Null Results in Brief

Long-term Exposure to Fine Particulate Matter and Breast Cancer Incidence in the Danish Nurse Cohort Study

Zorana Jovanovic Andersen[1], Line Ravnskjær[2], Klaus Kaae Andersen[2], Steffen Loft[1], Jørgen Brandt[3], Thomas Becker[3], Matthias Ketzel[3], Ole Hertel[3], Elsebeth Lynge[1], and Elvira Vaclavik Bräuner[4,5]

Abstract

Background: An association between air pollution and breast cancer risk has been suggested, but evidence is sparse and inconclusive.

Methods: We included 22,877 female nurses from the Danish Nurse Cohort who were recruited in 1993 or 1999 and followed them for incidence of breast cancer ($N = 1,145$) until 2013 in the Danish Cancer Register. We estimated annual mean concentrations of particulate matter with diameter <2.5 $\mu g/m^3$ ($PM_{2.5}$) and <10 $\mu g/m^3$ (PM_{10}), and nitrogen dioxide (NO_2) at nurses' residences since 1990 using an atmospheric chemistry transport model. We examined the association between the 3-year running mean of each pollut-

ant and breast cancer incidence using a time-varying Cox regression.

Results: We found no association between breast cancer and $PM_{2.5}$ (HR, 0.99; 95% confidence interval, 0.94–1.10 per interquartile range of 3.3 $\mu g/m^3$), PM_{10} (1.02; 0.94–1.10 per 2.9 $\mu g/m^3$), or NO_2 (0.99; 0.93–1.05 per 7.4 $\mu g/m^3$).

Conclusions: Air pollution is not associated with breast cancer risk.

Impact: Exposure to air pollution in adulthood does not increase the risk of breast cancer, but more data on the effects of early exposure, before first birth, are needed. *Cancer Epidemiol Biomarkers Prev; 26(3); 428–30. ©2016 AACR.*

Introduction

Traffic-related air pollution is a risk factor for lung cancer and classified as a carcinogen to humans. Experimental data provide some evidence of a link between a number of carcinogens in air pollution and breast cancer, including polycyclic aromatic hydrocarbons, which can cause mammary tumors in laboratory animals (1). Epidemiologic data are mixed, with case–control studies (2) detecting association and cohort studies (3–5) finding no association between air pollution and breast cancer incidence. The latest Canadian case–control study found a 26% to 32% increased risk of premenopausal, and 7% to 10% increased risk of postmenopausal breast cancer, per 10 ppb increase in nitrogen dioxide (NO_2; ref. 2). Three cohort studies did not detect association between breast cancer incidence and NO_2 (3), PM with diameter

<2.5 $\mu g/m^3$ ($PM_{2.5}$), or PM with diameter <10 $\mu g/m^3$ (PM_{10}; refs. 3, 4), or nitrogen oxides NO_x (5). Only two studies had data on $PM_{2.5}$ and PM_{10} (3, 4). Here, we examined the association between long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 at the residence and incidence of breast cancer in the nationwide, prospective Danish Nurse Cohort (DNC).

Materials and Methods

The DNC consists of 28,731 Danish female nurses (>44 years), recruited in 1993 (19,898) or 1999 (8,833) when they answered a questionnaire on working conditions, weight, height, lifestyle, and reproductive factors. Using the unique personal identifying number, we linked nurses to the Central Population Register to obtain residential address history (1971–2013) and vital status information and to the Danish Cancer Register for diagnosis of primary invasive breast cancer (International Classification of Diseases-10 code C50) between cohort baseline (1993 or 1999) and 2013, and any other cancer prior to cohort baseline. We used the Danish integrated air pollution modeling system (THOR and AirGIS) to estimate human exposure to outdoor air pollution at address level (6). We estimated annual mean concentration of $PM_{2.5}$, PM_{10}, and NO_2 at the residential addresses for nurses with complete information on residential address history 80% of the time between 1990 and 2013 and used the 3-year running mean of each pollutant concentrations as the main exposure proxy. We used the time-varying Cox proportional hazards regression to model association between breast cancer incidence and air pollution, with age as the underlying time scale, and stratified by year of birth, in three steps: age adjusted; adjusted additionally for smoking, alcohol consumption, physical activity,

[1]Department of Public Health, Center for Epidemiology and Screening, University of Copenhagen, Copenhagen, Denmark. [2]Danish Centre for Cancer Research, Danish Cancer Society, Copenhagen, Denmark. [3]Department of Environmental Science, Aarhus University, Roskilde, Denmark. [4]Research Center for Prevention and Health, Capital Region of Denmark, Rigshospitalet – Glostrup, University of Copenhagen, Glostrup, Denmark. [5]Department of Occupational and Environmental Medicine, Capital Region of Denmark Bispebjerg - Frederiksberg Hospital, Copenhagen, Denmark.

Corresponding Author: Zorana Jovanovic Andersen, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5A, Copenhagen 1014, Denmark. Phone: 452-074-0462; Fax: 453-532-7383; E-mail: zorana.andersen@sund.ku.dk

doi: 10.1158/1055-9965.EPI-16-0578

©2016 American Association for Cancer Research.

AACR

Table 1. Characteristics of the nurses from the DNC at baseline in 1993 or 1999, by incident breast cancer status at follow-up

	Total $n = 22,877$	Breast cancer $n = 1,145$	No breast cancer $n = 21,732$
Age, mean (SD)	52.9 (7.8)	53.2 (7.3)	52.9 (7.8)
Premenopausal, n (%)	11,579 (51.0)	583 (51.5)	10,996 (51.0)
Postmenopausal, n (%)	11,120 (49.0)	548 (48.5)	10,572 (49.0)
Menarche ≤ 12, n (%)	5,477 (24.1)	290 (25.6)	5,187 (24.0)
Menarche > 12, n (%)	17,222 (75.9)	841 (74.4)	16,381 (76.0)
BMI, mean (SD)	23.7 (3.5)	23.8 (3.5)	23.7 (3.5)
Underweight (<18.5 kg/m^2), n (%)	532 (2.3)	22 (1.9)	510 (2.4)
Normal (18.5–25 kg/m^2), n (%)	15,698 (69.2)	801 (70.8)	14,987 (69.1)
Overweight (25–30 kg/m^2), n (%)	5,167 (22.8)	239 (21.1)	4,928 (22.8)
Obese ($\geq$30 kg/m^2), n (%)	1,302 (5.7)	69 (6.1)	1,233 (5.7)
Never smoked, n (%)	7,956 (35.1)	359 (31.7)	7,597 (35.2)
Previously smoked, n (%)	6,922 (30.5)	330 (29.2)	6,592 (30.6)
Current smoker, n (%)	7,821 (34.5)	442 (39.1)	7,379 (34.2)
Smoking intensity (g/day), mean (SD)	7.8 (9.2)	8.4 (8.8)	7.8 (9.2)
Never consumed alcohol, n (%)	3,894 (17.2)	195 (17.2)	3,699 (17.2)
Alcohol use in drinkers (g/week), mean (SD)	112.5 (127.6)	120.7 (119.8)	112.1 (127.9)
Low physical activity, n (%)	1,496 (6.6)	71 (6.3)	1,425 (6.6)
Medium physical activity, n (%)	6,132 (27.0)	299 (26.4)	5,833 (27.0)
High physical activity, n (%)	15,071 (66.4)	761 (67.3)	14,310 (66.3)
Nulliparous, n (%)	3,163 (10.3)	180 (15.9)	2,983 (13.8)
Gave birth to 1 child, n (%)	2,680 (11.8)	140 (12.4)	2,540 (11.8)
Gave birth to 2 children, n (%)	9,648 (42.5)	467 (41.3)	9,181 (42.6)
Gave birth to 3 children, n (%)	5,499 (24.2)	271 (24.0)	5,228 (24.2)
Gave birth to 4 children or more, n (%)	1,709 (7.5)	73 (6.5)	1,636 (7.6)
Age at first birth 15–24 years, n (%)	8,123 (35.8)	383 (33.9)	7,740 (35.9)
Age at first birth 25–29 years, n (%)	8,350 (36.8)	384 (34.0)	7,966 (36.9)
Age at first birth 30 years, n (%)	3,065 (13.5)	184 (16.3)	2,881 (13.4)
Never used HT, n (%)	16,600 (73.1)	743 (65.7)	15,857 (73.5)
Previously used HT, n (%)	2,193 (9.7)	99 (8.8)	2,094 (9.7)
Current user of HT, n (%)	3,906 (17.2)	289 (25.6)	3,617 (16.8)
Never used OC, n (%)	9,202 (40.5)	475 (42.0)	8,727 (40.5)
Ever used OC, n (%)	13,497 (59.5)	656 (58.0)	12,841 (59.5)
Rural, n (%)	9,784 (43.1)	514 (45.4)	9,270 (43.0)
Provincial, n (%)	3,368 (14.8)	163 (14.4)	3,205 (14.9)
Urban, n (%)	9,547 (42.1)	454 (40.1)	9,093 (42.2)
Baseline annual PM$_{2.5}$ (μg/m^3), mean (SD)	19.7 (3.5)	20.2 (3.5)	19.6 (3.6)
Baseline annual PM$_{10}$ (μg/m^3), mean (SD)	23.5 (3.9)	24.1 (3.8)	23.5 (3.9)
Baseline annual NO$_2$ (μg/m^3), mean (SD)	12.5 (8.1)	12.7 (8.0)	12.5 (8.1)

Abbreviation: OC, oral contraceptives.

and body mass index (BMI); and additionally adjusted for age at first birth, parity, age at menarche, hormone therapy (HT), and oral contraceptive use (described in Table 1). Effect modification by smoking status, BMI, menopausal status at baseline, HT use, and urbanization level was examined by including interaction terms in the model. Effects are reported by HRs and 95% confidence intervals (CI), per interquartile range increase in 3-year mean of pollutant levels. The methods for establishing the cohort (7) and some prior accomplishments related to studying health effect of air pollution (6, 8) have been described previously.

Results

Of the 28,731 nurses, we excluded 1,924 with cancer and 3 with inactive vital status before cohort baseline, and 3,927 with missing data on address or confounder, leaving 22,877 for final analyses. A total of 1,145 nurses developed breast cancer during mean follow-up of 16 years. Nurses with breast cancer were more

likely nulliparous, HT users, and current smokers (Table 1). We found no association between breast cancer incidence and PM$_{2.5}$, PM$_{10}$, or NO$_2$ (Table 2), and no interaction by smoking status, BMI, or level of urbanization (results not shown). We detected stronger ($P_{\text{interaction}} = 0.07$) association between breast cancer and PM$_{2.5}$ in premenopausal (1.06; 0.94–1.18) than in postmenopausal (0.93; 0.85–1.05) women, and in past (1.19; 0.97–1.44) and current (1.05; 0.92–1.20) than in never HT users (0.95; 0.85–1.05; $P = 0.06$).

Discussion

We found no association between long-term exposure to air pollution and breast cancer incidence in DNC in agreement with other cohort (2, 3, 5), and in contrast to a case–control study (2). We found moderately stronger associations in pre- than in postmenopausal women, in agreement with two studies (2, 3). We present novel findings of enhanced association between PM$_{2.5}$

Andersen et al.

Table 2. Association between air pollution and breast cancer among the 22,877 nurses from DNC

	Unit	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
3-year mean				
PM$_{2.5}$	3.3 μg/m^3	1.03 (0.94–1.13)	1.02 (0.93–1.12)	1.00 (0.91–1.09)
PM$_{10}$	2.9 μg/m^3	1.04 (0.95–1.14)	1.03 (0.95–1.12)	1.02 (0.94–1.11)
NO$_2$	7.4 μg/m^3	1.03 (0.97–1.10)	1.02 (0.96–1.08)	1.00 (0.94–1.07)

[a]Adjusted for age.
[b]Model 1 additionally adjusted for smoking (status and intensity), alcohol use, BMI, and physical activity.
[c]Model 3 also adjusted for parity, age at first birth, age at menarche, hormone therapy use, oral contraceptive use, and menopausal status.

and breast cancer in past and ever HT users, which needs replication.

Ours and most other recent studies (2–5) examined air pollution exposure during adulthood, relatively close to breast cancer onset, which may not be the relevant exposure window for the development of breast cancer. A study found significantly increased breast cancer risk with exposure to traffic emissions at first childbirth, but no risk associated with later exposure windows (9), in line with growing evidence of relevance of early smoking on breast cancer risk (10).

We benefited from having a nationwide cohort of female nurses, with large air pollution exposure contrasts, detailed information on breast cancer risk factors, objective validated information on breast cancer onset, and a state-of-the-art high-resolution air pollution model with data on PM. Weakness of our study is lack of data on air pollution levels during puberty and early adulthood.

Results of our study contribute to growing evidence of a lack of association between exposure to air pollution in adulthood and postmenopausal breast cancer, but association with early exposure windows cannot be excluded. Studies with data on exposure to air pollution early in life and premenopausal breast cancer are needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Z.J. Andersen, K.K. Andersen, J. Brandt, E.V. Bräuner
Development of methodology: K.K. Andersen, J. Brandt, E.V. Bräuner
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.K. Andersen, J. Brandt, M. Ketzel, O. Hertel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Ravnskjær, K.K. Andersen, J. Brandt, M. Ketzel
Writing, review, and/or revision of the manuscript: Z.J. Andersen, L. Ravnskjær, S. Loft, J. Brandt, T. Becker, M. Ketzel, O. Hertel, E. Lynge, E.V. Bräuner
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z.J. Andersen, J. Brandt, T. Becker, M. Ketzel
Study supervision: Z.J. Andersen, E.V. Bräuner

References

1. Mordukhovich I, Pavel R, Terry MB, Santella R, Zhang YJ, Hibshoosh H, et al. Associations between polycyclic aromatic hydrocarbon-related exposures and p53 mutations in breast tumors. Environ Health Perspect 2010;118:511–8.
2. Hystad P, Villeneuve PJ, Goldberg MS, Crouse DL, Johnson K. Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: A case–control study. Environ Int 2015;74:240–8.
3. Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, Weinberg C, et al. Breast cancer risk in relation to ambient air pollution exposure at residences in the sister study cohort. Cancer Epidemiol Biomarkers Prev 2015;24:1907–9.
4. Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, Tamimi RM, et al. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the Nurses' Health Study II Prospective Cohort. Cancer Epidemiol Biomarkers Prev 2016;25:1274–6.
5. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M, et al. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ Health 2011;10:67.
6. Jørgensen JT, Johansen MS, Ravnskjær L, Andersen KK, Bräuner EV, Loft S, et al. Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort. Neurotoxicology 2016;55:122–30.
7. Hundrup YA, Simonsen MK, Jørgensen T, Obel EB. Cohort profile: The Danish Nurse Cohort. Int J Epidemiol 2012;41:1241–7.
8. Hansen AB, Ravnskjær L, Loft S, Andersen KK, Bräuner EV, Baastrup R, et al. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. Environ Int 2016;91:243–50.
9. Nie J, Beyea J, Bonner MR, Han D, Vena JE, Rogerson P, et al. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Cancer Causes Control 2007;18:947–55.
10. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst 2013;105:515–25.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Long-term Exposure to Fine Particulate Matter and Breast Cancer Incidence in the Danish Nurse Cohort Study

Zorana Jovanovic Andersen, Line Ravnskjær, Klaus Kaae Andersen, et al.

Updated version	Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-16-0578

Cited articles	This article cites 10 articles, 2 of which you can access for free at: http://cebp.aacrjournals.org/content/26/3/428.full#ref-list-1
Citing articles	This article has been cited by 3 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/26/3/428.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/26/3/428. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.