**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 the use of hormone therapy (HT), reproductive behaviour, and lifestyle-related factors such as alcohol consumption, smoking, physical inactivity, and obesity, but a role of environmental exposures has also been suggested in the etiology of breast cancer.

Methods: We conducted a pooled analysis among six European cohorts (N=199,719) on the association between residential exposure to nitrogen dioxide (NO2), fine particles (PM2.5), black carbon (BC), and ozone in the warm season (O3) and breast cancer incidence. 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 cancers. The results of the fully adjusted linear analyses showed a hazard ratio (95% confidence interval) of 1.03 (1.00, 1.06) per 10 μg/m³ NO2, 1.06 (1.01, 1.11) per 5 μg/m³ PM2.5, 1.03 (0.99, 1.06) per 0.5 10−5m−1 BC, and 0.98 (0.94, 1.01) per 10 μg/m³ O3. The effect estimates were most pronounced in the group of middle-aged women (50–54 years) and among never smokers.

Conclusion: The findings of this study suggest a role of NO2, PM2.5 and BC in the risk of developing breast cancer**.**

**Introduction**

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

Established risk factors for postmenopausal breast cancer include the use of hormone therapy (HT), reproductive behaviour in terms of nulliparity or postponed childbearing and other 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 among the premenopausal cases.6 The regional variation in combination with a rise in incidence reflect adaptation of the lifestyle-related risk factors in countries of growing economies and industrialisation, but also suggest 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 (IARC),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 hazard ratio (HR) of 1.02 (95% confidence interval [CI]: 1.01; 1.04) per 10 µg increase in nitrogen dioxide (NO2) across estimates from the existing literature (N=18) and a HR of 1.03 (95% CI 0.99; 1.06) per 10 µg increase in particulate matter (PM) with aerodynamic diameters less than or equal to 2.5 µm (PM2.5).8 The overall estimates, however, were somewhat affected by heterogeneity across different study designs, geographical regions, menopausal status, and breast cancer subgroups. Two Canadian studies addressing air pollution effect estimates in relation to age have shown higher risks of breast cancer in younger women (assumed premenopausal) in association with higher exposure to NO2 and PM2.5 and no association for older women (>50 years).9 10 Also, findings from the Danish Nurse Cohort Study indicated an association between PM2.5 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 PM2.5.12 The study also pointed towards possible effects of individual PM2.5 constituents especially for nickel and vanadium. All reported estimates, however, were limited by statistical uncertainty. Studies regarding possible effects of ozone (O3) are few, but so far not indicative of an association with breast cancer.13 14

In this study, we applied 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 in order 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 with a more comprehensive standardized exposure assessment and a longer follow-up period.

**Methods**

*Study population*

We applied data from the women of the following six out of nine cohorts included in the ELAPSE collaboration, which contained information on 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];15 Stockholm Screening Across the Lifespan Twin study [SALT];16 Stockholm 60 years old study [Sixty];17 and Stockholm Diabetes Prevention Program [SDPP]);18 the Danish Diet, Cancer and Health cohort (DCH);19 the Danish Nurse Cohort (DNC);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);21 the Etude Epid´emiologique aupr`es de femmes de la Mutuelle Générale de l’Education Nationale (E3N or EPIC-France);22 and the Austrian Vorarlberg Health Monitoring and Prevention Programme (VHM&PP).23 Cohorts were recruited between 1985 and 2005 with a follow up until 2011 to 2015. 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. Details on each included cohort and the covariates is provided in the online appendix.

 We included all women who were free of cancer at baseline (with the exception of non-melanoma 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, dispersion model estimates, land use, and traffic variables as predictors. We used 2010 AirBase routine monitoring data maintained by the European Environmental Agency (EEA) for the modelling of PM2.5, NO2 and O3 (warm season) and ESCAPE monitoring data for black carbon (BC).26 We applied models for 2010 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 pathological 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, International Classification of Diseases and Related Health Problems, 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. NO2, PM2.5, BC, and O3 were modelled as a linear function with increments of 10, 5, 0.5 and 10 µg/m3, respectively. 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: 1) 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; 2) 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/m2), smoking status (never, former, current), smoking duration (years of smoking) for current smokers, and smoking intensity (cigarettes/day) for current smokers; 3) (main model) further adjusted for area-level socio-economic status (SES) defined as mean income in 2001, 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: 1) Analysing the cohort in age groups of <50 years, 50–54 years, and 55+ years to account for pre-, peri- and postmenopausal status. We did not have information on menopausal status available in all cohorts. 2) Addressing potential effect measure modification between the exposures and the covariates smoking status and BMI (three categories of <25, 25­–29, and 30+ kg/m2), by including an interaction term in the model tested by the Wald test. 3) 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. 4) 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 back-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 back-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. Back-extrapolation was performed using the absolute difference and the ratio between the baseline period and 2010. Lastly, we performed two-pollutant models to test the sensitivity of the estimates of one pollutant to inclusion of another.

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.

**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). Generally, lower mean levels of NO2, PM2.5, and BC were observed in Northern European cohorts compared to the Southern (Figure S1).

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 unemployed 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 NO2, PM2.5, BC and O3 and breast cancer are presented in Table 3. We observed a higher risk of breast cancer with higher exposure to NO2, PM2.5, and BC with adjusted HRs of 1.03 (95% CI 1.00, 1.06), 1.06 ((95% CI 1.01, 1.11), and 1.03 (95% CI 0.99, 1.06), respectively. Effect estimates were modestly lower in the full adjusted model 3 compared to the marginally adjusted model 1, especially by inclusion of the area-level variable. We did not observe an association between higher exposure to O3 and breast cancer incidence (HR 0.99; 95% CI 0.95, 1.07).

 Table 4 shows the effect estimates for age groups of <50, 50–54, and 55+ years. For NO2 and PM2.5, we observed elevated HRs across all three age groups, most notably in the group of 50–54 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) in the 50–54 year-olds.

The results of the analysis of effect measure modification by smoking status and three categories of BMI are presented in Figure S1. We observed an elevated HR for breast cancer with higher exposure to NO2, PM2.5, and BC in never smokers – but not in former or current smokers (p-value for interaction 0.01 to 0.10). For BMI, the effect estimates of PM2.5 and BC were slightly higher in the categories of <25 and 25–29 compared to 30+ kg/m2, however differences were highly non-significant (p-value for interaction 0.62- 0.78).

In total, 112,857 subjects (57% of the full population) had information on the covariates alcohol consumption, HT use, and nulliparity. Additional adjustment for these factors resulted in attenuated HRs, though still indicative of increased risk at higher exposure especially for PM2.5 and NO2 (Table 5). A similar picture was observed when performing the same analysis in the three age groups of <50, 50–54, and 55+ years (supplementary Table S1).

The supplementary Table S2 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 back-extrapolated across the address history. In general, the back-extrapolated baseline exposures were higher than the 2010-concentration, especially for PM2.5 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 back-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 material Figure S2. Generally, the PM2.5 effect estimate was not sensitive to the inclusion of co-pollutants, whereas the estimate for NO2 and BC were sensitive to the inclusion of PM2.5.

The spline analyses did not suggest deviation from a linear association between the pollutants and breast cancer (Figure S3). 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 (Figure S4).

**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 NO2, PM2.5, 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 NO2 exposure and breast cancer incidence are generally in accordance with those of previous studies. Two meta-analytic papers concerning exposure to NO2 and PM2.5 and the risk of breast cancer (largely overlapping with regards to included studies) have been published recently.8 28 The reported meta-analytical relative risk (RR) was 1.02 (95% CI: 1.01, 1.04) for a 10-µg/m3 increase in NO2 in both studies which corresponds well with the results of our analysis (HR: 1.03; 95% CI: 1.00, 1.06). For PM2.5, HRs of 1.03 (95% CI: 0.99; 1.06) and 1.01 (95% CI: 0.94, 1.08) for increments of 10 µg/m3 were observed in the meta-analyses, which is lower than our estimate of 1.06 (95% CI: 1.01, 1.11) per 5 µg/m3 – corresponding to 1.12 (95% CI: 1.02, 1.23) per 10 µg/m3. However, Gabet et al reported geographic variations with a tendency towards higher risk estimates in European cohorts compared to Northern American. In a sensitivity analysis restricting to European populations, a RR of 1.08 (95% CI: 0.73, 1.61) per 10 µg/m3 was observed.28 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/m3 for NO2 and 1.08 (95% CI: 0.77, 1.51) per 5 µg/m3 PM2.5. 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 NO2 and 1.05 (95% CI: 0.99, 1.11) for PM2.5. 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 NO2 and PM2.5 in younger women (assumed premenopausal) and no association for older women (>50 years).9 10 Also, findings from the Danish Nurse Cohort Study indicated an association between PM2.5 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. Studies addressing the association between BC exposure and breast cancer are fewer. In the ESCAPE study no association was observed for PM2.5 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).12 With regard to O3 exposure, our results are in line with two other studies showing no association with breast cancer risk.13 14

Our results, showing a more pronounced association between air pollutants and breast cancer in never smokers, has also been shown in a previous study.29 One explanation could be, that smokers are already exposed to high levels of particulate matter, and thus the added effect on breast cancer risk of air pollutants in minimal in this sub group.

Air pollution is expected to induce cancer through mechanisms of oxidative stress and inflammation,30 both of which are considered key elements in the development and progression of cancer. PM may exert DNA damage, promotion of cell turnover and proliferation beyond the respiratory tract by entering the blood circulation through absorption, metabolism, and distribution of inhaled carcinogens 31 32. In addition, epigenetic modifications and telomere shortenings are proposed mechanisms linking air pollution to cancer 33. Breast cancer is a hormone-related disease and PM air pollution has demonstrated estrogenic properties and DNA-damaging activity in vitro,31 and endocrine-disrupting properties have also been suggested.34 35 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.36

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, which ensured high statistical power to perform sub group analysis and multi-pollutant models.

One major limitation is that we did not have access to data distinguishing the breast cancer cases according to morphology or hormonal receptor subtypes. Previous studies have reported differential associations for NO2 according to hormone-receptor status (ER/PR) with higher estimates observed for ER+/PR+ breast tumor subtypes compared to ER-/PR- tumors.37-39 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.40 Also, we did not have information on the participants’ family history of breast cancer and potential relevant gene variants which could increase their susceptibility to air pollution exposures.41 We assigned modelled exposure for the year 2010 at the baseline address for each participant. The spatial distribution of NO2, black smoke and traffic intensities has been found to be stable over several years in previous studies.42-44 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 PM2.5) at the European scale.24 We back-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. The results for PM2.5 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. 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.45 A few previous studies have indicated an association between childhood exposure to air pollutants and breast cancer risk.29 46 47

 In conclusion, the findings of this study suggest a role of NO2, PM2.5 and BC in the risk of developing breast cancer.

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