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Chronic exposure to traffic-related air pollution and cancer incidence among 10,000 patients undergoing percutaneous coronary interventions: A historical prospective study

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Abstract

Background: Exposure to traffic-related air pollution (TRAP) is considered to have a carcinogenic effect. The authors previously reported a nonsignificant association between TRAP and cancer risk in a relatively small cohort of myocardial infarction survivors. This study assessed whether TRAP exposure is associated with subsequent cancer in a large cohort of coronary patients.

Methods & results: Consecutive patients undergoing percutaneous coronary interventions in a major medical centre in central Israel from 2004 to 2014 were followed for cancer through 2015. Residential levels of nitrogen oxides (NO_x) – a proxy for TRAP – were estimated based on a high-resolution national land use regression model. Cox proportional hazards models were constructed to study relationships with cancer. Among 12,784 candidate patients, 9816 had available exposure data and no history of cancer (mean age, 68 years; 77% men). During a median (25th–75th percentiles) follow-up of 7.0 (3.9–9.3) years, 773 incident cases of cancer (8%) were diagnosed. In a multivariable-adjusted model, a 10-ppb increase in mean NO_x exposure was associated with hazard ratios (HRs) of 1.07 (95% confidence interval [CI] 1.00–1.15) for all-site cancer and 1.16 (95% CI 1.05–1.28) for cancers previously linked to TRAP (lung, breast, prostate, kidney and bladder). A stronger association was observed for breast cancer (HR = 1.43; 95% CI 1.12–1.83). Associations were slightly strengthened after limiting the cohort to patients with more precise exposure assessment.

Conclusion: Coronary patients exposed to TRAP are at increased risk of several types of cancer, particularly lung, prostate and breast. As these cancers are amenable to prevention strategies, identifying highly exposed patients may provide an opportunity to improve clinical care.

Keywords

Cancer incidence, percutaneous coronary interventions, traffic-related air pollution, exposure assessment

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Introduction

Evidence suggests higher incidence rates of cancer among individuals with cardiovascular disease compared to those without.[1–4] Both short- and long-term increased cancer risk following a cardiovascular disease manifestation were reported,[3] implying that factors other than surveillance bias and case finding may play a role in the observed association, including environmental pollutants.[5]

One major environmental pollutant that is recognised by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen is traffic-related air pollution (TRAP).[6] Epidemiological evidence suggests that chronic exposure to TRAP is associated with increased risk of several types of cancer, principally cancer of the lung,[7] breast[8,9] and prostate,[10,11] with a few reports on urinary bladder[12] and kidney cancers.[13] Nevertheless, uncertainty still remains regarding the strength of these associations, particularly among individuals with high susceptibility to environmental exposures. According to 2016 European guidelines on cardiovascular disease prevention in clinical practice, subjects with a high cardiovascular risk are considered more prone to the detrimental effects of air pollution.[14] Along with this, studies among cardiovascular patients focused on TRAP-associated mortality,[15,16] recurrent cardiovascular events[15,17] as well as the frailty syndrome.[18,19] However, cancer-related outcomes were not previously investigated in this population. This gap in knowledge led us to investigate the relationship between TRAP and incident cancer among patients with coronary artery disease. In a previous investigation, we observed a positive nonsignificant association between chronic exposure to TRAP and risk of cancer in a relatively small cohort of first myocardial infarction survivors followed-up for more than two decades.[20] However, power limitations prevented us from analysing specific cancers separately. Furthermore, the small number of women in that cohort precluded us from assessing breast cancer. In the present study, we assessed the association between TRAP and cancer in a much larger cohort of consecutive patients undergoing percutaneous coronary interventions (PCIs) in a large medical centre in central Israel, utilising its size and comprehensive clinical information to further investigate the association with various cancer types.

Methods

Study population

This study is designed as a historical prospective study comprising all consecutive patients ($n = 12{,}784$) undergoing PCI at the cardiology department of Rabin Medical Center (Beilinson and Hasharon Hospitals) in central Israel from April 2004 to October 2014. Patients with a prior cancer diagnosis at baseline were excluded from the study. As previously described,[21] data were retrieved from multiple data sources: clinical and laboratory data were extracted from the patients' electronic medical records; demographic data, including information on residential addresses, and mortality data were obtained from the Israeli Ministry of the Interior and the Clalit Health Organization data warehouse. The accuracy of mortality data was verified with the Israel Central Bureau of Statistics and the Ministry of Health. Neighbourhood socioeconomic status (nSES) was estimated through a 20-point scale index developed by the Israel Central Bureau of Statistics, based on the 2008 National Census, with a score of 20 representing the highest nSES.[22] All aspects of the study were approved by the appropriate institutional ethics committees.

Cancer incidence

Members of the cohort were linked to the Israeli National Cancer Registry (INCR) via their national identification numbers. The INCR has been in operation since 1961; reporting of cancer cases by medical facilities and pathology laboratories to the INCR has been mandatory since 1982, and therefore covers the entire Israeli population (approximately 8.5 million in 2016),[23] with 94% estimated completeness of ascertainment for solid tumors.[24] Data supplied by the INCR included date of diagnosis and diagnostic code assigned according to the International Classification of Diseases for Oncology (ICD-O), 3rd edition, regarding primary cancers only (i.e. not metastases). Using the INCR linkage, we classified incident cases of cancers of all sites (ICD-O codes: C00.0–C80.9). We also identified other cancer sites, particularly those suggested to be related to chronic exposure to TRAP, including cancers of the bronchus and the lung (C34.0–C34.9), breast (C50), prostate gland (C61.9), kidney (C64.9) and bladder (C67.9). Patients not diagnosed with cancer were right-censored at the date of death or last date of cancer update (July 2015).

Exposure assessment

Serving as an indicator of individual chronic exposure to TRAP, residential NO_x levels were estimated by a high-resolution national land use regression (LUR) model, using a 20-year-long record of air quality monitoring data in Israel.[25] In brief, ambient air pollution measurements in Israel are routinely performed by the National Air Quality Monitoring Center at the Israel Ministry of Environmental Protection,

several municipal associations for environmental protection and the Israel Electric Corporation, together including over 100 monitoring stations. Only sites with more than 75% data availability for a specific year were included in the analysis, comprising 765 annual averages from 104 sites. Geo-location, including latitude, longitude, elevation above sea level and air sample inlet elevation above street level, was collected for each monitoring site. Spatial variables were generated through development and reconstruction of geographic information system (GIS) data on a national scale, based on historical 1:50,000 topographic maps for each decade and satellite imagery.In addition, a database of annual changes in the traffic volume of Israel's highways was constructed based on samples of vehicle counts and the fleet composition of Israel's towns and cities from records of the Israel Central Bureau of Statistics. Altogether, 22 predictors were calculated (in 10 groups), 11 of them were extracted at 28 different radii each (buffers of 50 to 3000 m around monitoring station), including road networks (distance to highways, main and local roads as well as total length in the buffer zone), population density, land use classification, vegetation cover, traffic volume (all calculated within the buffer area), vehicle counts and type of air quality monitoring site (i.e. 'near-road' or 'general'), with the year of measurement as one of the predictors. These predictors were selected based on a priori knowledge about their effects on TRAP levels. A supervised forward stepwise procedure was used to select the model that would best predict NO_x levels over the entire study domain.[26] Due to the national coverage of the domain and in order to resolve intra-urban variability, a nested grid approach was adopted, calculating all predictors at a coarse spatial resolution of 200 m over the entire domain and a finer resolution of 50 m over the residential areas only. After calculating the model's prediction for each grid, the two grids were joined into a final grid of 50 m. A leave-one-out cross-validation procedure generated an adjusted R^2 of 0.74. For each study participant, annual estimates of NO_x concentrations were produced for each year between 2004 and 2012, representing TRAP exposure during the follow-up period, by assigning the exposure surfaces derived from the LUR model to the residential location. Since spatial distributions of NO_x did not change appreciably over the years, with very high correlations (Pearson's $r \geq 0.98$) between the annual estimates, we considered the mean NO_x exposure between 2004 and 2012.

Statistical analyses

Differences in baseline characteristics across NO_x exposure tertiles were examined using the χ^2 test for trend (categorical variables) or general linear models (continuous variables). Cox proportional hazards models[27] were constructed to estimate the associations between TRAP and cancer, with age serving as the time scale.[28] We examined associations of NO_x exposure with all-site cancer incidence as well as with site-specific cancers previously linked to vehicular traffic exposure, specifically cancers of the lung,[7] breast,[9] prostate,[11] kidney[13] and bladder.[12] These cancers were analysed together as a pooled outcome,[20] as well as individually. We also attempted to assess the specificity of the association between TRAP and the above cancers by examining other cancer categories that were not previously described in the air pollution context, including cancer of the digestive organs, haematopoietic and reticuloendothelial systems and melanoma. The heterogeneity in the association with different cancer groups was formally tested.[29] For all cancer outcomes, a crude analysis was initially conducted (with age serving as the time scale and therefore not being adjusted for). Subsequently, multivariable adjustment was performed, accounting for sociodemographic and clinical characteristics at the index PCI. Predictors were selected based on a priori knowledge if they were: (a) well-established cancer risk factors (including sex, smoking status and Arab/Jewish ethnicity[30]); (b) variables previously shown to be associated both with TRAP exposure as well as cancer incidence (including nSES,[31,32] diabetes mellitus,[33,34] chronic heart failure[1,35] and haemoglobin levels[36,37]); and (c) other clinical variables previously shown to have a prognostic importance in our cohort (including hypertension and renal failure).[21] The proportional hazards assumption was tested through the Schoenfeld residuals, and was met in all models. Missing values did not exceed 1% in any of the variables considered in the analysis except for nSES (14%). Two approaches were used to deal with nSES missing values. First, a complete case analysis was performed ($n = 8405$). Second, a separate analysis was conducted, with nSES defined as a categorical variable (according to tertiles), with missing values coded as an additional category. Because both approaches yielded similar results, only the complete case analysis is presented.

In order to assess the robustness of the TRAP–cancer association, a series of sensitivity analyses was performed. First, we repeated the main analysis including only subjects whose residential location was identified on the most accurate level (i.e. geocoded based on their household number, $n = 8849$). Second, based on the association between NO_x and cancer observed in the main analysis, a nonlinear relationship was tested. Applying spline methodology, a penalised spline term was used to assess the relationship between NO_x and cancer risk in a Cox regression model. Due to the

asymmetric distribution of NO_x estimates in our cohort (right skewed), we performed an additional analysis using the natural logarithm of NO_x as the exposure variable, thus comparing cancer risk associated with a 1-SD increment of NO_x in the logarithmic scale and in the original scale. Analyses were performed using R statistical software, version 3.4.1 (R Development Core Team) and IBM SPSS Statistics, version 23 (IBM SPSS, Inc.).

Results

Between 2004 and 2014, 12,784 patients underwent PCI at the Rabin Medical Center. Of those, 1395 (11%) who had a diagnosis of cancer before study entry and 55 who were non-Israeli residents were excluded from the study. Assessment of NO_x exposure was available for 9816 (87%) study participants. Among the 1518 patients without exposure data, 649 had incomplete information on residential location and 869 did not reside within the model computational domain (Figure 1).[25]

Table 1 shows the pertinent clinical characteristics of the cohort. Mean (SD) age was 68 (12) years, 77% were men and 35% reported smoking. Most participants (81%) had comorbid conditions, including hypertension, diabetes mellitus, renal failure, stroke, dementia or chronic heart failure. Mean (range) NO_x exposure during the follow-up period as predicted by the LUR model was 19.5 (2.4–79.7) ppb (Figure 2). NO_x exposure was only minimally associated with baseline clinical characteristics (Table 1).

The median follow-up period (among censored subjects) was 7.0 years (25th–75th percentiles, 3.9–9.3 years). During this period, 773 new cases of cancer (8%) were diagnosed, of which more than half were attributed to cancers previously linked to TRAP exposure, specifically cancer of the lung (13%), breast (6%), prostate (16%), kidney (4%) and bladder (10%) (Figure 3).

Cox proportional hazards models yielded a hazard ratio (HR) of 1.07 (95% confidence interval [CI] 1.00–1.15) for all-site cancer for a 10-ppb increase in NO_x exposure, after adjustment for sociodemographic and clinical factors; no effect modifications were observed for age, nSES and pre-existing comorbidity (all $p \geq 0.10$). Examining the association between NO_x exposure and specific cancers previously linked to TRAP as a combined end-point yielded a HR of 1.16 (95% CI 1.05–1.28) for cancer of the lung, breast, prostate, kidney or bladder. Analysed individually, a stronger association was shown for breast cancer (adjusted HR = 1.43; 95% CI 1.12–1.83). A sensitivity analysis excluding patients with residential locations identified on a coarse resolution resulted in slightly stronger associations for most cancer outcomes.

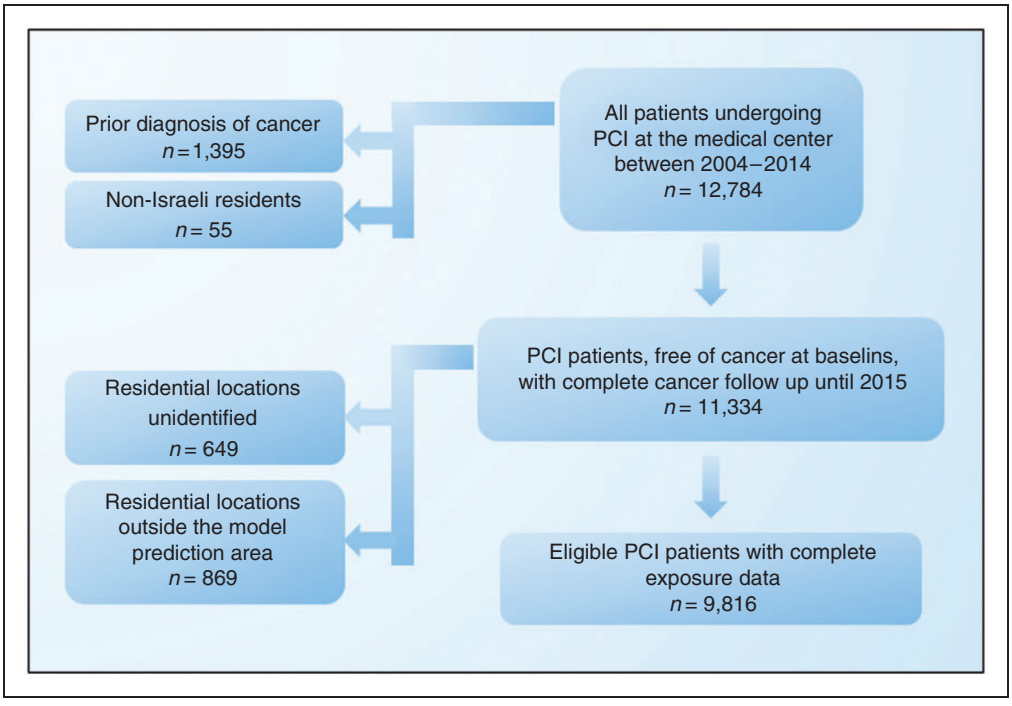

Figure 1. Study flow chart.
PCI: percutaneous coronary intervention.

Table 1. Pertinent baseline characteristics across nitrogen oxide exposure tertiles.

Characteristic		NO_x tertile			
	Overall ($n = 9816$)	Lower ($n = 3311$)	Medium ($n = 3256$)	Upper ($n = 3249$)	*p*-value for linear trend
NO_x, mean (range), ppb	19.5 (2.3–79.7)	12.8 (2.3–15.1)	16.7 (15.1–18.4)	29.2 (18.4–79.7)	–
Age, mean (SD), years	68.2 (12.1)	67.0 (12.0)	68.9 (12.1)	68.6 (12.0)	<0.001
Female, *n* (%)	2307 (23.5)	742 (22.4)	761 (23.4)	804 (24.7)	0.02
Smoking, *n* (%)	3466 (35.3)	1195 (36.1)	1130 (34.7)	1141 (35.1)	0.58
Neighbourhood SES score, mean (SD)[a]	11.2 (3.4)	11.0 (3.7)	11.4 (3.0)	11.2 (3.4)	0.05
Arab, *n* (%)	810 (8.3)	564 (17.0)	102 (3.1)	144 (4.4)	<0.001
Hypertension, *n* (%)	7140 (72.7)	2372 (71.6)	2385 (73.2)	2383 (73.3)	0.08
Diabetes, *n* (%)	4318 (44.0)	1516 (45.8)	1426 (43.8)	1376 (42.4)	0.01
Renal failure, *n* (%)	1816 (18.5)	599 (18.1)	627 (19.3)	590 (18.2)	0.61
Stroke, *n* (%)	567 (5.8)	182 (5.5)	217 (6.7)	168 (5.2)	0.70
Dementia, *n* (%)	141 (1.4)	48 (1.4)	49 (1.5)	44 (1.4)	0.67
Chronic heart failure, *n* (%)	912 (9.3)	304 (9.2)	320 (9.8)	288 (8.9)	0.90
Stable coronary artery disease, *n* (%)	3923 (40.0)	1432 (43.2)	1163 (35.7)	1328 (40.9)	0.03
STEMI, *n* (%)	688 (7.0)	220 (6.6)	256 (7.9)	212 (6.5)	0.86
Number of vessels disease					0.10
Single-vessel disease, *n* (%)	2358 (24.0)	860 (26.0)	757 (23.2)	741 (22.8)	
Two-vessel disease, *n* (%)	3168 (32.3)	994 (30.0)	1098 (33.7)	1076 (33.1)	
Three-vessel disease, *n* (%)	4290 (43.7)	1457 (44.0)	1401 (43.0)	1432 (44.1)	
Haemoglobin levels, mean (SD), g/dL	13.4 (1.7)	13.4 (1.7)	13.4 (1.7)	13.4 (1.7)	0.37

[a]Missing values for neighbourhood SES score: 1411 (14.3%).
SES: socioeconomic status; STEMI: ST-elevation myocardial infarction.

For example, the association between TRAP and prostate cancer in the full cohort (adjusted HR = 1.16; 95% CI 0.99–1.37) was strengthened among subjects with more precise exposure assessment (adjusted HR = 1.20; 95% CI 1.02–1.42) (Table 2).

Applying spline methodology, a nonlinear relationship between NO_x (on a continuous scale) and combined cancer of the lung, breast, prostate, kidney or bladder was seen; as NO_x levels increased, the risk of these cancers increased exponentially. No evidence for a nonlinear relationship was shown for all-site cancer risk (Figure 4).

Assessing the association between TRAP and other cancer sites (not previously linked to air pollution exposure) showed weaker or no association, thus supporting a specific association with lung, prostate and breast cancers (p for heterogeneity = 0.085) (Figure 5). Additionally, modelling NO_x on a logarithmic scale yielded similar associations with all-site and site-specific cancer risk.

Discussion

In this prospective cohort study of ~10,000 patients undergoing PCI at a large medical centre in Israel and subsequently followed up for cancer over a median duration of 7 years, chronic exposure to vehicular traffic, as indicated by residential NO_x levels, was positively associated with all-site cancer incidence. Furthermore, a stronger association was observed for specific cancers previously linked to TRAP, particularly cancer of the lung, prostate and breast, with weaker or no association for other cancer sites. The associations were not sensitive to adjustment for various individual measures and several sensitivity analyses that were performed. In addition, when restricting the cohort to patients with more precise exposure assessment, these associations were slightly strengthened. Notably, modelling NO_x on a continuous scale yielded a nonlinear relationship between NO_x and cancer of the lung, breast, prostate, kidney or bladder combined.

In our previous investigation, a positive yet non-significant association was observed between chronic exposure to TRAP and risk of cancer in a relatively small cohort of first myocardial infarction survivors.[20] A positive association was seen for all-site cancer (adjusted HR = 1.06; 95% CI 0.96–1.18) that was stronger for cancer of the lung, prostate, kidney or bladder (adjusted HR = 1.16; 95% CI 1.00–1.33). Power limitations prevented us from analysing these

specific cancers separately, and the small number of women in the cohort precluded us from assessing breast cancer. Addressing these issues in the current study, we were able to show statistically significant associations for all-site and TRAP-related cancers and to reveal a substantial association with breast cancer.

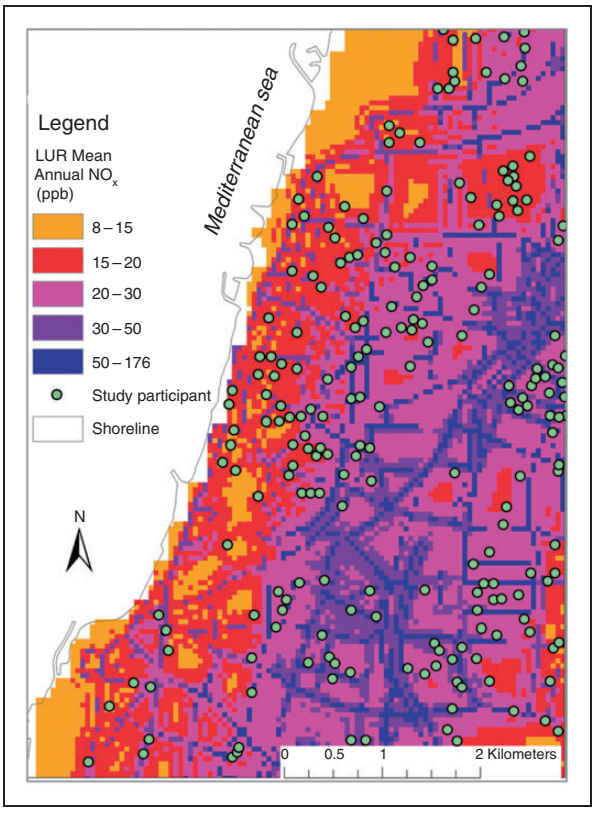

Figure 2. Exposure map representing mean annual nitrogen oxide (NO_x) levels between 2004 and 2012 estimated by a high-resolution national land use regression (LUR) model. The map shows estimated NO_x levels in a selected area in central Israel, demonstrating the fine-scale exposure estimation for each study participant.

Studies investigating the health effects of chronic exposure to TRAP among patients with established coronary disease generally focused on TRAP-associated mortality,[38,39] recurrent cardiovascular events[15,17] and also the frailty syndrome.[18,19] TRAP-associated cancer risk had not yet been explored in this patient group, although growing evidence shows an excess risk of cancer among patients with established cardiovascular disease, including heart failure,[1,2] myocardial infarction[3] and other disease manifestations.[4] Yet the mechanism behind the association remains largely unknown. A possible detection bias is one of the suggested explanations,[40] due to intensive follow-up accompanying the management of the disease, which may lead to earlier detection of occult cancer. Since most of the increased health demands of cardiovascular patients occur during the first year of diagnosis,[41] increased cancer diagnosis is expected in that time interval. However, the observed lag time of 1.5 years[2] and 3 years[3] between cardiovascular disease and cancer diagnoses reported previously and the findings of our study argue against detection bias as a major explanation in this setting. Shared risk factors are also suggested to play a role in the observed increased cancer risk among cardiovascular patients.[4] Nevertheless, adjustment for well-established risk factors, such as smoking, obesity and physical activity, did not influence the relationship between myocardial infarction and cancer,[3] suggesting that other factors may be responsible for the observed association, including environmental exposures.[5]

Environmental pollutants were previously shown to have a carcinogenic effect in the population in general and in highly susceptible subgroups in particular.[42,43] Diesel exhaust was classified as a Group 1 carcinogen

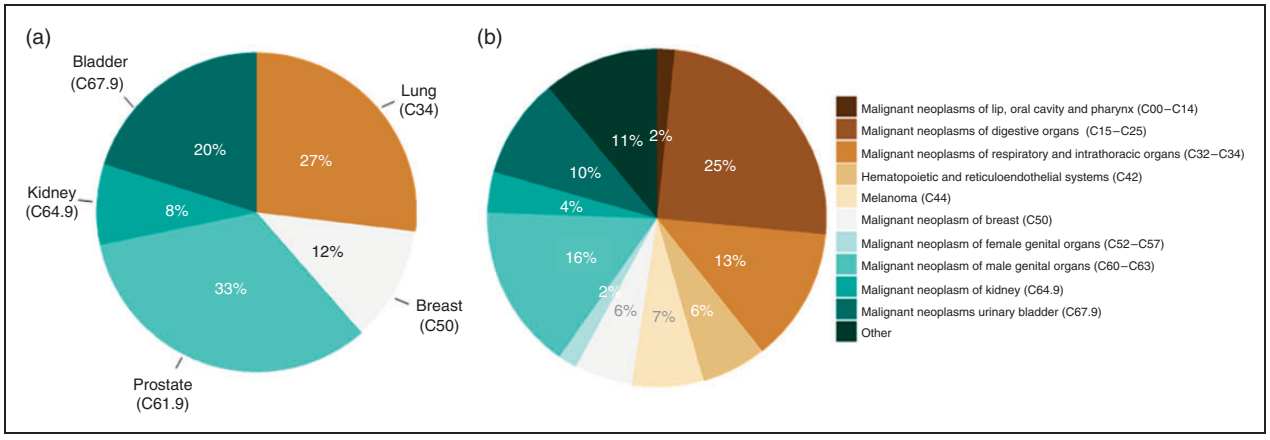

Figure 3. Distribution of cancer sites among incident cases of (a) specific cancers previously linked to traffic-related air pollution (n=368) and (b) all-site cancer (n=773) after percutaneous coronary interventions.

Table 2. Hazard ratios (95% confidence intervals) for incidence of all cancers and site-specific cancers associated with a 10-ppb increase in residential nitrogen oxide exposure.

	All cancers	Lung, breast, prostate, bladder or kidney	Lung	Breast	Prostate	Bladder
All patients free of cancer at baseline						
n	9816	9816	9816	2307	7509	9816
No. of cases	773	368	99	41	122	74
Unadjusted	1.08 (1.00–1.15)	1.17 (1.06–1.28)	1.15 (0.96–1.38)	1.48 (1.17–1.87)	1.17 (1.00–1.38)	1.04 (0.82–1.31)
Multiple adjustment[a]	1.07 (1.00–1.15)	1.16 (1.05–1.28)	1.13 (0.93–1.38)	1.43 (1.12–1.83)[b]	1.16 (0.99–1.37)	1.07 (0.83–1.37)
Including only patients with residential location identified on the finest resolution						
n	8849	8849	8849	2119	6730	8849
No. of cases	727	340	89	37	115	69
Unadjusted	1.09 (1.01–1.17)	1.19 (1.08–1.31)	1.17 (0.97–1.42)	1.52 (1.19–1.93)	1.20 (1.02–1.42)	1.03 (0.81–1.32)
Multiple adjustment[a]	1.09 (1.01–1.18)	1.20 (1.09–1.33)	1.18 (0.97–1.44)	1.44 (1.12–1.85)[b]	1.20 (1.02–1.42)	1.11 (0.86–1.42)

Age is used as the time scale. The small number of kidney cancer cases in the entire cohort did not allow for conducting a separate analysis.
[a]Adjusted for sex, smoking, neighbourhood socioeconomic status, ethnicity, hypertension, diabetes mellitus, chronic heart failure, renal failure and haemoglobin levels.
[b]Not adjusted for ethnic group due to small number of subjects in one category.

by the IRAC,[44] yet evidence regarding the magnitude of the association between TRAP and cancer is not consistent across the epidemiological literature. To our knowledge, only one study evaluated the association between ambient air pollution and all-site cancer mortality.[45] In this study, exposure to particulate matter was positively associated with increased risk of all-site cancer mortality (HR = 1.22; 95% CI 1.11–1.34), which is stronger than the association observed in our cohort (HR = 1.07; 95% CI 1.00–1.15). However, cancer mortality – rather than incidence – served as the primary outcome, so cancer risk was not assessed directly.

Epidemiological evidence regarding the relationship between TRAP and specific cancers is also conflicting. Lung cancer is the primary cancer outcome studied in this context, since the airways are the primary target organs of inhaled pollutants.[13] In two recently published meta-analyses, pooled estimates of the same magnitude were detected for the NO_x–lung cancer relationship, with a meta-HR of 1.03 (95% CI 1.01–1.05)[7] and a meta-odds ratio (OR) of 1.04 (95% CI 1.01–1.07).[46] All studies included in these meta-analyses were conducted in the general population. This may partially explain the slightly lower point estimates compared to those detected in our current investigation of coronary patients (HR = 1.13 in the full cohort and HR = 1.18 after limiting the cohort to subjects with more precise exposure assessment).

The relationship between exposure to diesel exhaust and the incidence of cancers other than lung was first examined in occupational settings,[47] and more recently in population-based epidemiological studies. Cancers of the prostate and breast are the most studied cancers in this context, with growing evidence for a positive association with TRAP exposure. In a recent case–control study conducted in Canada, concentrations of ultrafine particles were associated with an increased risk of prostate cancer (adjusted OR = 1.10; 95% CI 1.01–1.19).[11] In another Canadian case–control study, a positive association between chronic exposure to nitrogen dioxide (NO_2) and prostate cancer was also demonstrated (adjusted OR = 1.27; 95% CI 1.03–1.58).[10] These findings are consistent with our current findings, with a HR of 1.16 (95% CI 0.99–1.37) in the full cohort and a HR of 1.20 (95% CI 1.02–1.42) after limiting the cohort to subjects with more precise exposure assessment.

In our study, we observed a relatively strong association between TRAP and breast cancer (HR = 1.43; 95% CI 1.12–1.83). An association of the same magnitude was recently observed in a case–control study conducted in the USA using estimates of polycyclic aromatic hydrocarbons, which are environmental pollutants known to be mainly attributed to vehicular traffic.[9] The authors reported a positive association between breast cancer and long-term vehicular traffic estimates in the top 5% exposure compared with below the median (OR = 1.44; 95% CI 0.78–2.68). A positive association was also observed in another case–control study conducted in Canada, with an OR of 1.32 (95% CI 1.05–1.67) for premenopausal breast cancer associated with NO_2 exposure.[8] However, other epidemiological studies have shown weaker[48] or no associations[49,50] between TRAP and breast cancer risk.

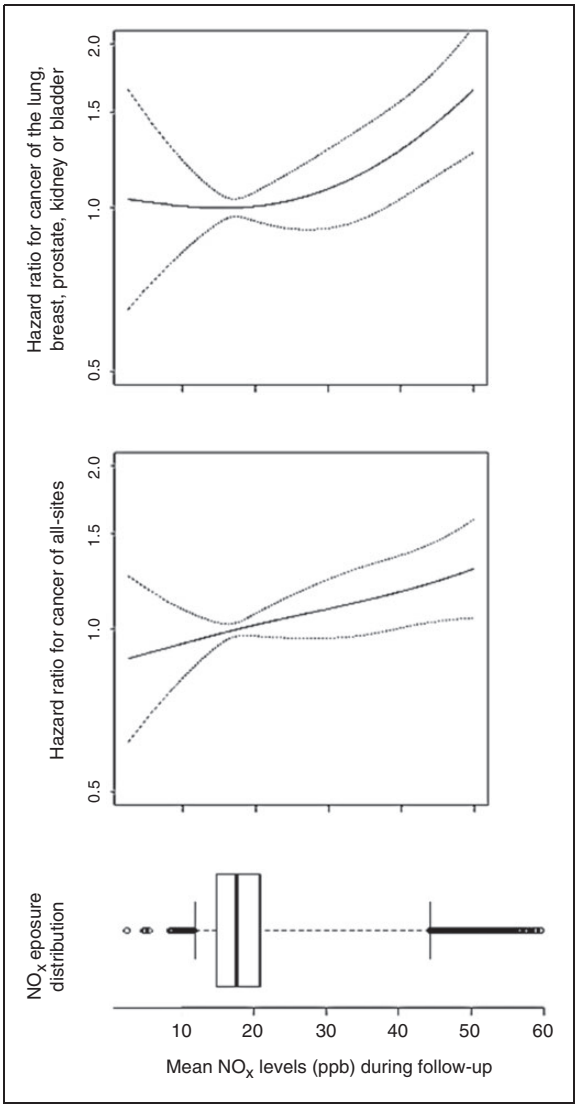

Figure 4. Splines-based hazard ratios for all-site and site-specific cancer associated with nitrogen oxide (NO_x) exposure. The solid lines represent the point estimates and the dashed lines represent the 95% confidence intervals. The boxplot describes the NO_x exposure distribution in the cohort.

Methodological considerations

The large-scale and well-defined cohort of coronary patients utilised in the current investigation is an important strength of our study. The size of the cohort enabled us to conduct site-specific analyses. Data on cancer diagnosis and mortality were ascertained through multiple national databases with high completeness of case ascertainment.[24] NO_x levels were estimated by a comprehensive LUR model with a national coverage and high spatial resolution, thus being suitable for assessing chronic TRAP exposure. However, in this context, the main concern of our study – similar to other studies on air pollution health effects – is exposure misclassification. Lack of information on other locations frequently visited besides home address, as well as data on participants' activity patterns, leaves uncertainty whether the modelled exposure correctly estimates the true inter-participant exposure variability.[51] In spite of this limitation, our exposure assessment has several strengths. First, NO_x estimates produced by the LUR model are obtained on a very high-resolution (50-m) grid (see map in Figure 2), enabling us to detect small-scale variability in pollutant levels that is mainly attributed to local sources in urban settings.[52] Second, seeking to reduce the uncertainty of exposure estimates, we performed a sensitivity analysis in which we restricted our cohort only to subjects with the most refined resolution exposure assessment. In this analysis, higher point estimates were observed for all cancer outcomes, implying a stronger association attributed to more precise exposure estimates. Third, NO_x levels served as an indicator for TRAP exposure in our study. Due to the high correlation between NO_x and other combustion by-products – many of which are known carcinogens – NO_x is considered the best indicator for TRAP exposure.[7,53] As annual NO_x levels were averaged only over the follow-up period, one may claim that the latency period was not taken into consideration, thus questioning the temporality of the association. However, the very high correlation between annual estimates allowed us to assume consistent distinction between subjects with high versus low levels of NO_x exposure throughout the years, including those preceding the index PCI. Nevertheless, not taking into account residential history, as well as occupational exposures, may constitute a bias in this context. In addition, as with many studies of this nature, although accounting for abundant individual clinical and sociodemographic characteristics, including nSES – an important confounder in the TRAP–health relationship[54] – there is still a concern regarding residual confounding.

Potential implications

Our findings are consistent with our previous report of an elevated cancer risk associated with chronic residential exposure to traffic-sourced air pollution. Associations of almost identical magnitude were observed in the two distinct cohorts of coronary patients for both all-site cancer and pooled specific cancers previously shown to be related to TRAP. In the current study, these associations were shown to be statistically significant and of greater precision, as evident by the much narrower CIs. The strength of the associations for specific cancers was further examined, revealing stronger associations for cancer of the lung,

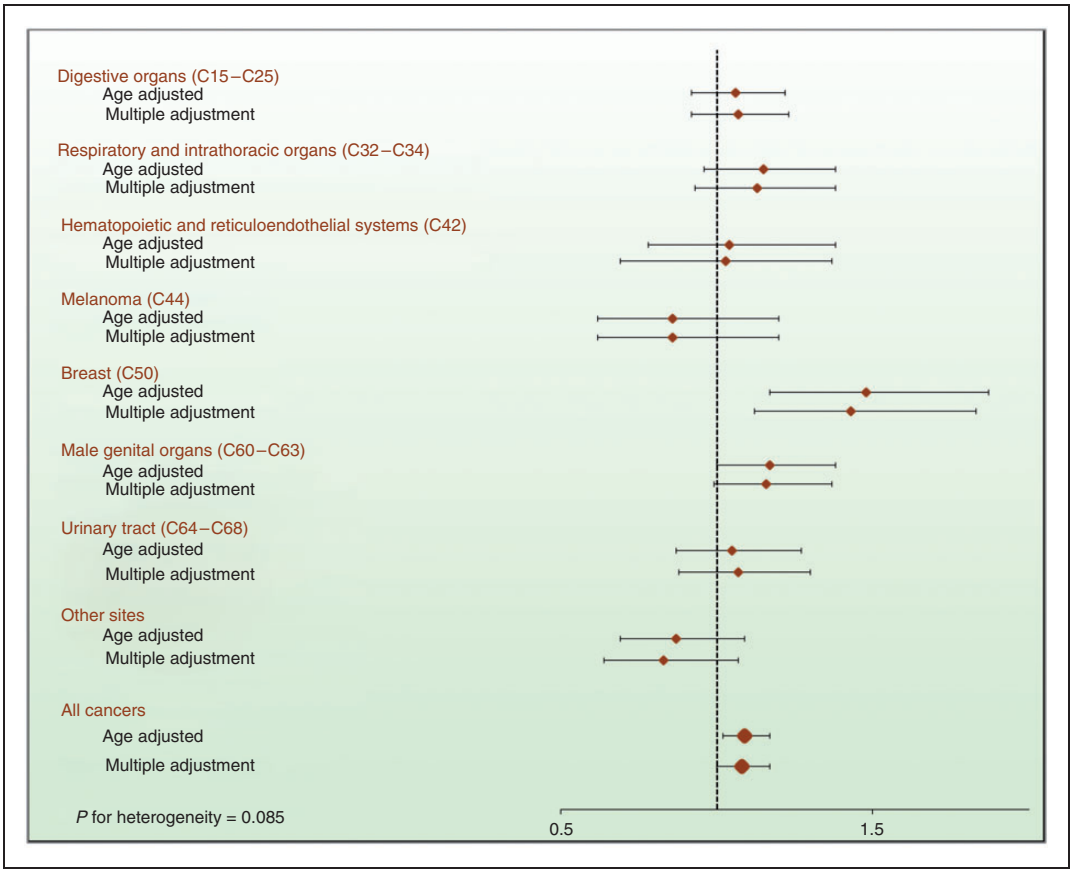

Figure 5. Hazard ratios and 95% confidence intervals for major cancer groups per 10-ppb increase in nitrogen oxide exposure. Multivariable models adjusted for sex, smoking, neighbourhood socioeconomic status, ethnicity, hypertension, diabetes mellitus, chronic heart failure, renal failure and haemoglobin levels. Classification of cancer categories according to International Classification of Diseases for Oncology, 3rd edition.

prostate and breast. Adjusting for potential confounders and performing several sensitivity analyses had almost no effect on the estimated HRs. Compared to the associations reported in studies conducted in the general population, the associations observed herein are slightly stronger, thereby supporting the hypothesis of higher susceptibility of coronary patients to TRAP exposure. As multi-morbidity among individuals with cardiovascular disease is a subject of substantial importance, preventive measures are being intensively taken by clinicians.[1] Along with previous recommendations for recognising air pollution as a major modifiable risk factor in the primary and secondary prevention of cardiovascular disease,[14,55] our results highlight the need to increase the awareness of both clinicians and patients regarding other harmful exposures besides the established cancer risk factors that may also have a hazardous effect in this population. Furthermore, as the two cancer types mostly associated with TRAP exposure – breast and prostate cancers – are those for whom effective screening and early detection measures are available, the findings of this study have considerable clinical relevance. Identifying patients at increased TRAP-related risk for breast/prostate cancer can result in intensifying the screening strategy (earlier initiation of mammography/prostate-specific antigen test) in an attempt to increase the probability of earlier detection and subsequently improved prognosis.

Conclusion

This cohort study supports the notion that chronic exposure to TRAP constitutes a risk factor for cancer incidence among coronary patients, particularly cancer of the lung, prostate and breast. As these cancers are amenable to prevention strategies, identifying highly exposed patients may provide an opportunity for improve clinical care.

Author contributions

GC and YG contributed to the conception and design of the work. GC, IL, Y, NL, JDK, GW, ZI, TB, DMB, DMS, RK and YG contributed to the acquisition, analysis or interpretation of data for the work. GC drafted the manuscript. IL, Y,

NL, JDK, GW, ZI, TB, DMB, DMS, RK and YG critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflicting interests

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