

ATMOSPHERIC FINE PARTICULATE MATTER AND BREAST CANCER MORTALITY: A POPULATION-BASED COHORT STUDY

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ABSTRACT**Objectives**

Atmospheric fine particulate matter (PM_{2.5}) has multiple adverse effects on human health. Global atmospheric levels of PM_{2.5} increased by 0.55 µg/m³/year (2.1%/year) from 1998 through 2012. There is evidence of a causal relationship between atmospheric PM_{2.5} and breast cancer (BC) incidence but few studies have investigated BC mortality and atmospheric PM_{2.5}. We investigated BC mortality in relation to atmospheric PM_{2.5} levels among patients living in Varese Province, northern Italy.

Methods

We selected female BC cases, archived in the local population-based cancer registry, diagnosed at age 50-69 years, between 2003 and 2009. The geographic coordinates of each woman's place of residence were identified and individual PM_{2.5} exposures were assessed from satellite data. Grade, stage, age at diagnosis, period of diagnosis, and participation in BC screening were potential confounders. Kaplan-Meier and Nelson-Aalen methods were used to test for mortality differences in relation to PM_{2.5} quartiles. Multivariable Cox proportional hazards modeling estimated hazard ratios (HR) and 95% confidence intervals (CI) of BC death in relation to PM_{2.5} exposure.

Results

Of 2021 BC cases, 325 died during follow-up to 31/12/2013, 246 for breast cancer. Risk of BC death was significantly higher for all three upper quartiles

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3 48 of PM exposure compared to the lowest, with HRs of death: 1.82 (95%CI
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5 49 1.15-2.89), 1.73 (95%CI 1.12-2.67), and 1.72 (95%CI 1.08-2.75).
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8 **Conclusions**

9
10 51 Our study indicates that the risk of BC mortality increases with PM_{2.5}
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12 52 exposure. Although further studies are required to confirm these findings,
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14 53 they are further evidence that PM_{2.5} exposure increases mortality and
15
16 54 indicate an urgent need to improve global air quality.
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21 **STRENGTHS AND LIMITATIONS OF THE STUDY**

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23
24 57 ▪ These is one of few studies to address the relation between atmospheric
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26 58 PM_{2.5} and breast cancer mortality.
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28 59 ▪ PM_{2.5} exposure was assessed using a new but validated method based on
29
30 60 satellite data, overcoming the major limitation of the usual method of
31
32 61 measuring PM_{2.5} at thinly and irregularly distributed ground stations.
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34 62 ▪ We controlled for the usual confounding factors and also for participation
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36 63 in screening that may have introduced length-time and lead-time biases.
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38 64 ▪ We used high quality population-based cancer registry data to identify all
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40 65 breast cancer cases in the study area over the study period, and assess
41
42 66 patient mortality.
43
44 67 ▪ A limitation is that exposure was assessed for the 10x10 km square
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46 68 containing the woman's residence at diagnosis: this is an imperfect
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48 69 assessment of exposure since time spent outside this square is unknown.
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71 INTRODUCTION

72 Atmospheric particulate matter (PM) may be natural or anthropogenic. In
73 industrial and urban areas, PM is mainly anthropogenic in origin.¹ PM of
74 diameter up to 10 μm (PM_{10}) and fine PM, up to 2.5 μm ($\text{PM}_{2.5}$), are
75 documented to have multiple adverse effects on human health², and are
76 classified by the World Health Organization (WHO) and the International
77 Agency for Research on Cancer (IARC) as group 1 carcinogens (carcinogenic
78 to humans).³

79 A recent prospective meta-analysis of 17 cohort studies from nine European
80 countries found a significant association between increasing levels of both
81 PM_{10} and $\text{PM}_{2.5}$ and increasing lung cancer risk. The study concluded that PM
82 air pollution contributed to lung cancer incidence in Europe.⁴

83 Notwithstanding the known toxicity of $\text{PM}_{2.5}$, global population-weighted
84 concentrations increased by 0.55 $\mu\text{g}/\text{m}^3/\text{year}$ (2.1%/year) from 1998
85 through 2012.⁵ It is noteworthy that the incidence of breast cancer is also
86 increasing worldwide: It is the most now common female cancer worldwide.⁶

87 In 2012 an estimated 1.67 million new cases were diagnosed across the
88 globe: 749,000 in developed countries and 883,000 in developing countries.⁶

89 Reasonable hypotheses are that the global increase in breast cancer
90 incidence might be linked to increasing in PM concentrations, and that high
91 PM might also worsen breast cancer survival. This is supported by the
92 findings of a population-based study in California⁷ which found that exposure
93 to higher PM_{10} (HR 1.13, 95%CI 1.02-1.25, per 10 $\mu\text{g}/\text{m}^3$) and $\text{PM}_{2.5}$ (HR
94 1.86, 95%CI 1.12-3.10, per 5 $\mu\text{g}/\text{m}^3$) was significantly associated with early

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3 95 mortality among women with breast cancer after adjusting for numerous
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5 96 covariates.⁷
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8 97 There are other reasons to suspect an association between breast cancer
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10 98 survival and PM levels in the atmosphere. A Canadian study which assessed
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12 99 NO₂ levels as a proxy of traffic-related air pollution found that breast cancer
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14 100 incidence increased with increasing NO₂ exposure.⁸ A Japanese study found
15
16 101 that PM_{2.5} levels estimated from measured PM₁₀ levels were significantly
17
18 102 associated with mortality for breast, endometrial and ovarian cancers after
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20 103 adjusting for smoking, population density, and hormone-related factors.⁹ A
21
22 104 2007 cohort study in Western New York State also found that high exposure
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24 105 to traffic emissions at the time of menarche was associated with increased
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26 106 risk of pre-menopausal breast cancer (OR 2.05, 95% CI 0.92–4.54, p trend
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28 107 0.03); and that high exposure at time of first birth increased the risk of
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30 108 postmenopausal disease (OR 2.57, 95% CI 1.16–5.69, p trend 0.19).¹⁰
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36 109 To further investigate the association of atmospheric PM with breast cancer
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38 110 mortality, we carried out a study in Varese Province, northern Italy. This area
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40 111 is characterized by high breast cancer incidence (world age standardized rate
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42 112 89.3/100,000)⁶, the highest PM_{2.5} levels in Europe⁵, and a high quality
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44 113 cancer registry that is likely to have registered essentially all breast cancer
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46 114 cases occurring over any relatively recent period.¹¹⁻¹²
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50 115 To estimate PM_{2.5} exposure we used satellite-based data that infers near-
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52 116 surface PM_{2.5} concentrations from the satellite-observed total column aerosol
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54 117 loading using a chemical transport model.⁵ This dataset has been shown to
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56 118 represent and correlate well with levels determined with ground-based PM_{2.5}
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3 119 detectors.⁵ Data from satellite observations have the advantage that they
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5 120 make available data at 10x10 km resolution, while ground-based observation
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7 121 stations are generally few and irregularly spaced. In Varese Province only
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10 122 four ground-based sites measure PM_{2.5}.

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124 **MATERIALS AND METHODS**

125 **Breast cancer cases**

126 We performed a retrospective study on a cohort of women diagnosed with
127 primary breast cancer. The cases were archived by the Varese Province
128 section of the Lombardy Cancer Registry. A search using site code C50 and
129 malignant epithelial morphology codes M8010-M8575 of the International
130 Classification of Disease for Oncology (ICDO-3) retrieved a total of 2021
131 primary breast cancers cases diagnosed in the predetermined study period
132 (2003-2009) and conforming to our selection criteria (50-69 years at
133 diagnosis, no other cancer diagnosed previously).¹³ Disease stage was as
134 specified by TNM (6th edition, 2002).¹⁴

135 **Study endpoint**

136 Study endpoint was breast cancer mortality. Mortality data are routinely
137 collected by the cancer registry by linkage to the Varese Province mortality
138 database. Other sources of mortality information are used routinely to ensure
139 completeness.

140 **Estimation of PM_{2.5}**

141 The procedure for estimating PM_{2.5} exposure involved first retrieving each
142 woman's address at diagnosis from the cancer registry (obtained from

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3 143 electronic sources and manual checks) and then determining the geographic
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5 144 coordinates (latitude and longitude) of each address using the ArcGis 10.0
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7 145 software.¹⁵ Ground level PM_{2.5} exposure at each address was then estimated
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9 146 from satellite observations and was considered a proxy of total exposure, so
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11 147 that exposure variations arising from daily or periodic movements away from
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13 148 home were not considered. The method described by van Donkelaar et al.⁵
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15 149 was used to estimate ground level PM_{2.5} exposure. This approach combined
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17 150 total column aerosol optical depth retrievals from the NASA Moderate
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19 151 Resolution Imaging Spectroradiometer (MODIS), Multiangle Imaging
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21 152 Spectroradiometer (MISR), and Sea-viewing Wide Field-of-view Sensor
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23 153 (SeaWIFS) satellite instruments, with vertical aerosol profile and scattering
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25 154 properties as estimated by the GEOS-Chem chemical transport model.⁵ Total
26
27 155 column aerosol optical depth is a measure of the total light extinction due to
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29 156 scattering and absorption by atmospheric aerosols.

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31 157 A three-year running median of PM_{2.5} concentration was used to reduce noise
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33 158 in the annual satellite-derived values. The ground-level PM_{2.5} estimates were
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35 159 available at a resolution of 10x10 km, and breast cancer case exposure was
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37 160 estimated as the PM_{2.5} concentration in the 10x10 km area containing each
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39 161 case's residence.

162 **Statistical methods**

163 First, factors known or thought to influence breast cancer prognosis were
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165 164 analyzed by univariate Cox proportional hazard modeling to verify their effect
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165 165 on breast cancer mortality in our cohort. Factors analyzed were diagnosis
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165 166 period (2003-2006; 2007-2009), stage (I-IV) , grade (I-III, unknown), age

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3 167 at diagnosis (two categories, 50-59 years and 60-69 years), and participation
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5 168 in a breast cancer screening program (Yes, No). Year of diagnosis was
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7 169 included since, over time, treatment may have improved and diagnosis may
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10 170 have occurred earlier. Cancers diagnosed in the screening context are
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12 171 affected by length-time and lead-time bias and may also be less aggressive
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14 172 than those diagnosed outside of screening.¹⁶
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17 173 We next ran univariate and multivariate Cox proportional hazard models to
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19 174 estimate hazard ratios (HRs) with 95% confidence intervals (CI) of breast
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21 175 cancer death according to quartiles of PM_{2.5} exposure. The multivariate
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23 176 model was stratified (separate baseline hazard functions for each variable
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25 177 category within the Cox model) by age, grade, stage, diagnosis period and
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27 178 participation in screening.
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31 179 Time to event or end of follow-up was calculated from date of diagnosis.
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33 180 Cases that died causes other than breast cancer were censored at date of
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35 181 death. Patients alive at study end were censored at that time (31/12/2013).
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37 182 Patients lost to follow-up were censored at date of loss to follow-up. The
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39 183 proportional hazards assumption was tested by analysis of scaled Schoenfeld
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41 184 residuals, estimating P values for each variable, adopting the method
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43 185 suggested by Therneau et al.¹⁷
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47 186 Missing data were handled using a separate "not specified" category for
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49 187 unavailable disease stage and a separate "not specified" category for
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51 188 unavailable tumor grade when performing data analysis.
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55 189 We also used the Kaplan–Meier method to produce survival curves for
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57 190 quartiles of PM_{2.5} exposure, testing the significance of differences between
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3 191 curves with the stratified log-rank test. We also used the Nelson-Aalen
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5 192 estimator to plot the cumulative hazard of breast cancer death for PM_{2.5}
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7 193 exposure categories. The analyses were performed using the R statistical
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9 194 package.¹⁸

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12 195 Italian legislation identifies cancer registries as collectors of personal data for
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14 196 research and public health purposes and does not consider that specific
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17 197 approval by an ethics committee is required to use this data for research and
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19 198 public health purposes. Although our study was an observational one based
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21 199 on individual data, all such data were anonymized prior to analysis.
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25 26 201 **RESULTS**

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29 202 Disease and other characteristics of the 2021 breast cancer patients are
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31 203 shown in Table 1. Eleven women moved outside the study area during
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33 204 follow-up and were censored at the date of leaving.

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36 205 A total of 325 (16.1%) women died in the period up to 31 December 2013,
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38 206 246 (12.2%) of these of breast cancer. Table 1 also shows HRs for breast
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40 207 cancer death according to categories of prognostic variables: HR of death
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42 208 increased significantly with advancing stage and grade, while participation in
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44 209 screening was associated with considerably reduced risk of death, at least
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47 210 over the study period. These findings are as expected.
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212 **Table 1. Patient (n=2021) and disease characteristics with univariate**
 213 **hazard ratios (HR) and 95% confidence intervals (CI) for breast**
 214 **cancer death**

Variable		Breast cancer cases (N)	Breast cancer deaths (N)	HR (95% CI) for breast cancer death
Period of diagnosis				
	2003-2006	1199	163	1
	2007-2009	822	83	1.08 (0.82-1.42)
Disease stage				
	I	887	25	1
	II	550	48	3.21 (1.98-5.21)
	III	292	93	13.31 (8.56-20.70)
	IV	35	27	75.94 (43.94-131.24)
	Not specified	257	53	8.26 (5.14-13.3)
Participation in screening				
	No	1341	213	1
	Yes	680	33	0.29 (0.20-0.41)
Tumor grade				
	I	193	3	1
	II	1132	97	5.43 (1.72-17.13)
	III	513	104	14.06 (4.46-44.33)
	Not specified	183	42	16.93 (5.25-54.63)
Age at diagnosis				
	50-59	923	110	1
	60-69	1098	136	1.05 (0.82-1.35)

Table 2 shows univariate and multivariate HRs with 95% CIs for breast cancer death according to quartiles of PM_{2.5} exposure. By the univariate model, breast cancer patients living in an area with PM_{2.5} levels above the lowest quartile had significantly greater risk of breast cancer death than those living in areas with lowest quartile of PM_{2.5} (<21.10 µg/m³). The increased risk of death ranged from 72% (fourth quartile) to 82% (second quartile). In the multivariate model, which controlled for confounding factors, risks of breast cancer death were numerically greater and still significant for all exposure quartiles above the lowest.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer death in relation to PM_{2.5} exposure.

PM _{2.5} quartiles (µg/m ³)	Cases (N)	Deaths (N)	HR (95%CI), breast cancer death	
			Univariate	Multivariate *
I (<21.10)	504	40	1	1
II (21.10-24.20)	462	56	1.56 (1.04-2.34)	1.82 (1.15-2.89)
III (24.20-26.50)	530	71	1.55 (1.06-2.29)	1.73 (1.12-2.67)
IV (≥26.50)	525	79	1.49 (1.02-2.19)	1.72 (1.08-2.75)

* Multivariate stratified by age, stage, grade, diagnosis and participation in screening.

Analysis of scaled Schoenfeld residuals showed that P values for increasing PM_{2.5} quartiles were 0.93, 0.40, 0.38 and 0.32, indicating that the null

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3 230 hypothesis of no variation of hazard with time could not be rejected,
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5 231 suggesting that the prognostic effect PM_{2.5} remained constant over the entire
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7 232 follow-up.
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10 233 Fig 1 shows Kaplan-Meier survival curves by PM_{2.5} quartiles. Fig 2 shows
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12 234 Nelson-Aalen estimates of the cumulative hazard of breast cancer death by
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14 235 PM_{2.5} quartiles. Figs 1 and 2 both indicate that breast cancer patients
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16 236 exposed to the three upper PM_{2.5} levels ($\geq 21.100 \mu\text{g}/\text{m}^3$) had a significantly
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18 237 ($P=0.04$, stratified log-rank test) greater risk of breast cancer death than
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20 238 those living in an area with the lowest quartile of PM_{2.5}.
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24 239 Yearly (2003-2009) averages of PM_{2.5} exposure for all study women were:
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26 240 26.57, 26.65, 26.43, 23.73, 21.78, 21.44, and 20.71 $\mu\text{g}/\text{m}^3$.
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30 31 242 **DISCUSSION**

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33 243 We have shown that high exposure to PM_{2.5} is associated with increased
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35 244 mortality for breast cancer after correcting for a range of factors considered
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37 245 to influence breast cancer survival. As regards possible mechanisms
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39 246 mediating this association, little evidence is available. A recent study
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41 247 collected airborne particles in Taiwan and investigated their effects on breast
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43 248 cancer cell lines.¹⁹ The particles themselves and their solvent extracts had a
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45 249 variety of effects on the cell lines, including in particular increased generation
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47 250 of reactive oxygen species (ROS), increased numbers of DNA strand breaks,
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49 251 and both estrogenic and anti-estrogenic activity (concentration dependent).
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51 252 It is noteworthy that particle-induced ROS generation was blocked by
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53 253 treatment with aryl hydrocarbon receptor antagonist suggesting that the aryl
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3 254 hydrocarbon receptor mediated the particle-induced toxicity. This is
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5 255 consistent with the positive association between exposure to polycyclic
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7 256 aromatic hydrocarbons from car traffic and breast cancer incidence, reported
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10 257 by the Long Island Breast Cancer Study.²⁰ The authors of the Taiwan study
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12 258 concluded that particle-induced ROS formation contributed to oxidative DNA
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14 259 damage that may mediate particle-induced carcinogenesis.¹⁹

16 260 The finding that particles have both estrogenic and DNA-damaging effects
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18 261 suggests a potential mechanism for an effect on breast cancer: if inhaled PM
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20 262 entered the circulatory system from the lungs, estrogenic particles might find
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22 263 their way to breast tissue. However to our knowledge no data are available
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24 264 to indicate whether PM can reach breast tissue and further research is
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26 265 required in this area.²¹ Most of the toxic effects of PM have been attributed
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28 266 either to direct damage to lung tissue or release of inflammatory mediators
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30 267 from airway cells into the circulatory system.²² Notwithstanding these
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32 268 considerations the biological mechanisms by which PM_{2.5} exposure increases
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34 269 to breast cancer mortality remain unknown.

35
36 270 Our study has several strengths. We used a population-based cancer registry
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38 271 to identify virtually all the breast cancer cases in the study area over the
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40 272 study period, in turn linking them to local and regional mortality databases to
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42 273 obtain accurate and complete survival information. Another strength is our
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44 274 use of satellite derived PM_{2.5} data produced by van Donkelaar et al.⁵
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46 275 Traditional ground-based PM measurement methods may be accurate, but
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48 276 because measurement sites are thinly and irregularly distributed, their data
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50 277 cannot be used to assess the exposure of individuals over a wide geographic
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3 278 area. The satellite data made it possible to estimate exposure in the 10x10
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5 279 km area that included each woman's home. We consider that this 10x10 km
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7 280 area is particularly apt for our study purposes as it comprises the area where
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10 281 the woman is likely to have walked, visited friends, done her shopping,
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12 282 worked, and carried out other daily activities. Of course some women may
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14 283 have spent a considerable fraction of their time outside this area, perhaps at
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17 284 work, and this is a study weakness. Importantly, none of the women had
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19 285 missing values for PM_{2.5} exposure.

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22 286 Another study strength is that we controlled for factors (e.g. stage, grade,
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24 287 and participation in screening) known or suspected to influence breast cancer
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26 288 mortality. However we did not control for lifestyle factors, including diet and
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28 289 alcohol consumption, that may also influence breast cancer mortality.²³⁻²⁴

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31 290 The Californian study⁷ – the only other published study on breast cancer
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33 291 mortality in relation to PM_{2.5} exposure – also found a strong association
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35 292 between breast cancer mortality and PM_{2.5} exposure. However PM_{2.5}
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37 293 exposure for people living in California was much lower than in Varese
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39 294 Province – which is among the highest in the world.⁵ The lowest exposure
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41 295 category for California was PM_{2.5} <11.64 µg/m³: only three patients in our
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43 296 dataset had such a low exposure. However, the California researchers
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45 297 reported an HR for the upper category of 1.76 that is similar to the HRs for
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47 298 our three upper categories (1.82, 1.73 and 1.72 respectively).

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50 299 A report of ongoing research in northern China on the link between PM₁₀ and
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52 300 breast cancer survival also indicated increased risk with increasing PM
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54 301 exposure, and also that survival was lower in women with estrogen receptor
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3 302 positive disease.²⁶ The authors suggested that PM may act as a
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5 303 xenoestrogen, in line with the data from the study on effects of PM on breast
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7 304 cancer cell lines.²⁵
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10 305 It is important to emphasize that the first quartile of exposure in our study is
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12 306 not a risk zero category, but only the reference category for the other
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14 307 quartiles.
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19 309 **CONCLUSIONS**

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21 310 Although our study has limitations, its findings are consistent with those of
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23 311 the California study and the report of a study in China indicating a strong
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25 312 association between breast cancer death and atmospheric PM exposure.
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28 313 Clearly further studies are justified to further explore this association,
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30 314 particularly in view of the increasing worldwide incidence of breast cancer
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32 315 and increasing worldwide PM concentrations.⁵⁻⁶ Our data add to the wealth of
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34 316 evidence that atmospheric PM has multiple adverse effects on human health,
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36 317 and increase pressure to lower PM levels worldwide.
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39 318

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49 323 **Competing interests**

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51 324 All authors declare they have no competing interests.
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3 326 **Data sharing statement**
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5 327 No additional data are available
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19 333 **Authors' contributions**
20

21 334 P. Contiero contributed to study conception, designed the study, performed
22
23 335 the statistical analysis and wrote the first draft of the paper.
24
25

26 336 G. Tagliabue contributed to study conception, coordinated the clinical section
27
28 337 of the study and contributed to writing the paper.
29
30

31 338 R. Tessandori and G. Barigelletti contributed to practical aspects of study
32
33 339 design.
34
35

36 340 A. Borgini, M. Bertoldi and A Tittarelli were responsible for the exposure
37
38 341 assessment.
39
40

41 342 A. van Donkelaar and R. V. Martin were responsible for developing the model
42
43 343 deriving PM data from satellite data.
44

45 344 A Tittarelli, S Fabiano, A Scaburri and G Barigelletti developed the
46
47 345 information system to archive and manage the data and performed the
48
49 346 descriptive statistics.
50

51
52 347 A Maghini and T Codazzi retrieved the clinical information and performed the
53
54 348 record linkage between the sources.
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56
57 349 I Favia and A Cau transferred the clinical data into the study database.
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3 350 All authors read and approved the final manuscript.
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352 **REFERENCES**

- 353 1. IARC Scientific Publication No. 161: AIR POLLUTION AND CANCER.
354 <http://www.iarc.fr/en/publications/books/sp161/AirPollutionandCancer>
355 161.pdf
- 356 2. Barman SC, Kumar N, Singh R, et al. Assessment of urban air pollution
357 and it's probable health impact. J Environ Biol. 2010 Nov;31(6):913-20
- 358 3. IARC MONOGRAPHS: Volume 109: OUTDOOR AIR POLLUTION.
359 <http://monographs.iarc.fr/ENG/Monographs/vol109/mono109.pdf>
- 360 4. Raaschou-Nielsen O1, Andersen ZJ, Beelen R, et al. Air pollution and
361 lung cancer incidence in 17 European cohorts: prospective analyses
362 from the European Study of Cohorts for Air Pollution Effects (ESCAPE).
363 Lancet Oncol. 2013;14(9):813-22.
- 364 5. Van Donkelaar A, Martin RV, Brauer M, et al. Use of satellite
365 observations for long-term exposure assessment of global
366 concentrations of fine particulate matter. Environ Health Perspect.
367 2015 Feb;123(2):135-43.
- 368 6. IARC: GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and
369 Prevalence Worldwide in 2012.
370 http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
- 371 7. Hu H, Dailey AB, Kan H, et al. The effect of atmospheric particulate
372 matter on survival of breast cancer among US females. Breast Cancer
373 Res Treat. 2013 May;139(1):217-26.
- 374 8. Hystad P, Villeneuve PJ, Goldberg MS, et al. Canadian Cancer
375 Registries Epidemiology Research Group. Exposure to traffic-related air

- 1
2
3 376 pollution and the risk of developing breast cancer among women in
4
5 377 eight Canadian provinces: a case-control study. *Environ Int.* 2015
6
7 378 Jan;74:240-8.
- 9
10 379 9. Iwai K, Mizuno S, Miyasaka Y, et al. Correlation between suspended
11
12 380 particles in the environmental air and causes of disease among
13
14 381 inhabitants: cross-sectional studies using the vital statistics and air
15
16 382 pollution data in Japan. *Environ Res.* 2005 Sep;99(1):106-17.
- 17
18
19 383 10. Nie J, Beyea J, Bonner MR, et al. Exposure to traffic emissions
20
21 384 throughout life and risk of breast cancer: the Western New York
22
23 385 Exposures and Breast Cancer (WEB) study. *Cancer Causes Control.*
24
25 386 2007 Nov;18(9):947-55.
- 26
27
28 387 11. Tagliabue G, Maghini A, Fabiano S, et al Consistency and accuracy of
29
30 388 diagnostic cancer codes generated by automated registration:
31
32 389 comparison with manual registration. *Popul Health Metr* 4:10
- 33
34
35 390 12. Contiero P, Tittarelli A, Maghini A, et al. Comparison with manual
36
37 391 registration reveals satisfactory completeness and efficiency of a
38
39 392 computerized cancer registration system. *J Biomed Inform.* 2008
40
41 393 Feb;41(1):24-32
- 42
43
44 394 13. International Classification of Diseases for Oncology, Third Edition, First
45
46 395 Revision. Geneva: World Health Organization, 2013
- 47
48
49 396 14. Sobin LH, Wittekind C. International Union Against Cancer (UICC) TNM
50
51 397 Classification Of Malignant Tumors. 6th ed. New York, NY: Wiley-Liss;
52
53 398 2002.
- 54
55
56 399 15. ESRI: ArcGIS. <http://www.esri.com/software/arcgis>

- 1
2
3 400 16. Berry DA. Failure of researchers, reviewers, editors, and the media to
4
5 401 understand flaws in cancer screening studies: application to an article
6
7 402 in Cancer. *Cancer*. 2014 Sep 15;120(18):2784-91
8
9
10 403 17. Therneau TM, Grambsch PM (2000) Testing proportional hazards. In:
11
12 404 Modeling survival data: extending the Cox model. Springer, New York
13
14 405 18. R Development Core Team (2007), R: a language and environment for
15
16 406 statistical computing. <http://www.r-project.org>
17
18
19 407 19. Chen ST, Lin CC, Liu YS, et al. Airborne particulate collected from
20
21 408 central Taiwan induces DNA strand breaks, Poly(ADP-ribose)
22
23 409 polymerase-1 activation, and estrogen-disrupting activity in human
24
25 410 breast carcinoma cell lines. *Environ Sci Health A Tox Hazard Subst*
26
27 411 *Environ Eng*. 2013;48(2):173-81.
28
29
30 412 20. Mordukhovich I, Beyea J, Herring AH, Hatch M, et al. Vehicular Traffic-
31
32 413 Related Polycyclic Aromatic Hydrocarbon Exposure and Breast Cancer
33
34 414 Incidence: The Long Island Breast Cancer Study Project (LIBCSP).
35
36 415 *Environ Health Perspect*. 2015 May 22.
37
38
39 416 21. Sutton P, Kavanaugh-Lynch MH, et al. California Breast Cancer
40
41 417 Prevention Initiatives: Setting a research agenda for prevention.
42
43 418 *Reprod Toxicol*. 2015 Jul;54:11-8.
44
45
46 419 22. Rundell KW. Effect of air pollution on athlete health and performance.
47
48 420 *Br J Sports Med*. 2012 May;46(6):407-12
49
50
51 421 23. Romieu I, Scocianti C, Chajès V, et al. Alcohol intake and breast
52
53 422 cancer in the European prospective investigation into cancer and
54
55 423 nutrition. *Int J Cancer*. 2015 Oct 15;137(8):1921-30
56
57
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- 1
2
3 424 24. McKenzie F, Ferrari P, Freisling H, et al. Healthy lifestyle and risk of
4
5 425 breast cancer among postmenopausal women in the European
6
7 426 Prospective Investigation into Cancer and Nutrition cohort study. Int J
8
9 427 Cancer. 2015 Jun 1;136(11):2640-8
10
11
12 428 25. Huo Q, Cai C, Yang Q. Atmospheric particulate matter and breast
13
14 429 cancer survival: estrogen receptor triggered? Tumour Biol. 2015
15
16 430 May;36(5):3191-3
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3 432 **Fig 1. Survival of breast cancer cases, diagnosed 2003-2009 and**
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5 433 **resident in Varese Province, northern Italy according to exposure to**
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7 434 **PM_{2.5} (quartiles)**
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12 436 **Fig 2. Cumulative hazard of breast cancer death in cases diagnosed**
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14 437 **2003-2009 and resident in Varese Province, according to exposure to**
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16 438 **PM_{2.5} (quartiles)**
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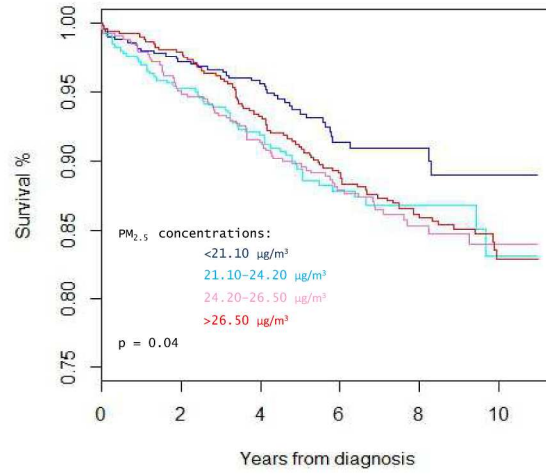


Fig 1. Survival of breast cancer cases, diagnosed 2003-2009 and resident in Varese Province, northern Italy according to exposure to PM_{2.5} (quartiles)

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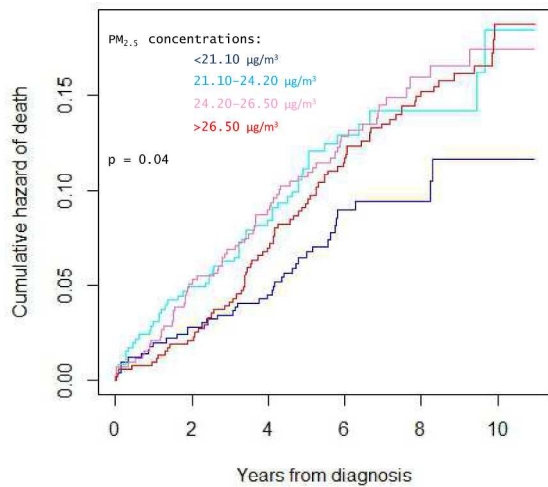


Fig 2. Cumulative hazard of breast cancer death in cases diagnosed 2003-2009 and resident in Varese Province, according to exposure to PM2.5 (quartiles)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1: Title: "A population-based cohort study"
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3: "Our study indicates that the risk of BC mortality increases with PM _{2.5} exposure."
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5: "PM2.5 [has] multiple adverse effects on human health, and is classified by WHO and IARC as carcinogenic to humans." "global PM2.5 concentrations increased by 2.1%/year from 1998 through 2012." "breast cancer incidence is also increasing worldwide".
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5: "To investigate the association of atmospheric PM with breast cancer mortality ." Hypothesis:"the global increase in breast cancer incidence might be linked to increasing in PM concentrations and high PM might also worsen breast cancer survival ".
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 6, Methods: "a retrospective study [of breast cancer mortality] on a cohort of women diagnosed with primary breast cancer".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 6-7, Methods: "...cases archived by Lombardy Cancer Registry.[...] A total of 2021 primary breast cancers cases diagnosed in predetermined study period (2003-2009)". Page 2: "Of 2021 BC cases, 325 died during follow-up

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			to 31/12/2013.”
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6 Methods – Breast cancer cases: “conforming to selection criteria (50-69 years at diagnosis, no other cancer diagnosed previously)”[were selected] Disease stage was as specified by TNM. “Mortality data are routinely collected by the cancer registry by linkage to the Varese Province mortality database. Other sources of mortality information are used routinely to ensure completeness.”
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A, it is not a matched study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6 : “Study endpoint was breast cancer mortality.” Pages 7-8 Statistical methods: [potential confounders] “were diagnosis, stage, grade, age at diagnosis and participation in a breast cancer screening program. [and] year of diagnosis.”
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 6-8 Methods - Breast cancer cases from Varese cancer registry. “ Mortality data [...] collected by the cancer registry by linkage to the Varese Province mortality database. Other sources of mortality information used to ensure completeness”, Estimation of PM _{2.5} , Statistical methods: “To estimate PM _{2.5} exposure we used satellite-based data that infers near-surface PM _{2.5} concentrations from the satellite-observed total column aerosol loading using a chemical transport model.”
Bias	9	Describe any efforts to address potential sources of bias	Page 8 Methods – Statistical methods: “Cancers diagnosed in the screening context are affected by length-time and lead-time bias and may also be less aggressive than those diagnosed outside of screening”

Study size	10	Explain how the study size was arrived at	Page 6 Methods – Breast cancer cases: The cancer database was searched “using site code C50 and malignant epithelial morphology codes M8010-M8575 of the ICDO-3.” “A total of 2021 primary breast cancers cases diagnosed in the predetermined study period (2003-2009) and conforming to selection criteria (50-69 years at diagnosis, no other cancer diagnosed previously)” were used.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-8 Methods – Statistical methods: “Factors analyzed were diagnosis period (2003-2006; 2007-2009), stage (I-IV) , grade (I-III, unknown), age at diagnosis (two categories, 50-59 years and 60-69 years), and participation in a breast cancer screening program (Yes, No)”
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 8 Methods – Statistical methods: “We ran univariate and multivariate Cox proportional hazard models to estimate HRs with 95% CI of breast cancer death according to quartiles of PM2.5 exposure. The multivariate model was stratified by age, grade, stage, diagnosis period and participation in screening.”
		(b) Describe any methods used to examine subgroups and interactions	We did not analyse subgroup and we did not study interactions.
		(c) Explain how missing data were addressed	Page 8 - Missing data were handled using a separate “not specified” category for unavailable disease stage and a separate “not specified” category for unavailable tumor grade when performing data analysis.
		(d) If applicable, explain how loss to follow-up was addressed	Page 8 – loss of follow-up was addressed by censoring at date of loss of follow-up
		(e) Describe any sensitivity analyses	Not performed
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	N/A

		follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 10-11 Results – Table1
		(b) Indicate number of participants with missing data for each variable of interest	Pages 10-11. Table 1 and above
		(c) Summarise follow-up time (eg, average and total amount)	Page 9, Results: Followed up to 31 December 2013
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9 – “A total of 325 (16.1%) women died in the period up to 31 December 2013, 246 (12.2%) of these of breast cancer.” Pages 10-11 Results – Table1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 11 Results – Table2 Page 11: “By the univariate model, breast cancer patients living in an area with PM _{2.5} levels above the lowest quartile had significantly greater risk of breast cancer death than those living in areas with lowest quartile of PM _{2.5} (<21.10 µg/m ³). The increased risk of death ranged from 72% (fourth quartile) to 82% (second quartile). In the multivariate model, which controlled for confounding factors, risks of breast cancer death were numerically greater and still significant for all exposure quartiles above the lowest.”
		(b) Report category boundaries when continuous variables were categorized	Pages 10-11 Results – Table1; Table2 PM _{2.5} was categorised into: I (<21.10); II (21.10-24.20), III(24.20-26.50) , IV (≥26.50) Page 11 Results – Table2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12 Discussion: “We have shown that high

			exposure to PM2.5 is associated with increased mortality for breast cancer after correcting for a range of factors considered to influence breast cancer survival.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14 Discussion: “...some women may have spent a considerable fraction of their time outside this area, perhaps at work, and this is a study weakness”. “...we did not control for lifestyle factors, including diet and alcohol consumption, that may also influence breast cancer mortality.”
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 13-14 Discussion Page 15 Conclusions: “Our data add to the wealth of evidence that atmospheric PM has multiple adverse effects on human health”.
Generalisability	21	Discuss the generalisability (external validity) of the study results	This is a preliminary study.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16: “This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.”

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

ATMOSPHERIC FINE PARTICULATE MATTER AND BREAST CANCER MORTALITY: A POPULATION-BASED COHORT STUDY

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Primary Subject Heading:	Occupational and environmental medicine
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Keywords:	Breast tumours < ONCOLOGY, particulate matter, environment, prognosis, survival, cancer registry

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3 **1 ATMOSPHERIC FINE PARTICULATE MATTER AND BREAST CANCER**
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5 **2 MORTALITY: A POPULATION-BASED COHORT STUDY**
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49
50 **Keywords:** Breast cancer, particulate matter, prognosis, survival, cancer
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52 registry
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55 **Word count:** 2.676
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25 **ABSTRACT**

26 **Objectives**

27 Atmospheric fine particulate matter (PM_{2.5}) has multiple adverse effects on
28 human health. Global atmospheric levels of PM_{2.5} increased by 0.55
29 µg/m³/year (2.1%/year) from 1998 through 2012. There is evidence of a
30 causal relationship between atmospheric PM_{2.5} and breast cancer (BC)
31 incidence but few studies have investigated BC mortality and atmospheric
32 PM_{2.5}. We investigated BC mortality in relation to atmospheric PM_{2.5} levels
33 among patients living in Varese Province, northern Italy.

34 **Methods**

35 We selected female BC cases, archived in the local population-based cancer
36 registry, diagnosed at age 50-69 years, between 2003 and 2009. The
37 geographic coordinates of each woman's place of residence were identified
38 and individual PM_{2.5} exposures were assessed from satellite data. Grade,
39 stage, age at diagnosis, period of diagnosis, and participation in BC screening
40 were potential confounders. Kaplan-Meier and Nelson-Aalen methods were
41 used to test for mortality differences in relation to PM_{2.5} quartiles.
42 Multivariable Cox proportional hazards modeling estimated hazard ratios
43 (HR) and 95% confidence intervals (CI) of BC death in relation to PM_{2.5}
44 exposure.

45 **Results**

46 Of 2021 BC cases, 325 died during follow-up to 31/12/2013, 246 for breast
47 cancer. Risk of BC death was significantly higher for all three upper quartiles

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3 48 of PM exposure compared to the lowest, with HRs of death: 1.82 (95%CI
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5 49 1.15-2.89), 1.73 (95%CI 1.12-2.67), and 1.72 (95%CI 1.08-2.75).
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8 **Conclusions**

9
10 51 Our study indicates that the risk of BC mortality increases with PM_{2.5}
11
12 52 exposure. Although additional research is required to confirm these findings,
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14 53 they are further evidence that PM_{2.5} exposure is harmful and indicate an
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16 54 urgent need to improve global air quality.
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20 **STRENGTHS AND LIMITATIONS OF THE STUDY**

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24 57 • These is one of few studies to address the relation between
25
26 58 atmospheric PM_{2.5} and breast cancer mortality.
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28 59 • PM_{2.5} exposure was assessed using a new but validated method based
29
30 60 on satellite data, overcoming the major limitation of measuring PM_{2.5} at
31
32 61 thinly and irregularly distributed ground stations.
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34 62 • We used high quality population-based cancer registry data to identify
35
36 63 breast cancer cases, and assess patient mortality.
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38 64 • We controlled for confounding factors and also for participation in
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40 65 screening that may have introduced length-time and lead-time biases.
41
42 66 • Limitations are that lifestyle factors and comorbidities were not
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44 67 considered, and that exposure was assessed in the 10x10 km square
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46 68 containing the woman's residence, while time spent outside this square
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48 69 is unknown.
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72 INTRODUCTION

73 Atmospheric particulate matter (PM) may be emitted or formed from natural
74 or anthropogenic sources. In industrial and urban areas, PM is mainly
75 anthropogenic.¹ PM of diameter up to 10 µm (PM₁₀) and fine PM, up to 2.5
76 µm (PM_{2.5}), are documented to have multiple adverse effects on human
77 health^{2,3}, and are classified by the World Health Organization (WHO) and the
78 International Agency for Research on Cancer (IARC) as group 1 carcinogens
79 (carcinogenic to humans).⁴

80 A recent prospective meta-analysis of 17 cohort studies from nine European
81 countries found a significant association between increasing levels of both
82 PM₁₀ and PM_{2.5} and increasing lung cancer risk. The study concluded that PM
83 air pollution contributed to lung cancer incidence in Europe.⁵

84 Notwithstanding the known toxicity of PM_{2.5}, global population-weighted
85 concentrations increased by 0.55 µg/m³/year (2.1%/year) from 1998
86 through 2012, largely driven by increases in developing countries such as
87 China and India.⁶ It is noteworthy that the incidence of breast cancer is also
88 increasing worldwide and it is now the most common female cancer
89 worldwide.⁷ In 2012 an estimated 1.67 million new cases were diagnosed
90 across the globe: 749,000 in developed countries and 883,000 in developing
91 countries.⁷

92 Reasonable hypotheses are that the global increase in breast cancer
93 incidence might be linked to increasing in PM concentrations, and that high
94 PM might also worsen breast cancer survival. This is supported by the
95 findings of a population-based study in California⁸ which found that exposure

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3 96 to higher PM₁₀ (HR 1.13, 95%CI 1.02-1.25, per 10 µg/m³) and PM_{2.5} (HR
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5 97 1.86, 95%CI 1.12-3.10, per 5 µg/m³) was significantly associated with early
6
7 98 mortality among women with breast cancer after adjusting for numerous
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10 99 covariates.

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12 100 There are other reasons to suspect an association between breast cancer
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14 101 survival and PM levels in the atmosphere. A Canadian study which assessed
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16 102 NO₂ levels as a proxy of traffic-related air pollution found that breast cancer
17
18 103 incidence increased with increasing NO₂ exposure.⁹ A Japanese study found
19
20 104 that PM_{2.5} levels estimated from measured PM₁₀ levels were significantly
21
22 105 associated with mortality for breast, endometrial and ovarian cancers after
23
24 106 adjusting for smoking, population density, and hormone-related factors.¹⁰ A
25
26 107 2007 cohort study in Western New York State also found that high exposure
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28 108 to traffic emissions at the time of menarche was associated with increased
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30 109 risk of pre-menopausal breast cancer (OR 2.05, 95% CI 0.92–4.54, p trend
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32 110 0.03); and that high exposure at time of first birth increased the risk of
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34 111 postmenopausal disease (OR 2.57, 95% CI 1.16–5.69, p trend 0.19).¹¹

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36 112 To further probe the association of atmospheric PM with breast cancer, we
37
38 113 carried out the present study in Varese Province, northern Italy. We
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40 114 investigated breast cancer mortality (primary study endpoint) in relation to
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42 115 residential exposure to atmospheric PM_{2.5} as determined by a satellite-based
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44 116 method.
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51 52 117 **MATERIALS AND METHODS**

53 54 118 **Study area**

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3 119 Varese Province, Region of Lombardy, northern Italy (Fig 1) has a population of
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5 120 877 000 and population density of 731.4/km². PM_{2.5} comes from mainly from
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7 121 non-industrial emissions (e.g. heating) (30-42%) and road traffic (30-32%).¹² As Fig.
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9
10 122 1 shows, Varese Province is situated in an area (the plain of the river Po)
11
12 123 enclosed by mountains which block atmospheric circulation. As a result
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14 124 atmospheric pollution tends to build up. In fact atmospheric PM_{2.5} levels in
15
16 125 the plain of the Po are among the highest in the world.⁶

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18
19 126 Varese Province is also characterized by high breast cancer incidence (world
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21 127 age standardized rate 89.3/100,000)⁷ and a high quality cancer registry that
22
23 128 is likely to have registered essentially all breast cancer cases occurring over
24
25 129 any relatively recent period.¹³⁻¹⁴

130 **Breast cancer cases**

31 131 We performed a retrospective study on a cohort of women diagnosed with
32
33 132 primary breast cancer. The cases were archived by the Varese section of the
34
35 133 Lombardy Cancer Registry. A search using site code C50 and malignant
36
37 134 epithelial morphology codes M8010-M8575 of the International Classification
38
39 135 of Disease for Oncology (ICDO-3) retrieved a total of 2021 primary breast
40
41 136 cancer cases diagnosed in the predetermined study period (2003-2009) and
42
43 137 conforming to our selection criteria (50-69 years at diagnosis, no other
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45 138 cancer diagnosed previously).¹⁵ All 2021 breast cancer cases were used in
46
47 139 the analysis. Disease stage was as specified by TNM (6th edition, 2002).¹⁶

52 140 **Mortality ascertainment**

54 141 Mortality data from the Varese Province mortality database are routinely
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56 142 collected by the cancer registry and linked to cancer cases by the Epilink

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3 143 software, which achieved 98.8% specificity and 96.5% sensitivity for linking
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5 144 in a published study.¹⁷ Epilink flags problematic cases for manual checking to
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8 145 enhance linkage accuracy. Each cancer case identified as deceased is
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10 146 checked against the Social Security List of all persons who receive health
11
12 147 caser in the Region of Lombardy (essentially the entire population). The vital
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14 148 status field for each person in the Social Security List is updated frequently
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16
17 149 and serves as an independent check of the vital status of cancer cases
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19
20 150 archived by the registry.

21 **Estimation of PM_{2.5}**

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23
24 152 The procedure for estimating PM_{2.5} exposure involved first retrieving each
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26 153 patient's address at the date of diagnosis (reference date) from the cancer
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28 154 registry and then determining the geographic coordinates (latitude and
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30
31 155 longitude) of each address using the ArcGis 10.0 software.¹⁸ Ground level
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33 156 PM_{2.5} exposure at each address was then estimated from satellite
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36 157 observations. The actual PM_{2.5} value used as exposure proxy was the median
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38 158 of ground level PM_{2.5} concentrations over the three years around the
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40 159 diagnosis date (so as to reduce noise in the annual satellite-derived values).
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43 160 Thus if a woman was diagnosed in 2006, the PM_{2.5} concentration used was
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45 161 the median of annual concentrations for the years 2005, 2006 and 2007. The
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47 162 method described by van Donkelaar et al.⁶ was used to estimate ground level
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50 163 PM_{2.5} exposure. This approach combined daily total column aerosol optical
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52 164 depth data from the NASA Moderate Resolution Imaging Spectroradiometer
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54 165 (MODIS), Multiangle Imaging Spectroradiometer (MISR), and Sea-viewing
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57 166 Wide Field-of-view Sensor (SeaWiFS) satellite instruments, with coincident
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3 167 vertical aerosol profile and scattering properties estimated by the GEOS-
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5 168 Chem chemical transport model, so as to produce longer-term means. ⁶ Total
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7 169 column aerosol optical depth is a measure of the total light extinction due to
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10 170 scattering and absorption by atmospheric aerosols.

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12 171 The ground-level PM_{2.5} estimates were available at a resolution of 10x10 km,
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14 172 and breast cancer case exposure was estimated as median PM_{2.5}
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17 173 concentration over three years in the 10x10 km area containing each case's
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19 174 residence. Exposure variations arising from daily or periodic movements
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21 175 away from home are not considered by this method.

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24 176 Data produced by this method have been shown to correlate well with levels
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26 177 determined by ground-based PM_{2.5} detectors,⁶ and have the advantage that
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28 178 they are available over an entire territory, while ground-based observation
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30 179 stations are generally few and irregularly spaced. In Varese Province only
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32 180 four ground-based sites measure PM_{2.5}.

33 34 35 36 181 **Statistical methods**

37
38 182 The analyses we performed are based on the Cox proportional hazard model
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40 183 which specifies the hazard as $\lambda(t) = \lambda_0(t)\exp(\beta X)$ where $\lambda(t)$ is the hazard
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42 184 function for the event in question (death). X is a vector of covariates, and β
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44 185 is a vector of coefficients to be estimated. The hazards for two subjects with
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46 186 fixed covariate vectors X_i e X_j are respectively $\lambda_i(t) = \lambda_0(t)\exp(\beta X_i)$ and $\lambda_j(t)$
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48 187 $= \lambda_0(t)\exp(\beta X_j)$. The hazard ratio (HR) is $\lambda_i(t)/\lambda_j(t) = \exp(\beta(X_i - X_j))$. To test
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50 188 the null hypothesis H_0 that $\beta = 0$ we used the likelihood ratio test. Because
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52 189 the Cox model assumes proportional hazards, this was tested by analysis of
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54 190 scaled Schoenfeld residuals, with associated p values. When the hazard was

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3 191 suspected to be non-proportional over time, we performed additional
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5 192 analyses, substituting the conventional Cox β coefficient (for a given
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7 193 variable) with a time-dependent function $\beta(t)$ obtained by adding the
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9
10 194 smoothed scaled Schoenfeld residuals to the conventional β coefficient.^{19,20,21}

11
12 195 Factors known or thought to influence breast cancer prognosis were initially
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14 196 analyzed by univariate Cox proportional hazard modeling to verify their effect
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17 197 on breast cancer mortality in our cohort. Factors analyzed were diagnosis
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19 198 period (2003-2006; 2007-2009), stage (I-IV) , grade (I-III, unknown), age
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21 199 at diagnosis (two categories, 50-59 years and 60-69 years), and participation
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23 200 in a breast cancer screening program (Yes, No). Year of diagnosis was
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26 201 included since, over time, treatment may have improved and diagnosis may
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28 202 have occurred earlier. Cancers diagnosed in the screening context are
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30 203 affected by length-time and lead-time bias and may also be less aggressive
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33 204 than those diagnosed outside of screening.²²

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36 205 We next ran univariate and multivariate Cox proportional hazard models to
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38 206 estimate HRs with 95% confidence intervals (CI) of breast cancer death
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40 207 according to quartiles of PM_{2.5} exposure. The multivariate model was
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42 208 stratified (separate baseline hazard functions for each variable category
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44 209 within the model) by age, grade, stage, diagnosis period and participation in
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46 210 screening. by age, grade, stage, diagnosis period and participation in
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48 211 screening to control for the possible confounding effects of these variables on
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50 212 mortality.

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53 213 Time to event or end of follow-up was calculated from date of diagnosis.

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55 214 Cases that died of causes other than breast cancer were censored at the date
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3 215 of death. Patients alive at study end were censored at that time
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5 216 (31/12/2013). Patients lost to follow-up were censored at the date of loss to
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7 217 follow-up. Cases with missing data (missing disease stage and tumor grade)
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9 218 were assigned to "not specified" categories in the analyses.

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12 219 We also used the Kaplan–Meier method to produce survival curves for
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14 220 quartiles of PM_{2.5} exposure, testing the significance of differences between
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17 221 curves with the stratified log-rank test. We also used the Nelson-Aalen
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19 222 estimator to plot the cumulative hazard of breast cancer death for PM_{2.5}
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21 223 exposure categories. The analyses were performed using the R statistical
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23
24 224 package.²³

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26 225 Italian legislation identifies cancer registries as collectors of personal data for
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28 226 research and public health purposes and does not consider that specific
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30 227 approval by an ethics committee is required to use this data for research and
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33 228 public health purposes. Although our study was an observational one based
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35 229 on individual data, all such data were anonymized prior to analysis.

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39 40 231 **RESULTS**

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42 232 Disease and other characteristics of the 2021 breast cancer patients are
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44 233 shown in Table 1. One hundred and one (5%) women changed address
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47 234 during the study period: 90 of these moved from one part of the Province to
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49 235 another (and may have changed PM_{2.5} exposure), while 11 moved outside
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51 236 the study area and were censored at the date of leaving. A total of 325
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53 237 (16.1%) women died in the period up to 31 December 2013, 246 (12.2%) of
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55 238 these of breast cancer. Table 1 also shows HRs for breast cancer death
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3 239 according to categories of prognostic variables: HR of death increased
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5 240 significantly with advancing stage and grade, while participation in screening
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8 241 was associated with considerably reduced risk of death, at least over the
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10 242 study period. These findings are as expected.
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244 **Table 1. Patient (n=2021) and disease characteristics with univariate**
 245 **hazard ratios (HR) and 95% confidence intervals (CI) for breast**
 246 **cancer death**

Variable		Breast cancer cases (N)	Breast cancer deaths (N)	HR (95% CI) for breast cancer death
Period of diagnosis				
	2003-2006	1199	163	1
	2007-2009	822	83	1.08 (0.82-1.42)
Disease stage				
	I	887	25	1
	II	550	48	3.21 (1.98-5.21)
	III	292	93	13.31 (8.56-20.70)
	IV	35	27	75.94 (43.94-131.24)
	Not specified	257	53	8.26 (5.14-13.3)
Participation in screening				
	No	1341	213	1
	Yes	680	33	0.29 (0.20-0.41)
Tumor grade				
	I	193	3	1
	II	1132	97	5.43 (1.72-17.13)
	III	513	104	14.06 (4.46-44.33)
	Not specified	183	42	16.93 (5.25-54.63)
Age at diagnosis				
	50-59	923	110	1
	60-69	1098	136	1.05 (0.82-1.35)

Table 2 shows the results of the univariate and multivariate analyses, presented as HRs with 95% CIs for breast cancer death according to quartiles of PM_{2.5} exposure. By the univariate model, breast cancer patients living in an area with PM_{2.5} levels above the lowest quartile had significantly greater risk of breast cancer death than those living in areas with lowest quartile of PM_{2.5} (<21.10 µg/m³). The increased risk of death ranged from 72% (fourth quartile) to 82% (second quartile). For the multivariate model, which controlled for confounding factors, the likelihood ratio test gave p = 0.029, indicating that the null hypothesis of no association between breast cancer mortality and PM_{2.5} could be rejected. In detail: HRs of breast cancer death were numerically greater than those produced by the univariate analyses and significant for all exposure quartiles above the lowest.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer death in relation to PM_{2.5} exposure.

PM _{2.5} quartiles (µg/m ³)	Cases (N)	Deaths (N)	HR (95%CI), breast cancer death	
			Univariate	Multivariate *
I (<21.10)	504	40	1	1
II (21.10-24.20)	462	56	1.56 (1.04-2.34)	1.82 (1.15-2.89)
III (24.20-26.50)	530	71	1.55 (1.06-2.29)	1.73 (1.12-2.67)
IV (≥26.50)	525	79	1.49 (1.02-2.19)	1.72 (1.08-2.75)

* Multivariate stratified by age, stage, grade, diagnosis and participation in screening.

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263 Analysis of scaled Schoenfeld residuals showed that P values for increasing
264 PM_{2.5} quartiles were 0.93, 0.40, 0.38 and 0.32, indicating that the null
265 hypothesis of no variation of hazard with time could not be rejected,
266 suggesting that the prognostic effect PM_{2.5} remained constant over the entire
267 follow-up.

268 Fig 2 shows Kaplan-Meier survival curves by PM_{2.5} quartiles. Fig 2 shows
269 Nelson-Aalen estimates of the cumulative hazard of breast cancer death by
270 PM_{2.5} quartiles. Figs 2 and 3 both indicate that breast cancer patients
271 exposed to the three upper PM_{2.5} levels ($\geq 21.100 \mu\text{g}/\text{m}^3$) had a significantly
272 (P=0.04, stratified log-rank test) greater risk of breast cancer death than
273 those living in an area with the lowest quartile of PM_{2.5}.

274 Yearly (2003-2009) averages of PM_{2.5} exposure for all study women were:
275 26.57, 26.65, 26.43, 23.73, 21.78, 21.44, and 20.71 $\mu\text{g}/006\text{D}^3$.

276

277 **DISCUSSION**

278 We have shown that high exposure to PM_{2.5} is associated with increased
279 mortality for breast cancer after correcting for a range of factors considered
280 to influence breast cancer survival. As regards possible mechanisms
281 mediating this association, little evidence is available. A recent study
282 collected airborne particles in Taiwan and investigated their effects on breast
283 cancer cell lines.²⁴ The particles themselves and their solvent extracts had a
284 variety of effects on the cell lines, including in particular increased generation
285 of reactive oxygen species (ROS), increased numbers of DNA strand breaks,

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3 286 and both estrogenic and anti-estrogenic activity (concentration dependent).
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5 287 It is noteworthy that particle-induced ROS generation was blocked by
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7 288 treatment with aryl hydrocarbon receptor antagonist suggesting that the aryl
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9 289 hydrocarbon receptor mediated the particle-induced toxicity. This is
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11 290 consistent with the positive association between exposure to polycyclic
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13 291 aromatic hydrocarbons from car traffic and breast cancer incidence, reported
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15 292 by the Long Island Breast Cancer Study.²⁵ The authors of the Taiwan study
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17 293 concluded that particle-induced ROS formation contributed to oxidative DNA
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19 294 damage that may mediate particle-induced carcinogenesis.²⁴
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21 295 The finding that particles have both estrogenic and DNA-damaging effects
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23 296 suggests a potential mechanism for an effect on breast cancer: if inhaled PM
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25 297 entered the circulatory system from the lungs, estrogenic particles might find
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27 298 their way to breast tissue. However to our knowledge no data are available
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29 299 to indicate whether PM can reach breast tissue and further research is
30

31 300 required in this area.²⁶ Most of the toxic effects of PM have been attributed
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33 301 either to direct damage to lung tissue or release of inflammatory mediators
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35 302 from airway cells into the circulatory system.²⁷ Notwithstanding these
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37 303 considerations, the biological mechanisms by which PM_{2.5} exposure increases
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39 304 to breast cancer mortality remain unknown.
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41 305 Our study has several strengths. We used a population-based cancer registry
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43 306 to identify virtually all the breast cancer cases in the study area over the
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45 307 study period, in turn linking them to mortality databases to obtain accurate
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47 308 and complete survival information. Another strength is our use of satellite
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49 309 derived PM_{2.5}. Traditional ground-based PM measurement methods are
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3 310 locally accurate, but are sparsely and irregularly distributed, adding
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5 311 considerable uncertainty to individual exposure assignments over a wide
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7 312 geographic area. The satellite data made it possible to estimate the exposure
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9 313 in each 10x10 km area containing each woman's home. We consider that this
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11 314 area is particularly apt for our purposes as it comprises the area where the
12
13 315 woman is likely to have carried out most of her daily activities. Of course
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15 316 some women may have spent a considerable fraction of their time outside
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17 317 this area, perhaps at work, and this is a study weakness. Importantly, none
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19 318 of the women had missing values for PM_{2.5} exposure.
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24 319 Another study strength is that we controlled for factors (e.g. stage, grade,
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26 320 and participation in screening) known or suspected to influence breast cancer
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28 321 mortality. However we did not control for lifestyle factors, including diet and
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30 322 alcohol consumption, or comorbidities, that may also influence breast cancer
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32 323 mortality.^{28,29,30}
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36 324 The Californian study – the only other published study on breast cancer
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38 325 mortality in relation to PM_{2.5} exposure – also found a strong association
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40 326 between breast cancer mortality and PM_{2.5} exposure. However PM_{2.5}
41
42 327 exposure for people living in California was much lower than in Varese
43
44 328 Province – which is among the highest in the world.⁶ The lowest exposure
45
46 329 category for California was PM_{2.5} <11.64 µg/m³: only three patients in our
47
48 330 dataset had such a low exposure. However, the California researchers
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50 331 reported an HR for the upper category of 1.76 that is similar to the HRs for
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52 332 our three upper categories (1.82, 1.73 and 1.72 respectively).
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3 333 A report of ongoing research in northern China on the link between PM₁₀ and
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5 334 breast cancer survival also indicated increased risk with increasing PM
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7 335 exposure, and also that survival was lower in women with estrogen receptor
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9 336 positive disease.³¹ The authors suggested that PM may act as a
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11 337 xenoestrogen, in line with the data from the study on effects of PM on breast
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13 338 cancer cell lines.²⁴

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17 339 It is important to emphasize that the first quartile of exposure in our study is
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19 340 not a risk zero category, but only the reference category for the other
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21 341 quartiles.

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24 342 In conclusion, although our study has limitations, its findings are consistent
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26 343 with those of the California study. 5and the report of a study in China
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28 344 indicating a strong association between breast cancer death and atmospheric
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30 345 PM exposure. Clearly more research is justified to further explore this
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32 346 association, particularly in view of the increasing worldwide incidence of
33
34 347 breast cancer and worldwide increases in PM concentrations.⁶⁻⁷ Our data add
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36 348 to the wealth of evidence that atmospheric PM has multiple adverse effects
37
38 349 on human health, and speak to the urgent need to lower atmospheric PM
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40 350 levels worldwide.

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48
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51 354 reading the manuscript.

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56 57 356 **Competing interests**

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3 357 All authors declare they have no competing interests.
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8 359 **Data sharing statement**
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10 360 No additional data are available
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12 361

13
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18
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23
24 366 **Authors' contributions**

25
26 367 P. Contiero contributed to study conception, designed the study, performed
27
28 368 the statistical analysis and wrote the first draft of the paper.

29
30
31 369 G. Tagliabue contributed to study conception, coordinated the clinical section
32
33 370 of the study and contributed to writing the paper.

34
35
36 371 R. Tessandori and G. Barigelletti contributed to practical aspects of study
37
38 372 design.

39
40
41 373 A. Borgini, M. Bertoldi and A Tittarelli were responsible for the exposure
42
43 374 assessment.

44
45
46 375 A. van Donkelaar and R. V. Martin were responsible for developing the model
47
48 376 deriving PM data from satellite data.

49
50 377 A Tittarelli, S Fabiano, A Scaburri and G Barigelletti developed the
51
52 378 information system to archive and manage the data and performed the
53
54 379 descriptive statistics.
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3 380 A Maghini and T Codazzi retrieved the clinical information and performed the
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5 381 record linkage between the sources.
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7
8 382 I Favia and A Cau transferred the clinical data into the study database.
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10 383 All authors read and approved the final manuscript.
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48
49
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REFERENCES

1. IARC Scientific Publication No. 161: AIR POLLUTION AND CANCER.
<http://www.iarc.fr/en/publications/books/sp161/AirPollutionandCancer161.pdf>
2. Barman SC, Kumar N, Singh R, et al. Assessment of urban air pollution and its probable health impact. *J Environ Biol.* 2010 Nov;31(6):913-20
3. Fantke P, Jolliet O, Evans JS, et al. Health effects of fine particulate matter in life cycle impact assessment: findings from the Basel Guidance Workshop. *The Int J Life Cycle Assess.* 2015 Feb; 20(2): 276–288
4. IARC MONOGRAPHS: Volume 109: OUTDOOR AIR POLLUTION.
<http://monographs.iarc.fr/ENG/Monographs/vol109/mono109.pdf>
5. Raaschou-Nielsen O1, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol.* 2013;14(9):813-22.
6. Van Donkelaar A, Martin RV, Brauer M, et al. Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environ Health Perspect.* 2015 Feb;123(2):135-43.
7. IARC: GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.
http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

- 1
2
3 409 8. Hu H, Dailey AB, Kan H, et al. The effect of atmospheric particulate
4
5 410 matter on survival of breast cancer among US females. Breast
6
7 411 Cancer Res Treat. 2013 May;139(1):217-26.
8
9
10 412 9. Hystad P, Villeneuve PJ, Goldberg MS, et al. Canadian Cancer
11
12 413 Registries Epidemiology Research Group. Exposure to traffic-related
13
14 414 air pollution and the risk of developing breast cancer among women
15
16 415 in eight Canadian provinces: a case-control study. Environ Int. 2015
17
18 416 Jan;74:240-8.
19
20
21 417 10. Iwai K, Mizuno S, Miyasaka Y, et al. Correlation between
22
23 418 suspended particles in the environmental air and causes of disease
24
25 419 among inhabitants: cross-sectional studies using the vital statistics
26
27 420 and air pollution data in Japan. Environ Res. 2005 Sep;99(1):106-
28
29 421 17.
30
31
32 422 11. Nie J, Beyea J, Bonner MR, et al. Exposure to traffic emissions
33
34 423 throughout life and risk of breast cancer: the Western New York
35
36 424 Exposures and Breast Cancer (WEB) study. Cancer Causes Control.
37
38 425 2007 Nov;18(9):947-55.
39
40
41 426 12. <http://www.inemar.eu/xwiki/bin/view/Inemar/>
42
43
44 427 13. Tagliabue G, Maghini A, Fabiano S, et al Consistency and
45
46 428 accuracy of diagnostic cancer codes generated by automated
47
48 429 registration: comparison with manual registration. Popul Health Metr
49
50 430 4:10
51
52
53 431 14. Contiero P, Tittarelli A, Maghini A, et al. Comparison with manual
54
55 432 registration reveals satisfactory completeness and efficiency of a
56
57
58
59
60

- 1
2
3 433 computerized cancer registration system. J Biomed Inform. 2008
4
5 434 Feb;41(1):24-32
6
7
8 435 15. International Classification of Diseases for Oncology, Third
9
10 436 Edition, First Revision. Geneva: World Health Organization, 2013
11
12 437 16. Sobin LH, Wittekind C. International Union Against Cancer (UICC)
13
14 438 TNM Classification Of Malignant Tumors. 6th ed. New York, NY:
15
16 439 Wiley-Liss; 2002
17
18
19 440 17. Contiero P, Tittarelli A, Tagliabue G, et al. The EpiLink record
20
21 441 linkage software: presentation and results of linkage test on cancer
22
23 442 registry files. Methods Inf Med. 2005;44(1):66-71.
24
25
26 443 18. ESRI: ArcGIS. <http://www.esri.com/software/arcgis>
27
28
29 444 19. Therneau TM, Grambsch PM. Testing proportional hazards. In:
30
31 445 Modeling survival data: extending the Cox model. 2000. Springer,
32
33 446 New York
34
35
36 447 20. Bellera CA, MacGrogan G, Debled M, et al. Variables with time-
37
38 448 varying effects and the Cox model: some statistical concepts
39
40 449 illustrated with a prognostic factor study in breast cancer. BMC Med
41
42
43 450 Res Methodol. 2010; 10-20
44
45
46 451 21. Harrell F. Regression Modeling Strategies. 2001. Springer
47
48 452 22. Berry DA. Failure of researchers, reviewers, editors, and the
49
50 453 media to understand flaws in cancer screening studies: application
51
52 454 to an article in Cancer. Cancer. 2014 Sep 15;120(18):2784-91
53
54
55 455 23. R Development Core Team (2007), R: a language and
56
57 456 environment for statistical computing. <http://www.r-project.org>
58
59
60

- 1
2
3 457 24. Chen ST, Lin CC, Liu YS, et al. Airborne particulate collected from
4
5 458 central Taiwan induces DNA strand breaks, Poly(ADP-ribose)
6
7 459 polymerase-1 activation, and estrogen-disrupting activity in human
8
9
10 460 breast carcinoma cell lines. *Environ Sci Health A Tox Hazard Subst*
11
12 461 *Environ Eng.* 2013;48(2):173-81.
- 14 462 25. Mordukhovich I, Beyea J, Herring AH, Hatch M, et al. Vehicular
15
16
17 463 Traffic-Related Polycyclic Aromatic Hydrocarbon Exposure and
18
19 464 Breast Cancer Incidence: The Long Island Breast Cancer Study
20
21
22 465 Project (LIBCSP). *Environ Health Perspect.* 2015 May 22.
- 24 466 26. Sutton P, Kavanaugh-Lynch MH, et al. California Breast Cancer
25
26 467 Prevention Initiatives: Setting a research agenda for prevention.
27
28 468 *Reprod Toxicol.* 2015 Jul;54:11-8.
- 31 469 27. Rundell KW. Effect of air pollution on athlete health and
32
33 470 performance. *Br J Sports Med.* 2012 May;46(6):407-12
- 36 471 28. Romieu I, Scocianti C, Chajès V, et al. Alcohol intake and breast
37
38 472 cancer in the European prospective investigation into cancer and
39
40 473 nutrition. *Int J Cancer.* 2015 Oct 15;137(8):1921-30
- 43 474 29. McKenzie F, Ferrari P, Freisling H, et al. Healthy lifestyle and risk
44
45 475 of breast cancer among postmenopausal women in the European
46
47 476 Prospective Investigation into Cancer and Nutrition cohort study. *Int*
48
49 477 *J Cancer.* 2015 Jun 1;136(11):2640-8
- 52 478 30. Søgaard M, Thomsen RW, Bossen KS, et al. The impact of
53
54 479 comorbidity on cancer survival: a review. *Clin Epidemiol.* 2013 Nov
55
56 480 1;5(1):3-29

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481 31. Huo Q, Cai C, Yang Q. Atmospheric particulate matter and breast
482 cancer survival: estrogen receptor triggered? Tumour Biol. 2015
483 May;36(5):3191-3
484

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3 485 **Fig 1. Map of the study area and satellite – derived PM_{2.5}**
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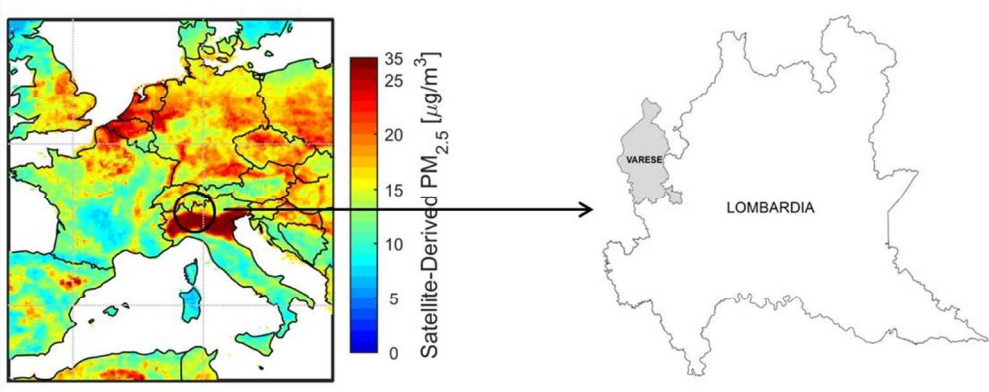
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8 487 **Fig 2. Survival of breast cancer cases, diagnosed 2003-2009 and**
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10 488 **resident in Varese Province, northern Italy according to exposure to**
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12 489 **PM_{2.5} (quartiles)**
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17 491 **Fig 3. Cumulative hazard of breast cancer death in cases diagnosed**
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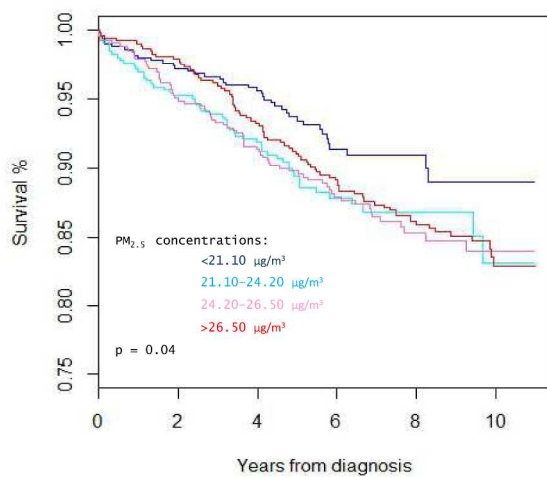
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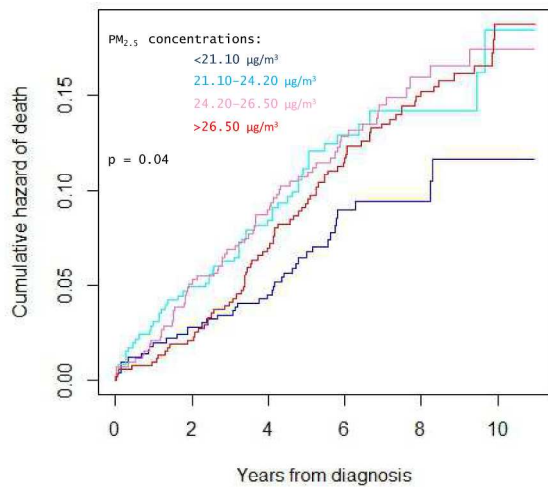


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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1: Title: "A population-based cohort study"
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3: "Our study indicates that the risk of BC mortality increases with PM _{2.5} exposure."
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5: "PM2.5 [has] multiple adverse effects on human health, and is classified by WHO and IARC as carcinogenic to humans." "global PM2.5 concentrations increased by 2.1%/year from 1998 through 2012." "breast cancer incidence is also increasing worldwide".
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5: "To investigate the association of atmospheric PM with breast cancer mortality ." Hypothesis:"the global increase in breast cancer incidence might be linked to increasing in PM concentrations and high PM might also worsen breast cancer survival ".
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 6, Methods: "a retrospective study [of breast cancer mortality] on a cohort of women diagnosed with primary breast cancer".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 6-7, Methods: "...-cases archived by Lombardy Cancer Registry.[...] A total of 2021 primary breast cancers cases diagnosed in predetermined study period (2003-2009)". Page 2: "Of 2021 BC cases, 325 died during follow-up

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			to 31/12/2013.”
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6 Methods – Breast cancer cases: “conforming to selection criteria (50-69 years at diagnosis, no other cancer diagnosed previously)”[were selected] Disease stage was as specified by TNM. “Mortality data are routinely collected by the cancer registry by linkage to the Varese Province mortality database. Other sources of mortality information are used routinely to ensure completeness.”
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A, it is not a matched study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6 : “Study endpoint was breast cancer mortality.” Pages 7-8 Statistical methods: [potential confounders] “were diagnosis, stage, grade, age at diagnosis and participation in a breast cancer screening program. [and] year of diagnosis.”
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 6-8 Methods - Breast cancer cases from Varese cancer registry. “ Mortality data [...] collected by the cancer registry by linkage to the Varese Province mortality database. Other sources of mortality information used to ensure completeness”, Estimation of PM _{2.5} , Statistical methods: “To estimate PM _{2.5} exposure we used satellite-based data that infers near-surface PM _{2.5} concentrations from the satellite-observed total column aerosol loading using a chemical transport model.”
Bias	9	Describe any efforts to address potential sources of bias	Page 8 Methods – Statistical methods: “Cancers diagnosed in the screening context are affected by length-time and lead-time bias and may also be less aggressive than those diagnosed outside of screening”

Study size	10	Explain how the study size was arrived at	Page 6 Methods – Breast cancer cases: The cancer database was searched “using site code C50 and malignant epithelial morphology codes M8010-M8575 of the ICDO-3.” “A total of 2021 primary breast cancers cases diagnosed in the predetermined study period (2003-2009) and conforming to selection criteria (50-69 years at diagnosis, no other cancer diagnosed previously)” were used.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-8 Methods – Statistical methods: “Factors analyzed were diagnosis period (2003-2006; 2007-2009), stage (I-IV) , grade (I-III, unknown), age at diagnosis (two categories, 50-59 years and 60-69 years), and participation in a breast cancer screening program (Yes, No)”
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 8 Methods – Statistical methods: “We ran univariate and multivariate Cox proportional hazard models to estimate HRs with 95% CI of breast cancer death according to quartiles of PM2.5 exposure. The multivariate model was stratified by age, grade, stage, diagnosis period and participation in screening.”
		(b) Describe any methods used to examine subgroups and interactions	We did not analyse subgroup and we did not study interactions.
		(c) Explain how missing data were addressed	Page 8 - Missing data were handled using a separate “not specified” category for unavailable disease stage and a separate “not specified” category for unavailable tumor grade when performing data analysis.
		(d) If applicable, explain how loss to follow-up was addressed	Page 8 – loss of follow-up was addressed by censoring at date of loss of follow-up
		(e) Describe any sensitivity analyses	Not performed
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	N/A

		follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 10-11 Results – Table1
		(b) Indicate number of participants with missing data for each variable of interest	Pages 10-11. Table 1 and above
		(c) Summarise follow-up time (eg, average and total amount)	Page 9, Results: Followed up to 31 December 2013
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9 – “A total of 325 (16.1%) women died in the period up to 31 December 2013, 246 (12.2%) of these of breast cancer.” Pages 10-11 Results – Table1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 11 Results – Table2 Page 11: “By the univariate model, breast cancer patients living in an area with PM _{2.5} levels above the lowest quartile had significantly greater risk of breast cancer death than those living in areas with lowest quartile of PM _{2.5} (<21.10 µg/m ³). The increased risk of death ranged from 72% (fourth quartile) to 82% (second quartile). In the multivariate model, which controlled for confounding factors, risks of breast cancer death were numerically greater and still significant for all exposure quartiles above the lowest.”
		(b) Report category boundaries when continuous variables were categorized	Pages 10-11 Results – Table1; Table2 PM _{2.5} was categorised into: I (<21.10); II (21.10-24.20), III(24.20-26.50) , IV (≥26.50) Page 11 Results – Table2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12 Discussion: “We have shown that high

			exposure to PM2.5 is associated with increased mortality for breast cancer after correcting for a range of factors considered to influence breast cancer survival.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14 Discussion: “...some women may have spent a considerable fraction of their time outside this area, perhaps at work, and this is a study weakness”. “...we did not control for lifestyle factors, including diet and alcohol consumption, that may also influence breast cancer mortality.”
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 13-14 Discussion Page 15 Conclusions: “Our data add to the wealth of evidence that atmospheric PM has multiple adverse effects on human health”.
Generalisability	21	Discuss the generalisability (external validity) of the study results	This is a preliminary study.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16: “This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.”

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.