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Long-term exposure to traffic-related air pollution and cancer among survivors of myocardial infarction: A 20-year follow-up study

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Abstract

Background: Previous studies suggested a carcinogenic effect of exposure to traffic-related air pollution. Recently, higher rates of cancer incidence were observed among myocardial infarction survivors compared with the general population. We examined the association between chronic exposure to nitrogen oxides, a proxy measure for traffic-related air pollution, and cancer incidence and mortality in a cohort of myocardial infarction patients.

Methods: Patients aged ≤65 years admitted to hospital in central Israel with a first myocardial infarction in 1992–1993 were followed to 2013 for cancer incidence and cause-specific mortality. Data on sociodemographic and cancer risk factors were obtained, including time-varying information on smoking. Using land use regression models, annual averages of nitrogen oxides during follow-up were estimated individually according to home addresses. Cox proportional hazards models were constructed to study the relationships with cancer outcomes.

Results: During a mean follow-up of 16 (SD 7) years, 262 incident cancers and 105 cancer deaths were identified among 1393 cancer-free patients at baseline (mean age 54 years; 81% men). In adjusted models, a 10 ppb increase in mean nitrogen oxide exposure was associated with a hazard ratio (HR) of 1.06 (95% confidence interval (CI) 0.96–1.18) for cancer incidence and HR of 1.08 (95% CI 0.93–1.26) for cancer mortality. The association with lung, bladder, kidney or prostate cancer (previously linked to air pollution) was stronger (HR 1.16; 95% CI 1.00–1.33).

Conclusions: Chronic exposure to traffic-related air pollution may constitute an environmental risk factor for cancer post-myocardial infarction. Variation in the strength of association between specific cancers needs to be explored further.

Keywords

Air pollution, cancer risk, cohort study, myocardial infarction

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Background

Evidence from epidemiological studies suggests a carcinogenic effect of long-term exposure to traffic-related air pollution (TRAP).[1–12] Multiple studies have linked air pollution exposure to lung cancer incidence[2–4,6] and mortality;[5,11] however, associations with other cancers have also been reported,[12] including bladder,[7,8] prostate,[9] kidney[12] and breast.[10,13] This evidence supported the recent classification of ambient air pollution and particulate matter as a group 1 carcinogen by the International Agency for Research on Cancer.[14]

Nevertheless, methodological limitations and inconsistencies across the literature leave uncertainties about

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several key issues. First, while assessment of cancer incidence and mortality requires long-term observational studies, few studies have managed to follow participants for an adequate duration (recently reviewed by Hamra et al.)[1] Second, estimating historic pollution levels is essential for accurate exposure assessment; however, studies often use available data of limited time periods during follow-up, thus not fully capturing past exposures.[2] In addition, although changes in smoking status over time are known to be associated with health risk, including mortality,[15,16] very few studies have accounted for time-varying information on smoking.[4]

Recent evidence for higher incidence rates of cancer among patients with pre-existing cardiovascular diseases compared to the general population has been reported.[17–21] For example, Hasin et al. demonstrated that patients with heart failure had a 68% higher risk of developing cancer (hazard ratio (HR) 1.68; 95% confidence interval (CI) 1.13–2.50) adjusted for clinical characteristics.[18] In addition, in recent decades, a shift in the cause of death after myocardial infarction (MI) from cardiovascular to non-cardiovascular has been observed,[22] with cancer being a main cause of death.[20,22,23] Previously observed air pollution-induced health effects among MI survivors, including mortality,[24,25] recurrent cardiovascular events[24,26] and frailty syndrome,[27] along with current evidence of increased risk for cancer in this population, generated our present hypothesis regarding a possible association between chronic exposure to TRAP and cancer incidence and mortality among MI survivors. For this purpose, we used data from a population-based cohort study of cancer-free MI patients, with a follow-up exceeding 20 years, and an abundance of time-varying information on potential confounders.

Methods

The study cohort

Participants of this study were drawn from the Israel Study of First Acute Myocardial Infarction, a longitudinal prospective multicentre study,[28] comprising all individuals aged ≤65 years who were hospitalised for incident MI between 1992 and 1993 in one of the eight hospitals in central Israel. Participants are all residents of central Israel, a well-defined geographical area of approximately 1500 km^2, which is predominantly urban. Of an initial 1626 patients admitted to hospital, 81 (5%) died during initial hospitalisation, and 24 withdrew consent after discharge from hospital. Of the remaining 1521, 35 (2%) had a history of cancer prior to study entry, and were therefore excluded from the study. Geographical coordinates of residential addresses were identified for 1393 (94%) patients, who were included in the study. Demographic, socioeconomic and clinical data were collected at baseline and follow-up interviews, 5 and 10–13 years after the MI. Residential addresses were recorded at baseline and confirmed after 5 years (Figure 1). All aspects of the study were approved by the appropriate institutional ethics committees.

Cancer incidence ascertainment

Members of the cohort were linked to the Israeli National Cancer Registry (INCR) via their national

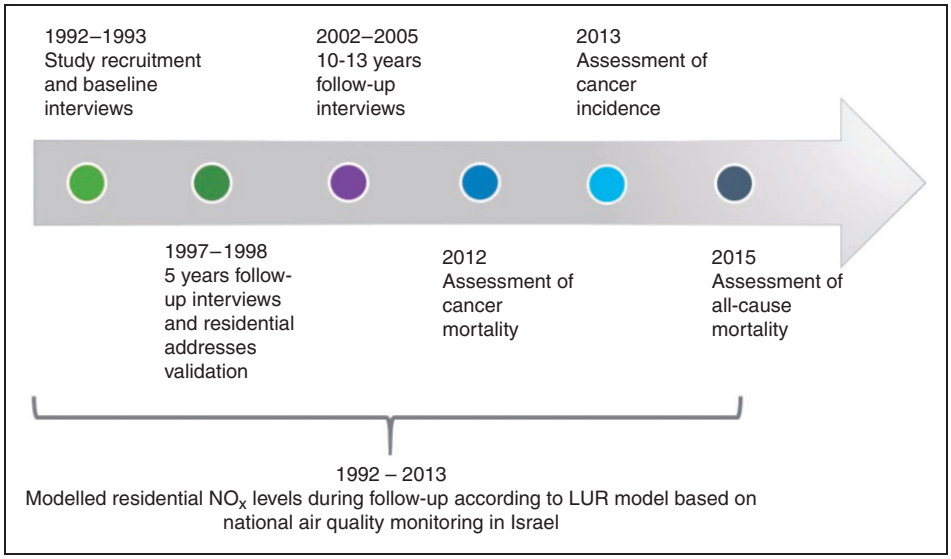

Figure 1. Study timeline.

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 it covers the entire Israeli population (approximately 8 million).[29] Registry staff review cases reported by laboratories and medical facilities, determine primary site and morphology, and assign diagnostic codes according to the International Classification of Diseases for Oncology (ICDO), third edition. Data supplied by the INCR included the diagnostic code and date of diagnosis. Using the INCR linkage, we classified incidence cases of cancers of all sites (C00.0–C80.9) diagnosed during the study period. We also identified specific cancers suggested to be related to chronic exposure to TRAP,[1,7,9,12] including cancers located in the bronchus and the lung (ICDO codes: C34.0–C34.9), prostate gland (C61.9), kidney (C64.9) and bladder (C67.9). We only included primary cancers (i.e. not metastases). Patients not diagnosed with cancer were right-censored at the date of death ($n = 524$) or last date of cancer update (31 December 2013).

Cancer mortality assessment

Mortality data were retrieved from the nationwide database of causes of death, managed by the Ministry of Health. Until the year 1998, causes of death were coded according to the International Classification of Diseases, 9th Edition (ICD-09), whereas since 1999 they are coded according to the International Classification of Diseases, 10th Edition (ICD-10). Linkage of the cohort participants to the database enabled us to assess all-cause and cause-specific mortality from the date of entry to the study until 14 May 2015 and 31 December 2012, respectively (Figure 1). Cases of cancer mortality were identified through codes 140.0 to 239.9 (ICD-09) until 1998, or C00.0 to D48.0 (ICD-10) since 1999. We assured all cases of cancer mortality were also reported as incidence cases in the INCR data.

Exposure assessment

Exposure to TRAP was estimated using residential nitrogen oxides (NO_x) levels modelled annually for each participant during the follow-up period by a land use regression (LUR) model, using a 20-year long record (1992−2011) of air quality monitoring data in Israel.[30] Ambient air pollution measurements in Israel are performed routinely 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 were collected for each monitoring site. Spatial variables were generated through development and reconstruction of 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 Israel's Central Bureau of Statistics. Altogether, 22 predictors were calculated (in 10 groups), including: road network, population density, power plants, land use, vegetation cover, traffic volumes, vehicle count and type of air quality site (i.e. 'near-road' or 'general'), with the year of measurement as one of the predictors. Our modelling approach was to find the model that will produce the best predicted NO_x levels over the entire study domain while assuring that the predictors match a priori knowledge about their effect on TRAP. Therefore, a supervised forward stepwise procedure was used to select the best model.[31] The model's leave-one-out cross-validation adjusted R^2 was 0.74. For each subject, annual estimates of NO_x exposure were created for each year between 1992 and 2011 by linking the exposure surfaces derived from the LUR model to residential addresses at baseline and 5 years post MI, thereby accounting for residential mobility. Since spatial distributions of NO_x did not change appreciably over the follow-up period, with very high correlations (Pearson's $r \geq 0.97$) between the annual estimates, we assigned for each subject the mean NO_x exposure during the follow-up period.

Additional individual measures

Individual measures were obtained through structured interviews and review of patients' medical records at the study entry and during follow-up; all clinical data were verified by a senior cardiologist. The number of cigarettes smoked per day was evaluated at baseline, 5 years and 10–13 years after the initial hospitalisation (categorised as none/up to 20 cigarettes per day/more than 20 cigarettes per day), as well as the smoking history for non-smokers at baseline (categorised as never smoker/former smoker). Additional variables, considered as potential confounders for the current analysis, included: individual socioeconomic status (SES) data (family income relative to the national average, education and employment status), ethnicity, physical activity, body mass index, self-rated health, hypertension, diabetes and hypercholesterolaemia.

Neighbourhood SES as a potential confounder

A body of evidence indicates that a person's health may be influenced by the socioeconomic characteristics of the neighbourhood in which he or she lives, over and above his or her own SES.[32] Along with this, neighbourhood SES (nSES) has been recently reported to be associated with both total and site-specific cancer incidence, as well as with total cancer mortality.[33] However, it is still unknown which of the neighbourhood's characteristics might explain these observed associations. A recent analysis from the Multi-Ethnic Study of Atherosclerosis demonstrated negative associations between NO_x and nSES.[34] Considering these relationships of nSES both with cancer and air pollution, we found it necessary to account for its potential confounding effect in the current analysis. We estimated nSES through a 20-point scale index developed by the Israel Central Bureau of Statistics, based on the 1995 National Census, with a score of 20 representing the highest SES.[35]

Statistical analysis

Differences in baseline characteristics across NO_x exposure groups were examined using the χ^2 test for trend (categorical variables) or generalised linear models (continuous variables). Cox proportional hazards models[36] were constructed to estimate the associations between NO_x exposure and cancer outcomes, including all-site cancer incidence and cancer mortality. In addition, we attempted to examine associations between incidence of specific cancers previously suggested to be affected by TRAP, especially diesel exhaust (lung, prostate, kidney and bladder) and NO_x exposure.[1,7,9,12] Due to the limited number of events in these cancer categories, they were grouped together. We could not perform a similar analysis for specific cancer deaths due to low statistical power. For participants who changed their residential address, NO_x exposure was modelled as a time-dependent variable, allowing the assigned exposure to change accordingly. Initial adjustment was made for age (base model). Subsequently, the percentage change in the regression coefficient for a 10-ppb increment in NO_x was estimated after inclusion of individual candidate confounding variables into the base model, applying a 5% threshold.[37,38] Neighbourhood SES, obesity at baseline, ethnicity, history of smoking, and current smoking (modelled as a time-dependent covariate) met the latter criterion and were included in the final model (multivariable-adjusted model).

Since association between exposure to air pollutants and health outcomes is suggested to exist mainly among those who are not chronically exposed to a high tobacco dose,[4,7,11] we sought to examine the exposure–cancer relationships among patients who might be more vulnerable to air pollution effects. Therefore, in a subsequent analysis, we identified patients who reported smoking more than 20 cigarettes per day in each assessment (defined as 'persistent heavy smokers'), and excluded them from the analysis. Repeating this analysis for never smokers alone was not possible, due to the high percentage of current and former smokers in the cohort (73%). The proportional hazards assumption was tested with the Schoenfeld residuals, with no violations detected. Missing values for family income (17%) and nSES (6%) were imputed using multiple imputation methodology.[39] The Markov Chain Monte Carlo method was used for this purpose. Five datasets were created, with missing values replaced by imputed values based on models incorporating demographic, socioeconomic, psychosocial and clinical variables. The results from analysing these datasets were then combined using Rubin's rules.[39] A complete-case analysis was subsequently performed, in order to ensure the robustness of the multiple imputation results. Because both approaches yielded similar results, only the multiple imputation results are presented. Analyses were performed using IBM SPSS Statistics version 23 (IBM SPSS Inc., Chicago, IL, USA).

Results

A total of 1393 patients free of cancer were included in the study. Table 1 shows selected baseline characteristics according to exposure groups. At time of recruitment, mean age was 54 (SD 8) years and 81% were men. The prevalence of smoking at baseline was high (52%), with 56% of the smokers smoking more than 20 cigarettes per day. In reassessments conducted 5 and 10 years after the beginning of the follow-up, the prevalence of smoking decreased by more than a half (23% and 21%, respectively), with only 5% of the survivors at each time point smoking more than 20 cigarettes per day.

Figure 2 presents a map of the study area, demonstrating the mean annual NO_x levels during follow-up as estimated by the LUR model. Mean NO_x exposure during follow-up was 24 (range 9–84) ppb. A total of 182 (13%) participants changed their residential addresses during the first 5 years of the follow-up. For these patients, the correlation between average NO_x exposure during follow-up according to first and second addresses was very weak (Pearson's $r = 0.08$).

During a mean follow-up of 16 (SD 7) years (21,684 person-years), 262 new cases of cancer were diagnosed, for an incidence rate of 12 per 1000 person years. Of these, 28, 36 and 47 were identified as malignant neoplasms of the bronchus and lung (11%), kidney and

Table 1. Pertinent baseline characteristics across NO_x exposure tertiles.

Characteristic	Missing, *n* (%)	Overall (*n* = 1393)	NO_x tertiles			*P* value for linear trend
			Lower (*n* = 465)	Medium (*n* = 463)	Upper (*n* = 465)	
NO_x, mean (range), ppb	–	23.7(9.3–84.1)	15.6 (9.3–18.1)	20.1 (18.2–22.4)	35.5 (22.4–84.1)	–
Age, mean (SD), years	–	54 (8)	53 (8)	54 (8)	54 (8)	0.30
Men, *n* (%)	–	1132 (81)	376 (81)	373 (81)	383 (82)	0.56
Socioeconomic measures						
Family income, *n* (%)	233 (17)					0.04
Below average		549 (47)	154 (40)	198 (51)	197 (51)	
Average		321 (28)	127 (33)	104 (27)	90 (23)	
Above average		290 (25)	105 (27)	84 (22)	101 (26)	
Education, mean (SD)	–	11.0 (4)	11.3 (4)	11.0 (4)	10.7 (4)	0.02
Pre-MI employment, *n* (%)	5 (0.4)	1054 (76)	366 (79)	340 (74)	348 (75)	0.12
Neighbourhood SES, mean (SD)	82 (6)	12.5 (3.8)	12.6 (3.7)	12.5 (3.7)	12.5 (4.0)	0.50
Smoking information at baseline						
Current smoking	–	731 (53)	254 (55)	224 (48)	253 (54)	0.95
Over than 20 cigarettes per day	15 (1)	407 (29)	137 (30)	127 (27)	143 (31)	0.86
Former smoker	–	281 (20)	92 (20)	100 (22)	89 (19)	0.81
Other risk factors and comorbid conditions						
Physical Activity	119 (9)					0.16
Not active		690 (54)	222 (51)	229 (55)	239 (56)	
Unregularly active		214 (17)	75 (17)	66 (16)	73 (17)	
Regularly active		370 (29)	135 (31)	119 (29)	116 (27)	
Obesity (BMI $\geq$ 30)	32 (2)	250 (18)	77 (17)	88 (19)	85 (19)	0.54
Self-rated health	–					0.22
Poor		259 (19)	79 (17)	85 (18)	95 (20)	
Average		327 (24)	112 (24)	106 (23)	109 (23)	
Good		807 (58)	274 (59)	272 (59)	261 (56)	
Hypertension	–	541 (39)	166 (36)	185 (40)	190 (41)	0.11
Hypercholesterolaemia	–	519 (37)	179 (39)	173 (37)	167 (36)	0.42
Diabetes	–	338 (24)	111 (24)	120 (26)	107 (23)	0.76
Secondary CVD prevention treatments						
Aspirin	–	1134 (81)	392 (84)	363 (78)	379 (82)	0.27
Beta blockers	–	492 (35)	165 (36)	157 (34)	170 (37)	0.73
ACE inhibitors	–	282 (20)	95 (20)	98 (21)	89 (19)	0.63

NO_x: Nitrogen oxides; ppb: parts per billion; SD: standard deviation; MI: myocardial infarction; SES: socioeconomic status; BMI: body mass index; ACE: angiotensin-converting enzyme.

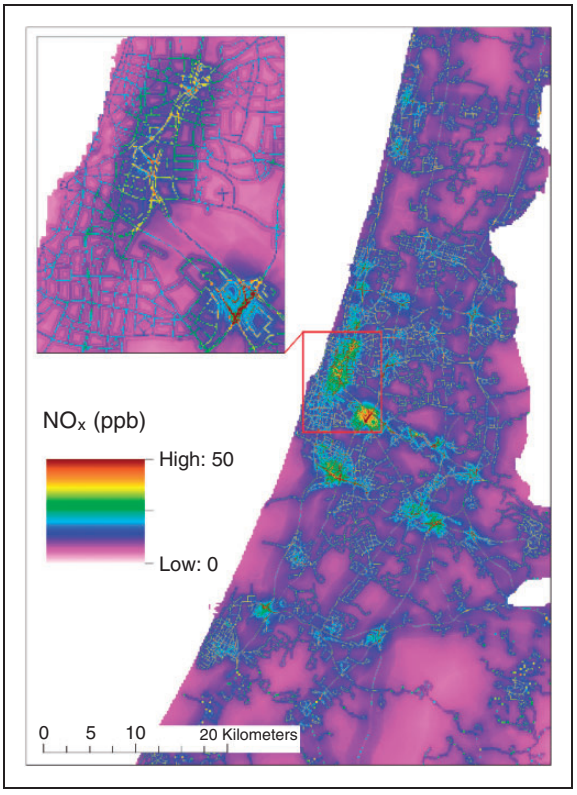

Figure 2. Mean annual NO_x levels in central Israel between 1992 and 2012 estimated through LUR model based on 104 national air quality monitoring sites. NO_x: nitrogen oxides; LUR: land use regression.

bladder (14%) and prostate gland (18%), respectively (Figure 3). Among 635 deaths during follow-up, 105 (17%) were classified as cancer deaths.

Table 2 shows the results of the Cox regression models for the relationship between modelled residential NO_x exposure and cancer incidence and mortality. The final models included only variables that met the criterion of 5% change in the regression coefficient for NO_x exposure. Education and relative income did not meet the latter criterion, and therefore were not included in the final models. In adjusted models, a 10 ppb increase in mean NO_x exposure was associated with HR 1.06 (95% CI 0.96–1.18) for cancer incidence. An association of similar magnitude was detected for cancer mortality with HR 1.08 (95% CI 0.93–1.26). Excluding persistent heavy smokers from the analysis ($n = 71$) made no material difference both for cancer incidence (HR 1.08; 95% CI 0.97–1.20) and cancer mortality (HR 1.11; 95% CI 0.95–1.29). We examined the association between NO_x exposure and lung, prostate, kidney and bladder cancers. As shown in Table 2, the HR estimate was doubled (HR 1.16; 95% CI 1.00–1.33), compared with the risk for all cancers. After excluding persistent heavy smokers, the HR was 1.17 (95% CI 1.01–1.36). We examined effect modification by age, sex and nSES for the different cancer outcomes; however, no evidence for such an effect was shown (all P values were > 0.20). Stratification according to these factors resulted in a stronger association for lung, prostate, kidney and bladder cancers among patients aged ≤ 54 years (HR 1.25; 95% CI 0.96–1.62) compared to older patients (HR 1.13; 95% CI 0.95–1.35), as well as among patients residing in neighbourhoods of upper SES (HR 1.26; 95% CI 1.02–1.57) compared to low and medium (HR 1.16; 95% CI 0.90–1.50 and HR 1.00; 95% CI 0.75–1.34, respectively).

Discussion

In this cohort study of MI survivors living in a predominantly urban area in central Israel, we observed positive associations, although not statistically significant, between long-term residential NO_x levels, as an indicator of TRAP exposure, and total cancer incidence and mortality. The associations were not substantially affected by adjustment for potential confounders, including time-varying information on smoking, and for residential mobility during follow-up. The association was stronger for specific cancers previously linked to TRAP, including lung, kidney, bladder and prostate.

Several other studies have examined the association between exposure to TRAP and cancer, with mixed results. A recent meta-analysis by Hamra et al.[1] found that a 10 $\mu g/m^3$ increase in NO_x exposure was associated with a meta-estimate of HR 1.03 (95% CI 1.01–1.05) for lung cancer. However, of the 20 studies identified in this meta-analysis, only eight showed HR higher than 1.05. Although lung cancer was not examined solely in our study due to power considerations, a stronger association (HR 1.16) was detected when grouped together with other cancers previously linked to TRAP.

Lung cancer is the main carcinogenic outcome investigated in epidemiological studies on air pollution,[1–5] because the airways are the primary target organs of inhaled carcinogenic substances. However, accumulating evidence from experiments in animals shows that ultrafine particles can translocate to other organs besides the lung, and their number in the secondary target – although several orders of magnitude lower than the lung dose – may not be negligible for carcinogenic processes.[12] Recent studies suggest other types of cancer to be associated with air pollution exposure,[12] in particular prostate,[9] kidney,[12] bladder[7,8,34] and also breast cancers,[10] particularly in relation to oestrogen and progesterone receptors status.[13] In a case–control study conducted in Spain,[7] residential exposure to emissions of polycyclic aromatic hydrocarbons (PAHs) and

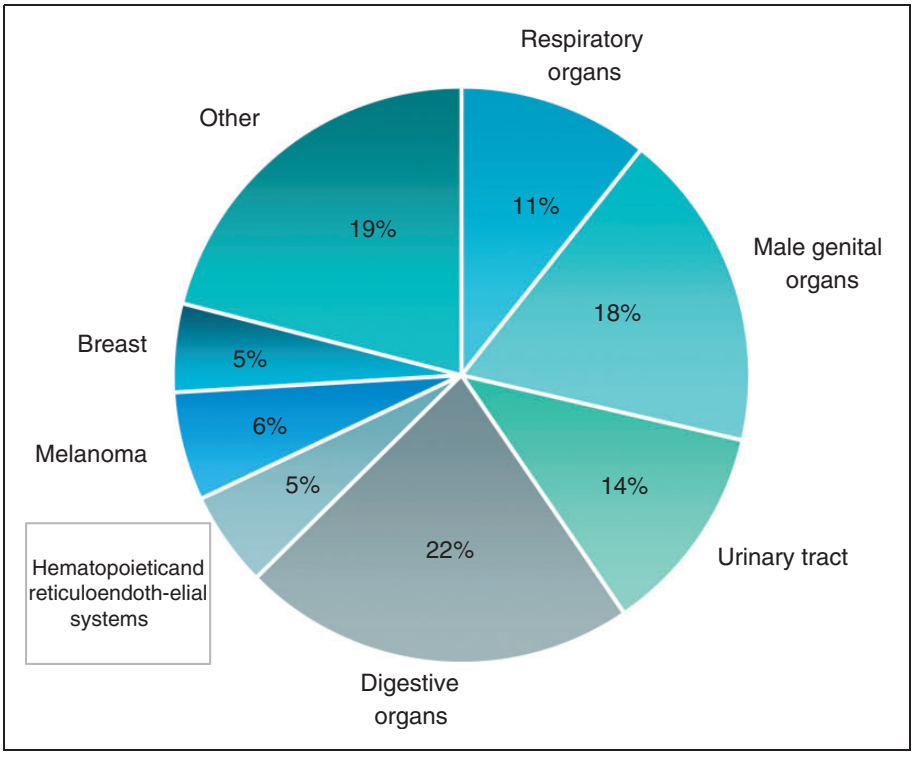

Figure 3. Distribution of cancer sites among incident cancer cases ($n = 262$) during follow-up (1992–2013).

diesel was associated with an increased risk for bladder cancer (odds ratio (OR) 1.29, 95% CI 0.85–1.98). In another case–control study conducted in Taiwan,[8] a positive association between air pollution and bladder cancer mortality was detected with adjusted ORs of 1.37 (95% CI 1.03–1.82) and 1.98 (95% CI 1.36–2.88) associated with medium and high air pollution levels, respectively. Risk for kidney cancer was also shown to increase with NO_x concentrations at the place of residence in a large population-based cohort study conducted in Denmark (incidence rate ratio 1.73, 95% CI 0.89–3.73).[12] In a case–control study conducted in Canada,[9] prostate cancer was found to be associated with nitrogen dioxide (NO_2) levels, with OR of 1.27 (95% CI 1.03–1.58) after adjusting for personal and contextual factors.

Several studies observed a stronger carcinogenic effect of TRAP among non-smokers, compared to smokers.[4,6,40] Puett et al.[4] found a stronger association between $PM_{2.5}$ and lung cancer after restricting the Nurses' Health Study cohort to never smokers and former smokers who had quit at least 10 years before. Castano-Vinyals et al.[7] also found stronger OR for bladder cancer associated with several indicators of exposure to air pollution among non-smokers, compared to smokers. Turner et al.[11] investigated the relationship between long-term ambient $PM_{2.5}$ concentrations at the place of residence and lung cancer mortality in a 26-year prospective study of a large cohort of lifelong never smokers, and found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a 15–27% increase in lung cancer mortality. These findings, along with newly published evidence pointing to an increasing proportion of never smokers with non-small cell lung cancer,[41] suggest that cigarette smoking partly masks the effect of TRAP, and therefore a stronger carcinogenic effect is observed among people who are not frequently exposed to tobacco smoke. In our study, analysing non-smokers only was not feasible due to a high proportion of former and current smokers in the cohort, and therefore we conducted a sub-analysis excluding only persistent heavy smokers. Although slightly higher risk estimates for all cancer outcomes were observed, they did not differ materially from those in the entire cohort. The small number of patients excluded in this analysis ($n = 71$) probably prevented us from detecting a material difference.

A stronger carcinogenic effect of air pollution was previously observed in other populations besides non-smokers. Molecular epidemiological research provides compelling evidence that the risk for cancer attributed to environmental carcinogens is strongly influenced by both genetic and acquired susceptibility.[40] Acquired susceptibility to air pollution-induced health effects might be partly explained by conditions associated with increased oxidative stress and inflammation,[42]

Table 2. Hazard ratios (95% confidence intervals) for incidence of all cancers, site-specific cancers and cancer death associated with a 10 ppb increase in residential NO_x exposure among MI survivors.

	Cancer incidence		Lung, prostate, kidney, or bladder cancer incidence		Cancer mortality	
	Full cohort ($n = 1393$)	Excluding persistent heavy smokers[a] ($n = 1322$)	Full cohort ($n = 1393$)	Excluding persistent heavy smokers[a] ($n = 1322$)	Full cohort ($n = 1393$)	Excluding persistent heavy smokers[a] ($n = 1322$)
Number of events	258	245	111	103	105	97
Person years	21,684	21,056	21,684	21,056	22,301	21,667
Age-adjusted	1.07 (0.96–1.18)	1.08 (0.97–1.19)	1.15 (1.00–1.33)	1.16 (1.01–1.35)	1.10 (0.95–1.29)	1.13 (0.96–1.32)
Multivariable adjustment[b]	1.06 (0.96–1.18)	1.08 (0.97–1.20)	1.16 (1.00–1.33)	1.17 (1.01–1.36)	1.08 (0.93–1.26)	1.11 (0.95–1.29)

[a]Survivors repeatedly reporting smoking > 20 cigarettes during follow-up.
[b]Adjusted to age, sex, ethnicity, nSES, obesity at baseline, past smoker and smoking coded as a categorical time-dependent variable, incorporating assessments at baseline and follow-up interviews, 5 and 10–13 years post-MI (three categories: none-smoker, smoking up to 20 cigarettes per day and smoking more than 20 cigarettes per day).
NO_x: Nitrogen oxides; nSES: neighbourhood socioeconomic status; MI: myocardial infarction.

including old age and chronic lung diseases, as well as pre-existing chronic heart diseases.[43,44] Along with this assumption and taking into consideration common environmental and behavioural factors exerting both atherogenic and carcinogenic effects,[42,45] excess risk for cancer among cardiovascular patients has been lately investigated. Findings from recent studies suggest a higher risk for cancer among individuals with cardiovascular diseases, including patients with heart failure[18] and MI survivors.[19,20] Few studies that investigated the risk for the different types of cancers, observed a particularly higher risk for prostate,[46] lung and bladder cancers,[17] yet no increased risk for colorectal cancer.[47] In addition, in recent decades a shift in the long-term cause of death after MI has been reported from cardiovascular to non-cardiovascular,[22] with cancer as one of the main causes of death.[23]

While adverse health effects of air pollution, including all-cause mortality, among MI survivors have previously been investigated,[44,48] its carcinogenic effect among this population in terms of both incidence and mortality has received very little attention. To the best of our knowledge, this is the first study to specifically examine the relationship between exposure to air pollution and cancer outcomes among this high-risk population of MI survivors.

Methodological considerations

Our study has several strengths. First, the study sample is a well-defined post-MI cohort, a population established as vulnerable to the effects of air pollution, as well as being geographically defined, thereby improving relevance and generalisability. Second, residential NO_x levels, serving as a proxy for TRAP, were estimated by LUR, which was developed using a 20-year long record (1992−2011) of national air quality monitoring network data in Israel, incorporating extensive spatial information on a national scale. The role of NO_x as a marker for TRAP is most plausible in urban settings, where traffic is often the primary source of NO_x in the atmosphere and the main source of variability in NO_x levels.[1] Therefore, we find our exposure metrics suitable to estimate the effect of traffic pollution carcinogenicity. Third, address confirmation conducted 5 years after the baseline enabled us to account for residential mobility. Although we were not able to identify individuals who changed their addresses in the remaining time of the follow-up, we assume that a small proportion of participants changed their residential addresses in the late years of the follow-up, as the participants' mean age at the second interview was 59 years. Fourth, extensive high quality clinical and sociodemographic data were available from multiple sources, including medical records and structured interviews, allowing us more

accurately to control for confounding factors, including detailed time-varying information on smoking, which is suggested to be a substantial modifier of the exposure–cancer relationship.[4,6] In addition, data on cancer incidence and mortality were obtained by linking the cohort with two nationwide quality-assured registries.

Several limitations of our study should be acknowledged. Data on TRAP exposure was based on residential addresses alone, without information on time-activity patterns, time spent outdoors, or time spent at the residence. Because of a paucity of monitoring stations for NO_x in Israel before 1998, our models for the earlier years are less precise than our models in the later years. However, due to low temporal variability in NO_x levels, we assigned mean annual NO_x levels during follow-up to each participant, reducing model imprecision for the early years. Our sample size did not afford analysis of certain subgroups of particular interest, including cases of lung cancer alone, other traffic-related cancers, different histological types of these cancers, as well as cause-specific cancer mortality. As our cohort is composed of MI survivors, there is a substantially high proportion of current and former smokers, which prevented us from excluding them from the analysis. As with all studies, residual confounding is of concern. Although we obtained detailed information on active smoking, we did not have information on other cancer risk factors, including exposure to environmental tobacco smoke, occupational exposures and residential radon, as well as fruit consumption.[2] In addition, we did not have information on low-dose ionising radiation from medical imaging and several cardiovascular medications suggested to contribute to the occurrence of malignancy among cardiovascular patients.[18]

Clinical implications

Our study provides some support that TRAP may be associated with the risk of cancer among patients with pre-existing heart diseases. These findings suggest a potential mechanism underlying the recently observed increased risk of cancer among this group of patients.[18–20] As air pollution is thought to be 'the most widespread environmental carcinogen',[14] chronic exposure to its cancer-causing substances might play a role in malignancy occurrence among this vulnerable subpopulation. Since multi-morbidity among patients living with chronic diseases is a subject of high priority in clinical care,[18] understanding its determinants is important, both to reduce adverse outcomes and implement appropriate preventive interventions. For example, in light of the evidence-based recommendations for physical activity given to patients in cardiac rehabilitation, the outdoor environment where the activity takes place should be taken into consideration, as health effects may vary between environments with different pollution levels.[49,50]

Conclusion

In conclusion, this cohort study of MI survivors followed-up for more than two decades shows a positive association, although not statistically significant, between TRAP at the place of residence and total cancer incidence, and a stronger association with pooled cancer sites previously suggested to be associated with TRAP. With the few studies available, future research is clearly needed, particularly further investigation of the variation in the strength of association between specific cancers.

Author contribution

Study concept and design: GC, YG. Acquisition of data: YG, GC, IL, NL, Y, JDK. Analysis and interpretation of data: GC, YG, IL, NL, Y, JDK, DMB, DMS. Drafting of the manuscript: GC, YG. Critical revision of the manuscript for intellectual content: GC, YG, DMS, JDK, DMB, Y, NL, IL. Statistical analysis: GC, YG. Obtaining funding: YG, DMB, DMS. Study supervision: YG, DMB, JDK, DMS. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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