Prospect	13,640	1993–1997	31–12–2012	57.6 (6.0)	35.9 (5.4)	16.9 (0.8)	1.7 (0.3)	72.7 (2.7)	730
E3N, France	36,258	1989–1991	08–12–2014	52.8 (6.7)	26.3 (9.7)	17.0 (2.9)	1.8 (0.5)	87.7 (8.0)	2,640
VHM&PP, Vorarlberg, Austria	78,796	1985–2005	31–12–2014	41.5 (15.4)	22.0 (5.3)	15.8 (2.6)	1.6 (0.3)	92.6 (3.6)	2,230
Pooled cohort	199,719	1985–2005	2011–2015	49.0 (13.2)	25.3 (8.3)	15.1 (3.2)	1.5 (0.4)	85.0 (9.0)	9,659

[a]2010 exposure model.

Table 2. Baseline characteristics of the included (sub)cohort studies.

	% BMI ≥ 25 kg/m^2	% Not employed	% Married/ cohabiting	% Current smokers	Cigarettes/ day[a]	Years of smoking[a]	Mean income area-level[b]
CEANS Stockholm, Sweden							
SDPP	47	11	82	26	12.1 (6.2)	27.8 (8.7)	24.4 (4.2)
SIXTY	60	36	69	22	12.8 (6.5)	34.8 (9.9)	24.4 (6.9)
SALT	33	40	61	20	11.7 (7.1)	37.3 (8.4)	25.0 (6.6)
SNAC-K	48	82	32	15	11.1 (7.8)	42.6 (13.7)	28.5 (2.2)
DCH, Copenhagen/Aarhus, Denmark	48	28	66	33	12.7 (5.5)	34.9 (8.0)	20.2 (3.4)
DNC, Denmark							
DNC-1993	28	31	68	38	13.8 (8.1)	31.4 (9.9)	19.2 (2.5)
DNC-1999	30	5	76	28	13.2 (7.4)	27.1 (7.1)	19.0 (2.4)
EPIC-NL, Netherlands							
MORGEN	43	41	63	35	14.9 (7.9)	24.0 (10.0)	12.2 (1.6)
PROSPECT	55	48	77	22	13.6 (8.7)	36.7 (7.6)	13.1 (1.4)
E3N, France	21	31	83	13	11.3 (9.1)	28.5 (7.6)	11.2 (3.0)
VHM&PP, Vorarlberg, Austria	35	33	65	19	13.1 (8.1)	11.9 (7.8)	22.9 (1.7)
Pooled cohort	36	32	70	22	13.0 (7.7)	25.7 (12.7)	18.9 (5.6)

[a]Among current smokers.
[b]Euros x 1,000, year 2001.

We evaluated the shape of the concentration-response function by natural cubic splines (3 degrees of freedom) and violation of the proportional hazards assumption of the Cox Models for all covariates by test of a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. We performed all analyses in R version 3.4.0.

Data availability

The exposure maps are available on request from K. de Hoogh (c.dehoogh@swisstph.ch). The ELAPSE study protocol is available at http://www.elapseproject.eu/. Further information and a detailed statistical analysis plan is available on reasonable request from the corresponding author.

Results

The pooled cohort included 199,719 women who experienced a total of 9,659 incident breast cancers during 3,592,885 person-years of follow-up (**Table 1**). The participants of the six included cohorts were recruited in the period 1985–2005 at a mean age of 49.0 years (median 50.8 years). Participants were on average exposed to levels of air pollution below the EU limit values of 25 μg/m^3 for $PM_{2.5}$ and 40 μg/m^3 for NO_2. Generally, lower mean levels of NO_2, $PM_{2.5}$, and BC were observed in Northern European cohorts compared to the Southern (Supplementary Fig. S1). In most of the subcohorts, exposure to $PM_{2.5}$ was moderately to highly correlated with exposure to NO_2 and BC (Supplementary Table S1). Correlations between $PM_{2.5}$ and O_3 was generally moderately negative but varied substantially between the cohorts.

The percentage of overweight or obese women varied from 21 to 60 in the individual (sub) cohorts with a pooled mean of 36% (**Table 2**). A mean of 32% of the women were not employed at baseline, ranging from 5% in the Danish DNC-1999 sub-cohort to 82% in the Swedish CEANS SNAC-K sub-cohort, and 70% were married or cohabiting. Current smokers at baseline ranged from 13% to 38% across the individual (sub) cohorts with a pooled percentage of 22.

The linear associations with increasing levels of confounder adjustment between NO_2, $PM_{2.5}$, BC and O_3 and breast cancer are presented in **Table 3**. We observed positive associations between breast cancer and exposure to NO_2, $PM_{2.5}$, and BC with adjusted HRs of 1.03 (95% CI, 1.00–1.06) per 10 μg/m^3, 1.06 (95% CI, 1.01–1.11) per 5 μg/m^3, and 1.03 (95% CI, 0.99–1.06) per 0.5 $10^{-5}m^{-1}$, respectively (model 3). Effect estimates were modestly lower in the fully adjusted model 3 compared to model 1, mainly due to the inclusion of the area-level

Table 3. Pooled analyses of air pollution exposure and risk of breast cancer.

	Increment	Model 1[a] *N* = 199,719 HR (95% CI)	Model 2[b] *N* = 199,719 HR (95% CI)	Model 3[c] *N* = 199,719 HR (95% CI)
NO_2	10 μg/m^3	1.06 (1.03–1.08)	1.05 (1.02–1.08)	1.03 (1.00–1.06)
$PM_{2.5}$	5 μg/m^3	1.09 (1.04–1.14)	1.08 (1.03–1.13)	1.06 (1.01–1.11)
BC	0.5 $10^{-5}m^{-1}$	1.05 (1.02–1.08)	1.04 (1.01–1.07)	1.03 (0.99–1.06)
O_3w	10 μg/m^3	0.96 (0.93–1.00)	0.97 (0.93–1.01)	0.98 (0.94–1.01)

Abbreviation: O_3w, Ozone in the warm season.
[a]Adjusted for study (strata), age, year of baseline visit.
[b]Further adjusted for smoking status, duration, intensity, BMI, marital status, and employment status.
[c]Further adjusted for 2001 mean income at the area level.

Table 4. Pooled analyses of air pollution exposure and risk of breast cancer according to age.

	<50 years (Cases = 795) HR (95% CI)	50–54 years (Cases = 1,065) HR (95% CI)	≥55 years (Cases = 7,799) HR (95% CI)
NO_2 (per 10 μg/m^3)			
Model 3[a]	1.02 (0.91–1.15)	1.08 (0.99–1.17)	1.03 (0.99–1.06)
$PM_{2.5}$ (per 5 μg/m^3)			
Model 3[a]	1.05 (0.91–1.22)	1.13 (0.99–1.30)	1.05 (0.99–1.11)
BC (per 0.5 $10^{-5}m^{-1}$)			
Model 3[a]	1.01 (0.90–1.14)	1.09 (0.99–1.18)	1.02 (0.98–1.05)
O_3w (per 10 μg/m^3)			
Model 3[a]	0.95 (0.82–1.06)	0.95 (0.85–1.05)	0.99 (0.95–1.07)

Abbreviation: O_3w, Ozone in the warm season.
[a]Adjusted for study (strata), age, year of baseline visit, smoking status, duration, intensity, BMI, marital status, employment status, and mean income at the area level.
Test for heterogeneity: NO_2 $I^2 = 0.04\%$ $P = 0.28$; $PM_{2.5}$ $I^2 = 2.52\%$ $P = 0.59$; BC $I^2 = 45.23\%$ $P = 0.10$; O_3w $I^2 = 0.00\%$ $P = 0.56$.

variable. We did not observe an association between O_3 and breast cancer incidence (HR, 0.98; 95% CI, 0.94–1.01 per 10 μg/m^3).

Table 4 shows the effect estimates for age groups of <50, 50 to 54, and 55+ years. For NO_2 and $PM_{2.5}$, we observed elevated HRs across all three age groups, most notably in the group of 50 to 54 year-olds. This difference was more pronounced for BC with HRs close to 1 in the youngest and in the oldest age groups and a HR of 1.09 (95% CI 0.99, 1.18) per 10 μg/m^3 in the 50 to 54 year-olds.

In total, 112,857 subjects (57% of the full population) had information on alcohol consumption, HT use, and nulliparity. Additional adjustment for these factors resulted in attenuated HRs, though still indicative of an increased risk at higher exposure especially for $PM_{2.5}$ and NO_2 (**Table 5**). A similar picture was observed when performing the same analysis in the three age groups of <50, 50 to 54, and 55+ years (Supplementary Table S2).

The results of the analysis of effect measure modification by smoking status, BMI, and area-level SES are presented in **Fig. 1**. We observed an elevated HR for breast cancer with higher exposure to NO_2, $PM_{2.5}$, and BC in never smokers – but not in former or current smokers ($P_{interaction}$ = 0.01–0.10). For BMI, the effect estimates of $PM_{2.5}$ and BC were slightly higher in the categories of <25 and 25 to 29 compared with 30+ kg/m^2; however, differences were highly nonsignificant ($P_{interaction}$ = 0.62–0.78). We did not observe effect measure modification for area-level SES, however, the estimate of O_3 was slightly higher among areas of high SES compared with low.

Table 5. Sensitivity analyses including additional confounders in the subset of the pooled cohort with the available information (N = 112,857)[c].

Cases = 7,135	Model 3[a] HR (95% CI)	Model 3[a] + additional covariate adjustment[b] HR (95% CI)
NO_2	1.04 (1.00–1.07)	1.02 (0.99–1.06)
$PM_{2.5}$	1.06 (0.99–1.12)	1.04 (0.98–1.10)
BC	1.02 (0.99–1.06)	1.01 (0.98–1.04)
O_3	0.98 (0.94–1.02)	0.99 (0.95–1.03)

[a]Adjusted for study (strata), age, year of baseline visit, smoking status, duration, intensity, BMI, marital status, employment status, and 2001 mean income at the area level.
[b]Nulliparity, HT use, and alcohol consumption.
[c]Excluding CEANS Sixty, CEANS SNAC-K and the VHM&PP cohort.

The Supplementary Table S3 shows the means, standard deviations (SD) and effect estimates for the analysis of exposures back-extrapolated to the baseline year of the cohort participants and of the time-varying exposure extrapolated across the address history. In general, the back-extrapolated baseline exposures were higher than the 2010 concentration, especially for $PM_{2.5}$ with a mean (SD) of 29.3 (7.6) and 28.7 (8.1) for the difference and ratio method, respectively, compared to a mean of 15.1 (3.2) for the 2010 exposure model. Generally, the effect estimates for the extrapolation of exposure to baseline and the time-varying exposure, did not vary considerably from those of the 2010 exposure model.

The results of the two-pollutant analyses are provided in the Supplementary Fig. S2. Generally, the $PM_{2.5}$ effect estimate was not sensitive to the inclusion of copollutants, whereas the estimate for NO_2 and BC were attenuated by the inclusion of $PM_{2.5}$. The HRs for each pollutant from a multi-pollutant model (marginal risk) are presented per IQR in Supplementary Fig. S3 with the CRI derived from this model. The CRI exceeded any of the individual pollutant HRs from the single-pollutant models, which indicates a role of multiple pollutants in the risk of breast cancer.

The analysis of concentration-response functions did not suggest deviation from a linear association between the pollutants and breast cancer (Supplementary Fig. S4). We detected deviation from the proportional hazards assumption for employment status, smoking intensity and duration. A sensitivity analysis incorporating these in strata (grouping intensity per 10 cigarettes per day and the duration in categories per 5 years) did not show results deviating from those of the main analysis (Supplementary Fig. S5).

Discussion

The results from this large pooled cohort analysis covering six cohorts from across Europe, indicate a higher risk of breast cancer incidence in relation to higher exposure to NO_2, $PM_{2.5}$, and BC. The HRs were most pronounced in the group of middle-aged women (50–54 years) and among never smokers.

The findings of our study concerning NO_2 exposure and breast cancer incidence are generally in accordance with those of previous studies. Two meta-analytic papers concerning exposure to NO_2 and $PM_{2.5}$ and the risk of breast cancer (largely overlapping with regards to included studies) have been published recently (8, 29). The reported meta-analytical relative risk was 1.02 (95% CI: 1.01, 1.04) for a 10-μg/m^3 increase in NO_2 in both studies which corresponds well with the

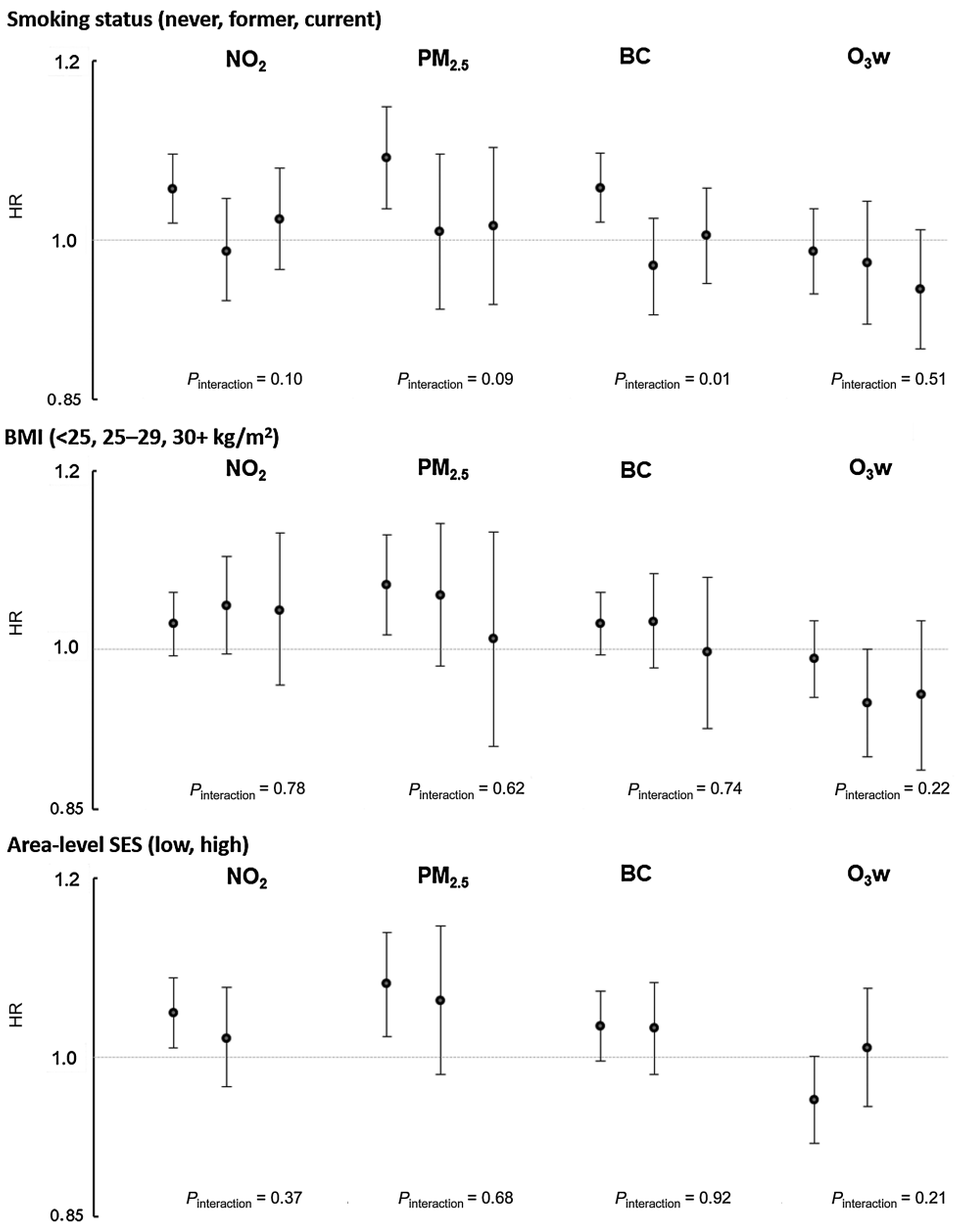

Figure 1.
Effect modification by smoking, BMI, and area-level SES on the relation between NO_2, $PM_{2.5}$, BC, and O_3 and breast cancer incidence ($N = 199{,}719$). BMI was categorised in groups of <25, 25–29, and 30+ kg/m^2 and area-level socio-economic status in two-categories below and above the mean area-level income of 18,900 Euros.

results of our analysis. The estimate for $PM_{2.5}$ was somewhat lower than our estimate, however, Gabet and colleagues reported geographic variations with a tendency towards higher risk estimates in European cohorts compared to Northern American and in a sensitivity analysis restricting to European populations, results closer to ours were observed (29). The ESCAPE study, which included only the postmenopausal part of the study population at baseline (either reported postmenopausal or older than 55 years), reported a HR of 1.02 (95% CI, 0.98–1.07) per 10 μg/m^3 for NO_2 and 1.08 (95% CI, 0.77–1.51) per 5 μg/m^3 $PM_{2.5}$. Our corresponding results among cases occurring at age 55 years or older were similar with a HR of 1.03 (95% CI, 0.99–1.06) for NO_2 and 1.05 (95% CI, 0.99–1.11) for $PM_{2.5}$. The confidence intervals of our current analysis were much narrower than in the ESCAPE analysis, related to longer follow up and pooling data.

Two Canadian studies showed higher risks for breast cancer with higher exposure to NO_2 and $PM_{2.5}$ in younger women (assumed premenopausal) and no association for older women (>50 years; refs. 9, 10). Also, findings from the Danish Nurse Cohort Study indicated an association between $PM_{2.5}$ exposure and premenopausal – but not postmenopausal breast cancer (11). Our estimates were generally strongest in the age group of 50–54 years, but all CIs overlapped across the age groups. It is relevant, however, to consider mammography screening programs as a possible explanation for this tendency. If screening attendance is related to air pollution exposure, for instance through educational level (30), the lack of control for this factor may have biased the results.

Studies addressing the association between BC exposure and breast cancer are fewer. In the ESCAPE study no association was observed for

$PM_{2.5}$ absorbance – a marker for black carbon – which corresponds well with our estimate of 1.02 (95% CI, 0.98–1.05) in the similar age group (55+ years; ref. 12). With regard to O_3 exposure, our results are in line with two other studies showing no association with breast cancer risk (13, 14).

Our result of a more pronounced association between air pollutants and breast cancer in never smokers, has also been shown by others (31). One explanation could be that smokers are already exposed to high levels of particulate matter, and thus an added effect on breast cancer risk of air pollutants could be relatively smaller in this sub group.

Air pollution is expected to contribute to cancer risk through mechanisms of oxidative stress and inflammation (32), both of which are considered key elements in the development and progression of cancer. Carcinogenic constituents of inhaled PM may also exert DNA damage, promote cell turnover and proliferation beyond the respiratory tract, by entering the blood circulation through absorption, metabolism, and distribution (33, 34). In addition, epigenetic modifications and telomere shortenings are proposed mechanisms linking air pollution to cancer (35). Breast cancer is a hormone-related disease and PM air pollution has demonstrated estrogenic properties and DNA-damaging activity *in vitro* (33), and endocrine-disrupting properties have also been suggested (36, 37). Also, specific periods of susceptibility to environmental exposures may be at play (e.g., puberty, pregnancy, and menopause) due to significant structural and functional changes occurring in the mammary gland (38).

The strengths of our study include the large sample size with detailed information on lifestyle factors as well as socioeconomic information at both the individual and area level harmonized across the (sub) cohorts specifically for this project. Our study was based on a more comprehensive standardized hybrid exposure assessment compared to the ESCAPE study, ensuring comparable exposure estimates for the whole study population. In addition, we had a longer follow-up, with 3,592,885 person-years of follow-up as opposed to 991,353 in the ESCAPE study, which ensured high statistical power to perform subgroup analysis and multi-pollutant models.

One major limitation is that we did not have access to data distinguishing the breast cancer cases according to menopausal status, morphology, or hormonal receptor subtypes. Previous studies have reported differential associations for NO_2 according to hormone-receptor status (ER/PR) with higher estimates observed for ER+/PR+ breast tumor subtypes compared to ER-/PR- tumors (39–41). A more specific outcome attainment could perhaps have served to better understand the observed age differences in effect estimates, as the hormonal receptor status varies across age groups with ER+/PR+ breast cancers occurring more frequently among older women (42). Also, we did not have information on the participants' family history of breast cancer and potential relevant genetic variants which could increase their susceptibility to air pollution exposures (43).

In addition, we lacked information on detailed information on reproductive history and also on participation in breast cancer screening. Information on other risk factors for breast cancer such as HT use, alcohol consumption, and nulliparity were only available in a subset of the pooled cohort. Such factors are related to air pollution exposure through factors such as ethnicity, individual SES and a person's health consciousness, which may determine the choice of residency. Likewise, SES of the residential neighborhood is associated with both physical characteristics (distance to health care, walkability, or access to fast-food, liquor stores, etc.), as well as social cohesion and shared values which could affect the residents' health and reproductive behaviors and risk of breast cancer. We were able to account for the mean neighborhood income level and employment status at the individual level, but we cannot rule out cannot rule out the possibility of residual confounding by other missing covariates. The sensitivity analyses with additional adjustment for HT use, alcohol consumption, and nulliparity did show attenuated HRs. Also, we were not able to take into account exposure to indoor air pollution or air pollution at locations other than at the registered residential address. We assigned modelled exposure for the year 2010 at the baseline address for each participant. The spatial distribution of NO_2, black smoke and traffic intensities has been found to be stable over several years in previous studies (44–46). A validation study of the stability of the spatial structure of predictions from the exposure model used in our study, showed high correlations with models developed for 2000 and 2005 (2013 for $PM_{2.5}$) at the European scale (24). We extrapolated the 2010-exposures to the enrolment year of the cohort participants and to the address history of participants, to take into account time-trends in air pollutants and moving patterns, thereby testing the sensitivity of the main exposure approach of applying a single year. The results for $PM_{2.5}$ were sensitive to the back-extrapolation of exposure to the enrolment year, which probably reflects that the exposures in 2010 were lower than at enrolment. The analysis which assigned exposure to the address history of each participant may not represent the relevant induction-latency period for a cancer outcome, however, the results of this time-varying analysis did not differ notably from the main results. Also, other exposure periods may be more etiologically relevant for the study of breast cancer, for instance during puberty where rapid breast cell proliferation takes place (47). A few previous studies have indicated an association between childhood exposure to air pollutants and breast cancer risk (31, 48, 49). Finally, we did not take into account road traffic noise, which has been linked to breast cancer in a few previous studies (50, 51).

In conclusion, the findings of this study suggest a role of exposure to ambient NO_2, $PM_{2.5}$, and BC for the development of breast cancer.

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Authors' Contributions

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Note

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