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Association between airport-related ultrafine particles and risk of malignant brain cancer: a multiethnic cohort study

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Abstract

Ultrafine particles (UFP) (diameter less than or equal to 100 nanometers), may reach the brain via systemic circulation or the olfactory tract and have been implicated in the risk of brain tumors. The effects of airport-related UFP on the risk of brain tumors are not known. Here we determined the association between airport-related UFP and risk of incident malignant brain cancer (n=155) and meningioma (n=420) diagnosed during 16.4 years of follow-up among 75,936 men and women residing in Los Angeles County from the Multiethnic Cohort study. UFP exposure from aircrafts was estimated for participants who lived within a 53 by 43 kilometer grid area around the Los Angeles International Airport (LAX) from date of cohort entry (1993–1996) through December 31, 2013. Cox proportional hazards models were used to estimate the effects of time-varying, airport-related UFP exposure on risk of malignant brain cancer and meningioma, adjusting for sex, race/ethnicity, education, and neighborhood socioeconomic status. Malignant brain cancer risk in all subjects combined increased 12% (95% CI 0.98–1.27) per interquartile range (IQR) of airport-related UFP exposure (~6700 particles per cm^3) for subjects with any address in the grid area surrounding the LAX airport. In race/ethnicity-stratified analyses, African Americans, the subgroup who had the highest exposure, showed a hazard ratio (HR) of 1.32 (95% CI 1.07–1.64)

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for malignant brain cancer per IQR in UFP exposure. UFP exposure was not related to risk of meningioma overall or by race/ethnicity. These results support the hypothesis that airport-related UFP exposure may be a risk factor for malignant brain cancers.

Introduction

The etiology of brain cancers remains largely unknown, and while only ionizing radiation and a history of allergies or atopic disease are the main environmental risk factors that have been consistently associated with risk (1–3), significant progress has been made in the past decade in elucidating the inherited predisposition of brain cancers (4). Glioma represents about 80% of malignant brain cancers. The majority of the genetic component of glioma appears to be explained by a polygenic contribution from at least 25 risk polymorphisms identified through genome-wide association studies (5). Although there is suggestive evidence from studies conducted in Europe (6–9) and Los Angeles County (10) that some air pollutants may increase the risk of brain cancer, results are not at all consistent (11–15). However, a recent study conducted in Toronto and Montreal, Canada, reported for the first time an association between ambient ultrafine particles (UFP) exposure and risk of brain cancer incidence; the hazard ratio (HR) was 1.11 (95% CI 1.04–1.19) per 10,000/cm^3 UFP after adjusting for sociodemographic factors and other air pollutants (16).

UFP are a subset of particulate matter (PM) that are generally defined as smaller than 100 nm (≤0.1 μm) in diameter. $PM_{2.5}$ and PM_{10} but not UFPs are routinely monitored and have well established standards based on documented adverse health effects attributed to these pollutants (17). Routine monitoring of UFPs are not available in the US and in most countries, and the spatiotemporal variability of UFP concentrations over large distances and the health effects of UFPs are not well studied. Nevertheless, recently several studies have documented the contributions of major airports to UFP concentrations at least 10 km away including from airports in Los Angeles, New York, Boston, Amsterdam and elsewhere (18–23). Most relevant to this study, a mobile monitoring platform campaign conducted around the Los Angeles International Airport (LAX) uncovered airport-related UFP concentrations being at least two-times greater than adjacent background levels covering 60 km^2, an area extending 20 km downwind from LAX. Within 10 km of LAX, UFP concentrations were increased by 4–5 fold (20,24). These studies suggest that aircraft exhaust emissions are a significant source of UFP and can result in several-fold increases in ground-level particle number concentrations over large areas downwind (20,21,24–26) as well as upwind (27) of the airport.

Because of UFPs' small size and dynamic diffusion properties, they can be deposited throughout the airways including the lung alveoli, allowing cellular interstitial penetration and entrance into the lung's blood stream. From there, UFPs can translocate throughout the body including the central nervous system (CNS) where they may cross the blood brain barrier or enter the brain through the nose and olfactory pathway (28,29). Inflammation and oxidative stress are the suspected pathways related to UFP toxicity (30,31). Two recent studies conducted around LAX suggested noteworthy health effects associated with airport-related UFPs. In a randomized crossover study, levels of IL-6, a circulating marker of

acute systemic inflammation, were found to be increased with airport-related UFPs (32). In addition, a Los Angeles County-based birth record study found that in utero exposure to airport-related UFP was associated with preterm birth (odds ratio (OR) per quartile of UFP=1.04, 95% confidence interval (CI) 1.02–1.06)(33).

We recently reported an increased risk of malignant brain cancer but not meningioma in relation to long-term exposure to ambient benzene, ozone, and possibly PM_{10} within the California component of the Multiethnic Cohort (MEC), in which Latin Americans and African Americans represent approximately 75% of the study participants (10). Utilizing the same study population, we now investigate the role of airport-related UFP and risk of malignant brain cancer and meningioma by estimating downwind airport-related UFPs using a meteorological dispersion model based on flight path and landing frequencies along with measured UFP values generated by a mobile measurement platform that was moved around LAX (33). This investigation provides the first prospective results on UFP exposure and brain tumors in a cohort that included a substantial number of nonwhite participants who have been found to have higher exposure to pollutants that may be attributed to structural racism resulting in racial/ethnic residential segregation (34,35).

Materials and Methods

Study population

The MEC is a large cohort designed to investigate the etiology of cancer among a multiethnic population of US adults (36). From 1993 through 1996, 96,810 men and 118,441 women aged 45–75 years from five racial/ethnic groups (African American, Japanese American, Latin American, Native Hawaiian, and European American), residing in Hawaii (HI) or California (CA: primarily Los Angeles County (LAC)), were enrolled. At baseline, participants completed a twenty-six page mailed questionnaire with questions pertaining to demographic, education, smoking, anthropometrics, occupation, other lifestyle factors, and reproductive history (women only).

Ascertainment of malignant brain cancers and meningioma

Participants were followed prospectively for diagnosis of incident invasive brain cancer (C71.0–C71.9, C72.0–C72.4) through routine linkage with the CA and HI statewide cancer registries, which are a part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER), and for vital status through linkages to the National Death Index and death certificate files. MEC participants older than 65 years were linked to Centers for Medicare Services claims (1999–2016) to identify chronic conditions. Thus to ascertain meningioma cases, we included MEC participants who were linked to Medicare data using well-established methods (37) as well as cancer registry information on non-malignant brain tumors (meninges, spinal cord, and other CNS tumors) that became a reportable disease on January 1, 2004 (38).

Only the California component of the MEC was included in our studies on air pollution(10). Eligible CA MEC participants were those who completed a baseline questionnaire and provided valid addresses that were geocoded to latitude and longitude coordinates based

on address points or street locators across the study period (n=109,603). Subjects not in the main five racial/ethnic groups, with a brain cancer or meningioma diagnosis prior to cohort entry, death date prior to diagnosis date, or invalid baseline data (n=6,174), with questionable address data (n=22) or other invalid entry/exit dates (n=99) were ineligible in our brain cancer analysis (10). Of the 103,308 remaining CA participants, we also excluded those whose residences were not within the UFP exposure grid (n=19,192) or required >50% imputed exposure (n=8,180) due to address gaps or missing UFP data at one or more address records in their residential history in the grid area shown in Figure 1, leaving 75,936 participants for this analysis (Table 1). This cohort was followed from the date of cohort entry (1993–1996) to the earliest date of diagnosis of malignant brain cancer or meningioma, death, or December 31, 2013 (study end date), whichever came earlier (mean± SD follow-up was 16.4 ± 5.4 years).

Address history, geocoding, and ultrafine particle (UFP) assessment

The MEC actively maintains accurate and up-to-date addresses on all participants via periodic mailings of newsletters, follow-up questionnaires, and linkages to administrative data and registries. For the 75,936 CA MEC participants included in this study, there were 141,655 addresses recorded during the follow-up period. Each participant was assigned a composite measure of neighborhood socioeconomic status (nSES) (39) at the level of the census block group at baseline and time of event. The measure was developed using principal components analysis of seven indicator variables: poverty, education, home value, rent, occupation, employment, and income.

To estimate UFP concentrations from LAX flight activity for the period 1993 through 2013 (Figure 1, panels A-D), we used EPA's recommended American Meteorological Society/ Environmental Protection Agency Regulatory Dispersion Model (AERMOD). As described previously (33), the model accounted for hourly variations in meteorology including wind speed, wind direction, atmospheric stability and mixing height, as well as hourly changes in flight activity within a 53 × 43 km grid at a 1km spatial resolution. The 1km grid size was shown to adequately capture the UFP spatial gradients because, unlike ground level sources, the impacts from landing jets are typically very broad when they reach the ground, e.g., they produce plumes that are hundreds or thousands of meters across (20). When we previously compared model results to real-time, mobile measurements taken over seven days along six transects downwind of LAX, we found good agreement, e.g., Pearson's R^2 was 0.71 with a mean absolute percentage error of 6% (20).

For the 75,936 participants included in this analysis, we used monthly UFP data at each centroid of 1 km x 1 km grids (i.e., at a specific longitude/latitude) to develop annual UFP trend maps and continuous kriging surfaces to assign residential UFP exposures to participants' residences for each month. Thus, baseline and cumulative UFP exposure averages were estimated using the dates lived at each residence across the participant's residential history during follow-up (10). Figure 1 (panels A-D) displays baseline (1993–1996) airport-related UFP levels and baseline residential locations for African American, Latin American, Japanese American, and European American MEC participants in the UFP exposure grid and the impact zone. We defined an impact zone as an oval aligned with areas

of high airport-related UFP concentrations to restrict our analyses as much as possible to the area around the airport which included the highest UFP concentrations and also was well covered by the previous mobile platform measurements that allowed us to generate and validate our AERMOD based UFP estimates. An arbitrary length-to-width ratio of 2:1 was chosen that encompassed the area of high airport impact, yet was wide enough to provide exposure contrast by also including subjects with little or no airport UFP exposures; i.e., the oval was purposefully wider than the modeled area of high airport-related UFP concentrations. The oval was aligned along the orientation of the predominant daytime wind direction (and airport runway orientation) with one, long-axis edge aligned with the upwind airport property line. The long axis therefore aligns with maximum centerline UFP concentrations for all the modeled 1993 to 2013 July months. The major axis length was extended until centerline maximum airport UFP concentrations were no larger than 1500 particles/cm^3. As a sensitivity test, analyses were conducted by comparing subjects living within this oval to all subjects in the larger rectangular grid.

There were 55,088 participants with residential histories (any addresses) within this impact zone across the study period. We used 2.3×10^6 as the conversion factor of UFP impact to particle number concentrations (33) based on AERMOD dispersion model predictions compared with 2013 field measurement data (20).

As we have described in detail previously, information on gaseous (NO_x, NO_2, CO, O_3) and PM (PM_{10}, $PM_{2,5}$) co-pollutants was based on kriging interpolation which estimated largely regional air pollution exposures obtained from routine continuous air monitoring data in California. Ambient benzene measurements from EPA were used in which the proximity of air monitors to the participants' residential addresses was also considered (10). Vehicular-related UFP was estimated using NO_2 as a surrogate, based on LUR model estimates of NO_2, based on a large passive sampler study conducted in LA outside of the modeled airport-related UFP impacts (40).

Statistical analysis

Because UFP exposures varied over time and the duration of exposure differed across participants, we employed a time-dependent analysis approach to examine the association of UFP exposures with risk of brain cancer and meningioma. For every participant we calculated an overall average exposure based on averaging each month spent living at a given address until the censoring month (i.e., diagnosis of brain cancer/meningioma, death, or study end). These average exposures were entered into Cox proportional hazard models, with age as the primary time scale (41), as time-dependent variables computed separately for each member of each risk set from the time of cohort entry up to the time that each risk set member reached the age of the index case for that risk set. That is, for the regression calculation, the average exposure across the time interval starting at entry time until the time of the event was used for hazard ratio calculations. In the regression analyses, we modeled age at cohort entry (continuous), sex, race/ethnicity, education, and nSES at both baseline and at time of event. We also conducted analyses by including covariates shown in Table 1 as some of these variables have been implicated in previous studies of brain cancer and meningioma including our publication in the MEC (42). Results obtained from

the more fully adjusted models were largely similar and are not shown. We calculated HR and 95% CI for the association between airport-related UFP exposures and brain cancer risk for four subgroups: participants with any or all addresses in the UFP grid or impact zone. HRs were scaled per increase in respective IQR of UFP (particle/cm^3) based on all subjects: 5280 for any address in grid, 5390 for all addresses in grid, 6300 for any address in impact zone, and 6490 for all addresses in impact zone. We also repeated analyses separately in men and women, restricting analyses among non-movers and those with gliomas (C71.0–C71.9) who represented 80% of the malignant brain cancer cases included in this analysis. We also conducted co-pollutant analysis by mutually adjusting for UFP and kriging air pollutant estimates (10). Deviations from the Cox proportionality hazard assumptions were checked using an analysis of Schoenfeld residuals and we found no violation of this assumption. Quadratic terms for UFP exposure were not statistically significant, suggesting that linear models were appropriate. Subgroup analyses were conducted to assess differences in associations by self-reported race/ethnicity recognizing race/ethnicity as a social construct that captures different lived experiences resulting from fundamental causes of health inequities as structural racism (34,43). We tested for heterogeneity of effect estimates by including an interaction term between UFP and race/ethnicity in the model using a global test of interaction.

Results

Characteristics of the MEC participants included in this analysis are shown in Table 1. African Americans and Latin Americans represented ~75% of the study participants. As expected, there was a predominance of women among meningioma cases. None of the covariates were significantly associated with risk for malignant brain cancer while risk of meningioma was significantly higher among college graduates, those with a history of hypertension, ex-smokers, and women who reported a history of surgical menopause.

Table 2 presents the distribution (estimated annual mean, 95% CI and range) of UFP levels for MEC participants at baseline and during follow-up. Mean baseline and follow-up UFP levels were highest among African American participants whereas the levels in the other racial/ethnic groups were more similar. Nevertheless, there was a large range in UFP exposures in each of the racial/ethnic groups; baseline UFP range (particles/$cm^{3)}$) was highest in Latin Americans (320 to 73,630) and African Americans (450 to 70,250), intermediate in European Americans (300 to 64,830), and lowest in Japanese Americans (510 to 55,750). A similar pattern was observed for UFP exposures at follow-up. The percent of any addresses in the impact area versus in the grid area was highest for African Americans (91.0%), intermediate in Latin Americans (71.9%), and lowest for Japanese (62.0%) and European Americans (54.5%). Baseline annual mean UFP levels (particles/cc^3) were higher in the impact zone than in the modeled grid area (Table 2), but this difference was smallest among African Americans (9,260 vs 8,520, 9%), intermediate for Latin American (5,990 vs 4,860, 23%) and Japanese (5,700 vs 4,450, 28%), and largest in European Americans (6,820 vs 4,560, 53%). Comparable results were observed during the follow-up period (Table 2). Similar patterns were observed comparing all addresses in grid vs all addresses in impact zone (Supplementary Table 1)

Risk estimates for brain cancer in relation to UFP exposure based on subjects with any addresses in the grid and impact zone are shown in Table 3. In all subjects, risk of malignant brain cancers increased 12% and 8%, respectively, per IQR increase in UFP when we considered any addresses in the grid and in the impact zone. There were suggestive but statistically nonsignificant differences in the HR estimates by race/ethnicity; HRs were less than 1.0 in European Americans and Japanese Americans, slightly elevated in Latin Americans (HR =1.15 (grid) vs 1.11 (impact zone)), and statistically significantly increased in African Americans (HR= 1.32 (grid) vs 1.36 (impact zone)) (Table 3, top; p heterogeneity = 0.17 for HRs (grid) and 0.35 for HRs (impact zone)). HR results for all addresses in the grid or impact zone were similar (Supplementary Table 2). Analyses conducted among non-movers showed slightly higher hazard ratios in all subjects combined with all of their addresses in the grid (HR=1.12, 95% CI 0.97–1.31). Risk estimates for African American non-movers remained statistically significant with HRs of 1.39 (95% CI 1.08–1.80) and 1.49 (95% CI 1.07–2.06) for those with all of their addresses contained within the grid and impact zone, respectively (Table 3). Effect estimates for UFP and brain cancer risks did not differ by sex. For any address in the grid the HR was 1.06 (95% CI 0.86–1.31) in men and 1.16 (95% CI 0.99–1.35) in women ($P_{heterogeneity}$=0.54). Results were largely unchanged when we restricted the analyses to gliomas only (C71.0–C71.9). In all racial/ethnic groups combined, the HR was 1.12 (95% CI 0.98–1.27) for any address in the grid (145 gliomas) and 1.08 (95% CI 0.90–1.30) for any address in the impact zone (104 gliomas). The corresponding HRs for gliomas only among African Americans were 1.35 (95% CI 1.08–1.68) and 1.40 (95% CI 1.05–1.85), respectively.

In contrast, UFP exposure was not associated with risk of meningioma in all subjects (all HRs were around 1.0) or by race/ethnicity (Table 3, bottom). The null results were observed in both men and women despite the nearly three times more meningioma cases in women than in men. In men, for any address in the grid, the HR for meningioma was 0.98 (95% CI 0.80–1.20) and it was 0.99 (95% CI 0.89–1.09) in women ($P_{heterogeneity}$=0.96).

UFP exposure was slightly negatively correlated with kriging NO_2 (rho= −0.12), PM_{10} (rho=−0.19), $PM_{2,5}$ (rho=−0.10), and ambient benzene (rho=−0.03) and was slightly positively correlated with kriging NO_x (rho=0.07), O_3 (rho=0.05), and CO (rho=0.05). These kriged estimates for gaseous and particulate pollutants as well as ambient benzene were obtained from routine continuous air monitoring data in California (10). In co-pollutant analyses conducted in all subjects combined (Table 4), the effect of UFP remained unchanged with adjustment for benzene. The HR of UFP (any address in the grid) remained stable and was 1.12 in each of the co-pollutant model run which adjusted for NO_x, NO_2, CO, or O_3; and was 1.14 (95% CI 1.00–1.30) and 1.14 (95% CI 1.00–1.30), with adjustment for PM_{10} or $PM_{2.5}$, respectively. Other pollutants (benzene, NO_x, NO_2, CO, O_3, PM_{10}, $PM_{2,5}$) were not associated with brain cancer risk in the co-pollutant models but some of the HRs had very wide confidence intervals and the risk estimates were reduced slightly compared to our earlier publication because of a smaller number of brain cancer cases with airport-related UFP data. For example, with adjustment of UFP, the effect of ambient benzene was reduced to 1.42 (95% CI 0.76–2.66) in the co-pollutant model based on 154 brain cancers whereas the HR for benzene was 1.65 (95% CI 0.98–2.78) in our published results which included 199 brain cancer cases (10). The corresponding HR estimates for UFP among African

Americans also remained similar and statistically significant with adjustment for other kriging pollutants.

Discussion

We observed a small increase in risk of malignant brain cancer in relation to airport-related UFP in all subjects. This increase appeared to be driven by the results in Latin Americans and African Americans, who are disproportionately exposed to high UFP concentrations as well as burdened by structural racism which contributes to environmental, occupational, economic, access to health care, and other inequities (34,43). We observed a formally statistically significant association in African Americans, the subgroup with the highest UFP exposures across follow-up and the highest concentration of residents within the modeled UFP exposure grid as displayed in Figure 1. The results were somewhat stronger when the analyses were restricted to non-movers despite a reduction in sample size and the association persisted when we adjusted for gaseous and particulate matter co-pollutants. The findings in non-movers provide support for the assumption that relative airport-related UFP exposure rankings over this period remained the same and that our UFP model adequately captured the effects of flight activity trends at LAX despite lacking data reflecting possible changes in UFP emissions. We found no evidence for a link between UFP exposure and meningioma, either in all subjects or in any of the racial/ethnic subgroups. Given that causes of malignant brain cancer remains poorly understood with very few established risk factors (2,44), these results on UFP and risk of brain cancer are potentially important if confirmed in future studies as there is growing evidence that outdoor air pollution may have adverse effects on numerous cancers sites including the brain (17).

Our results for malignant brain cancer and UFP exposure are consistent with results from a Canadian study of within-city spatial variations in ambient UFPs (16) where distances to the nearest highway, the nearest bus route, and Pearson airport explained about two-thirds of the measured variation in ambient UFPs (45). Our HR estimate of 1.12 (95% CI 0.98–1.27) per 5280 particle/cm^3 (or 1.23 per 10,000 particle/cm^3) for all subjects with any of their addresses in the grid is compatible with the estimate of 1.11 (95% CI 1.04–1.19) per 10,000 particle/cm^3 of UFPs reported in the Canadian study. The overall consistency of findings is noteworthy despite the differences in UFP exposure assessment between studies. The Canadian study used a LUR Smodel derived from mobile monitoring data collected in 2010–2011, and assigned UFP exposures as 3-year moving averages with 1-year lag. The mean estimated UFP levels in the Canadian study were ~24,000 particles/cm^3, compatible with estimates of urban background UFP levels (46), whereas the airport-related UFP levels along flight paths in this study were ~70,000 particles/cm^3. Results from one of the first studies to interrogate UFP profiles associated with aircraft and roadway traffic lend further support (27). Austin and investigators noted that although concentrations of total UFPs were higher near roadways compared to near-airport transects, the roadway UFP likely only affect a narrow strip of near-roadway residences because of the relatively short distances over which UFP decays downwind of major roads. In contrast, the areas experiencing elevated aircraft UFPs tended to be large with concentrations more homogenously distributed around airports and these elevated particle number concentrations may affect far more people around airports for this reason than roadway sources. In addition, those living within the area

affected by landing aircraft emissions may be exposed to relatively higher concentrations of smaller sized UFPs (27).

It is of note that our findings of an association between UFP exposure and malignant brain cancer among African Americans was formally statistically significant as this was based on a modest number of cases (n=38). While the unit for risk calculations (i.e., overall IQR) was identical for all racial/ethnic specific analysis, UFP exposure was 40–90% higher for African Americans than the other groups at baseline and during follow-up and their higher exposure may be one reason for the observed results. Air pollutants and specifically UFP may affect the CNS either directly through the transport of nanosized particles into the CNS or secondarily through systemic inflammation. The direct or indirect effects can be caused by the physical characteristics of the particle itself or by toxic compounds that adsorb on these nanoparticles (47,48). A recent study of Narita Airport in Japan found airport-related nanoparticles may have a unique toxicity profile due to unburned lubrication oil being mixed via bypass flow with hot exhaust, unlike vehicular generated UFP where all oils are combusted (49). Also in a recent study, continuous exposure of ultrafine particulates in the form of an airborne fungal allergen triggered innate inflammatory responses not only in the lung but also the brain (50). Thus, while the exact mechanisms underlying brain pathology induced by air pollution are not fully understood, evidence currently points to the involvement of neuroinflammation, oxidative stress, glial activation, and cerebrovascular damage as primary pathways (51–53).

Despite having almost three times more meningioma cases for analysis, there was little evidence of an effect of UFP on risk of meningioma. We are not aware of previous findings on UFP and meningioma but results on air pollution and benign brain tumors were largely null in two large European studies (7,9) and suggestive positive associations were reported only in a small Danish study of nurses (11). Results to date on air pollution and risk of malignant brain cancer are also mixed. A small increased risk of malignant brain cancer and exposure to $PM_{2.5}$ was reported in a majority (10,12,14,15,54) of studies with such data but not all (7,9–16). Although $PM_{2.5}$ overall was unrelated to malignant brain cancer risk in the ESCAPE cohort, there was a 67% (95% CI 0.89–3.14) elevated risk in association with $PM_{2.5}$ absorbance which the authors suggested may be a better proxy for traffic-related particles in the UFP size range(9). Exposure to NO_x was associated with brain cancer risk in the Danish Diet and Health Cohort (6) but this finding was not confirmed in subsequent European studies (7,9,11), two of which had much larger sample sizes. NO_2 exposure was weakly positively associated with malignant brain cancer risk in a large Danish registry study (7) but this was not observed in other studies (9–11,13,14,16). Differences in study design, methods of air pollution exposure assessment, the specific pollutants examined, modest number of brain cancers, study population variations including differences in the distribution of histologic subtypes by sex and race/ethnicity, as well as known etiologic heterogeneity of brain tumor subtypes, contribute to the complexity of these investigations. There are other challenges in conducting and interpreting results from these air pollutant analyses. For example, our findings of a stronger UFP association among African Americans in the current analysis but a prior stronger finding of benzene, PM_{10} and O_3 among Latin Americans (10) highlight that these subgroup differences by race/ethnicity may be related to differences in exposure patterns to air pollutants, related cofactors such as occupation and

neighborbood SES. Although we adjusted for neighborhood SES at cohort entry and at event time, we still observed differences in air pollution exposures by race/ethnicity, which can be viewed as a proxy for residential segregation, neighborhood disinvestment and increased air pollution exposure (34,43). Nevertheless, consistent results from this analysis and from the Canadian study (16) emphasize the importance of further studies of UFP from all sources as well as components of particulate matter in relation to risk of brain cancer development (54).

Study strengths include our investigation of both malignant and benign brain tumors in men and women of multiple races/ethnicities, including large number of African Americans and Latin Americans, who have faced long-standing structural racism, social isolation, and differential treatment (34,43) and adjusted for potential confounders as well as other air pollutants. Information on covariates was complete with little missing data and none of the covariates were associated with risk of brain cancer in the MEC, consistent with the few known risk factors for malignant brain cancer (2). The availability of a long-term residential address history enabled us to generate better exposure estimates as suggested by the strongest effect sizes estimated in those for whom all of their addresses were located in the grid or impact zone and among non-movers. However, there are study limitations. As in other studies, we lacked information on UFP exposures prior to cohort entry and were not able to assess air pollution exposures at work places or during commuting. The number of malignant brain cancer cases were modest and multiple tests were conducted; we recognize that results may be due to chance and/or uncontrolled confounding of individual-level SES. We assessed airport-related UFP, which limited the number of participants to 74% (75,936 of 103,308) of the original study population in California (the Hawaii component of the MEC was not included in studies on air pollution). Although participants included in the UFP analyses were similar to those not included in most of the baseline demographic and lifestyle factors, excluded subjects were more likely to be from neighborhoods of high socioeconomic status (nSES Q4 and Q5) (43.0% men, 39.0% women) compared to those included in the analyses (high nSES: 26.8% men, 24.4% women) (Supplementary Table 3). This is partly related to the residential addresses of those we excluded who lived outside the LAX UFP grid area. We carefully considered nSES at baseline and event time in our analysis and found that the correlations of nSES over time were comparable by race/ethnicity (rho was 0.66 in Japanese Americans, 0.68 in African Americans and Latin Americans, and 0.71 in European Americans), and that changes in nSES during follow-up across these racial/ethnic groups were modest. Although we did not directly measure traffic-related UFPs in this study, our co-pollutant models adjusted for NO_2 exposure as a surrogated for traffic-related pollutants including traffic-related UFPs. Finally, to our knowledge there is no information on how aircraft UFP emissions have changed since the 1960s. Hence, there are caveats with the use of absolute values of UFP concentrations in our HR analyses. We used a conversion factor to estimate particle number concentrations based on a comparison of the AERMOD dispersion model predictions with 2013 data. While modeling showed small differences in the spatial exposure pattern over time, the absolute concentrations within these spatial patterns may have changed. Thus, the uncertainties of the conversion factors for historical estimates of particle number concentrations may lead to exposure misclassification for UFP. Yet, this bias is likely to be non-differential in affecting our risk estimate and the same bias applies to all racial/ethnic groups included in this

analysis. As such, this likely has contributed to larger exposure misclassification for movers compared to non-movers and may explain why non-movers showed stronger associations.

In conclusion, results from this prospective study suggest that high airport-related UFP exposure is associated with risk of malignant brain cancer. We have captured airport-related UFP as an important source of air pollutant exposure. Further investigation into the role of UFP from additional sources may help to better understand links between air pollutants and malignant brain cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AERMOD	American Meteorological Society/Environmental Protection Agency Regulatory Dispersion Model
CA	California
CNS	central nervous system
CI	confidence interval
HI	Hawaii
HR	hazard ratio
IQR	interquartile range
LAC	Los Angeles County
LAX	Los Angeles International Airport
LUR	land use regression
MEC	Multiethnic Cohort
nSES	neighborhood socioeconomic status
SEER	Surveillance, Epidemiology, and End Results Program
UFP	ultrafine particles

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Significance

Malignant brain cancer risk increases with airport-related ultrafine particle (UFP) exposure, particularly among African Americans, suggesting UFP exposure may be a modifiable risk factor for malignant brain cancer.

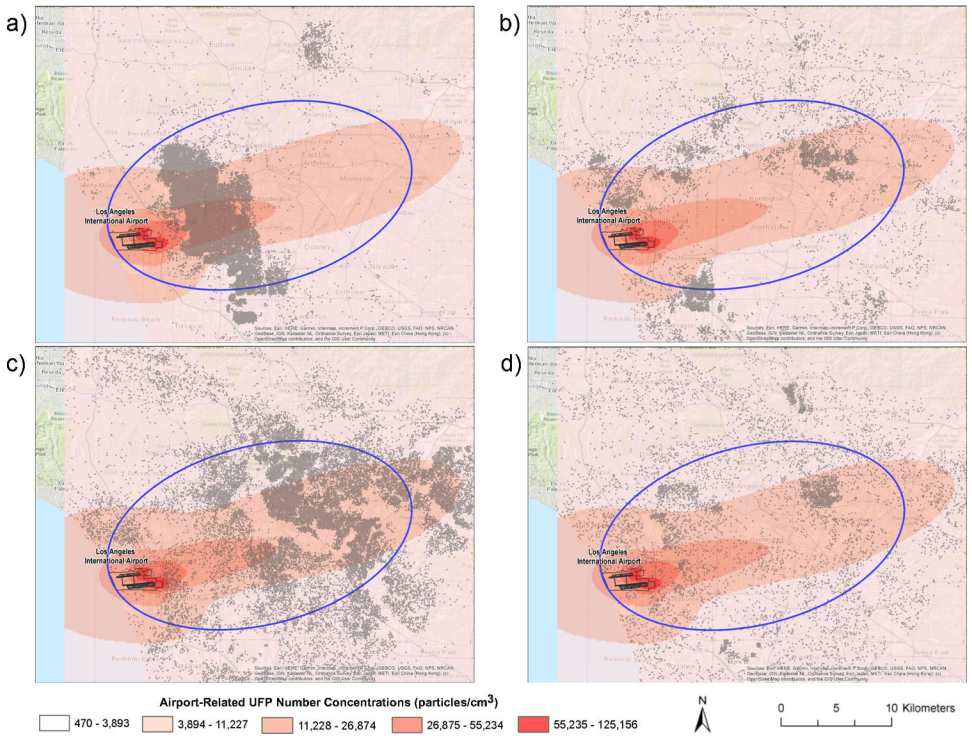

Figure 1.

(panels A-D). Airport-related ultrafine particle (UFP) exposure estimates (particles/cm^3; see Methods) for a 53 × 43 kilometer grid area around the Los Angeles International Airport (1993–2013). Natural breaks were used to classify five UFP exposure categories displayed in gradations of red. For privacy reasons, residential locations of MEC participants at baseline (1993–1996) were randomly offset up to 350 meters for: a) African Americans (n=25,398), b) Japanese Americans (n=9,532), c) Latin Americans (n=31,568), and d) European Americans (n=9,328). The impact UFP zone was defined as an oval with an aspect ratio of 2:1 aligned along with the orientation of the airport runways and predominate daytime wind direction, with one, long-axis edge aligned with the upwind airport property line. The long axis represented the distribution of maximum centerline UFP concentrations for all the July months between 1993 and 2013, while the impact zone encompassed a subset of subjects with higher exposures than the modeled grid. The major axis length was extended until centerline maximum UFP concentrations decreased to 1,500 particles/cm^3. The natural breaks were used to facilitate the visualization of UFP number concentrations that had a highly right-skewed distribution.

Table 1.

Baseline characteristics of 75936 study participants (1993–1996) considered in analyses on risk of brain cancer and meningioma and exposure to airport-related ultrafine particles

Baseline characteristics	All cohort (n=75936)	Brain cancer (n=155)		Meningioma (n=420)	
		N	HR (95% CI) [a]	N	HR (95% CI) [a]
Mean age at cohort entry (SD)	60.5 (8.3)		61.5 (7.7)		62.3 (7.9)
Gender					
Men	32009	64	1.39 (0.16–11.75)	94	**0.24 (0.10–0.60)**
Women	43927	91	1.0	326	1.0
Race/ethnicity [b]					
African American	25398	38	0.70 (0.45–1.08)	170	1.07 (0.84–1.37)
Japanese American	9532	19	0.76 (0.45–1.08)	30	0.57 (0.38–0.87)
Latin American	31568	72	1.0	168	1.00
European American	9328	26	1.16 (0.73–1.97)	52	1.00 (0.71–1.40)
Education					
≤ High school	39312	78	1.00	210	1.00
Some college	21413	38	0.96 (0.62–1.47)	127	**1.32 (1.03–1.69)**
College graduate	7446	12	0.86 (0.44–1.67)	32	1.08 (0.72–1.63)
Graduate/professional	6564	21	1.62 (0.92–2.86)	44	**1.57 (1.89–2.27)**
Missing	1201	6	2.37 (0.90–6.23)	7	1.02 (0.46–2.29)
Baseline neighborhood SES [b]					
Quintile 1 (low)	21058	35	1.00	124	1.00
Quintile 2	20658	35	0.93 (0.56–1.56)	127	1.03 (0.79–1.36)
Quintile 3	14867	28	0.98 (0.54–1.77)	76	0.85 (0.61–1.19)
Quintile 4	12490	43	1.70 (0.93–3.13)	59	0.76 (0.51–1.11)
Quintile 5 (high)	6838	14	1.02 (0.45–2.32)	34	0.78 (0.45–1.29)
Current (at event) neighborhood SES					
Quintile 1 (low)	16847	27	1.00	97	1.00
Quintile 2	17803	33	1.11 (0.64–1.93)	99	0.98 (0.72–1.32)
Quintile 3	16597	34	1.13 (0.62–2.05)	98	1.15 (0.83–1.59)

Baseline characteristics	All cohort (n=75936)	Brain cancer (n=155)		Meningioma (n=420)	
		N	HR (95% CI) [a]	N	HR (95% CI) [a]
Quintile 4	12901	41	1.43 (0.75–2.70)	68	1.14 (0.78–1.67)
Quintile 5 (high)	7712	17	1.02 (0.47–2.24)	46	1.31 (0.83–2.07)
Missing	4076	3	0.37 (0.11–1.25)	12	0.50 (0.27–0.92)
Occupation					
No industry-office/professional	32138	71	1.00	174	1.00
No industry- labor/craftsman	10183	27	1.25 (0.76–2.07)	55	1.16 (0.83–1.63)
No industry- office and or labor/craftsman	20069	36	0.82 (0.53–1.29)	130	1.14 (0.88–1.47)
Yes industry- office/professional	3076	4	0.59 (0.21–1.63)	11	1.00 (0.54–1.85)
Yes industry- labor/craftsman	8234	14	0.81 (0.43–1.54)	36	1.19 (0.80–1.77)
Yes industry- missing occupation	2236	3	0.66 (0.20–2.17)	14	1.73 (0.98–3.05)
History of high blood pressure					
No	43812	98	1.00	212	1.00
Yes	32124	57	0.86 (0.61–1.22)	208	**1.27 (1.04–1.56)**
Body mass index (kg/m^2)					
<25	25612	53	1.00	131	1.00
25–<30	31125	63	1.00 (0.68–1.46)	162	0.95 (0.75–1.21)
≥30	18617	38	1.12 (0.72–1.76)	121	1.06 (0.81–1.38)
Missing	582	1	0.85 (0.11–6.27)	6	1.74 (0.76–4.00)
Smoking history					
Never smoker	32775	74	1.00	191	1.00
Ex-smoker	28308	54	0.89 (0.62–1.29)	156	**1.25 (1.00–1.56)**
Current smoker,	13113	21	0.91 (0.55–1.50)	62	1.21 (0.90–1.63)
Missing	1740	6	1.07 (0.40–2.83)	11	0.97 (0.50–1.88)
Use of birth control pills[c]					
No	35391	78	1.00	267	1.00
Yes	8536	13	0.76 (0.41–1.39)	59	1.10 (0.82–1.49)
Age at first live birth[c]					
Nulliparious	5576	10	1.00	37	1.00
<20 years	15666	39	1.65 (0.81–3.38)	114	1.06 (0.72–1.55)

Table 2.

Distribution (estimated mean (95% CI), and range) of airport-related ultrafine particles (UFP) (particles/cm^3) for 12 months at baseline (1993–1996) and follow-up period (1993–2013) in 75,936 MEC participants overall and by race/ethnicity for any address in the grid and impact zone

	Time period of	Any address in grid		Any address in impact zone		% of any address in impact zone vs grid
Participants		**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
All	N addresses	75,936 125,330		55,088 94,426		
	Mean UFP[a]	5590	6720	7390	8180	75.3
	95% CI	5950, 6040	6680, 6760	7340, 7450	8130, 8230	
	Range	300 to 73630	580 to 77220	490 to 73630	1140 to 77220	
African Americans	N addresses	25,398 42,598		22,829 38,763		
	Mean UFP[a]	8520	9750	9260	10,550	91.0
	95% CI	8440, 8600	9660, 9830	9170, 9350	10460, 10640	
	Range	450 to 70,250	580 to 65,700	550 to 70,250	1230 to 65,700	
Latin Americans	N addresses	31,568 55,104		21,637 39,614		
	Mean UFP[a]	4860	5310	5990	6390	71.9
	95% CI	4800, 4910	5260, 5360:	5920, 6060	6330, 6460	
	Range	320 to 73,630	610 to 77,220	490 to 73,630	1140 to 77,220	
Japanese Americans	N Addresses	9,532 13,102		5,640 8,126		
	Mean UFP[a]	4450	4900	5700	6100	62.0
	95% CI	4370, 4530	4830, 4970	5590, 5810	6000, 6210	
	Range	510 to 55,750	830 to 58,000	630 to 55,750	1270 to 58,000	
European Americans	N Addresses	9,328 14,363		4,928 7,833		
	Mean UFP[a]	4560	5130	6820	7400	54.5
	95% CI	4450, 4670	5020, 5240	6640, 7000	7230, 7600	
	Range	300 to 64,830	830 to 69,100	600 to 64,830	1260 to 69,100	

[a]Mean levels of UFP, corresponding 95% CI, and ranges were rounded

Table 3.

Risk[a] of brain cancer and meningioma in association with per interquartile range (IQR)[b] of airport-related ultrafine particle exposure (particle/cm^3) in all subjects and non-movers

Malignant		All subjects		Non-movers	
Brain Cancer		**Any address in grid[b]**	**Any address in impact zone[b]**	**All addresses in grid[b]**	**All addresses in impact zone[b]**
All	#cases	155	113	121	87
	HR (95% CI)	1.12 (0.98–1.27)	1.08 (0.91–1.29)	1.12 (0.97–1.31)	1.09 (0.88–1.34)
African Americans	#cases	38	36	28	26
	HR (95% CI)	**1.32 (1.07–1.64)**	**1.36 (1.03–1.79)**	**1.39 (1.08–1.80)**	**1.49 (1.07–2.06)**
Latin Americans	#cases	72	53	53	40
	HR (95% CI)	1.15 (0.96–1.38)	1.11 (0.86–1.44)	1.14 (0.89–1.45)	1.03 (0.70–1.50)
Japanese Americans	#cases	19	11	18	10
	HR (95% CI)	0.90 (0.40–2.05)	0.61 (0.17–2.14)	0.87 (0.35–2.14)	0.58 (0.16–2.20)
European Americans	#cases	26	13	22	11
	HR (95% CI)	0.56 (0.27–1.23)	0.18 (0.03–1.16)	0.69 (0.35–1.39)	0.26 (0.04–1.95)
$P_{heter(race)}$		0.17	0.35	0.25	0.13
Meningioma					
All	#cases	420	301	315	218
	HR (95% CI)	0.98 (0.90–1.08)	1.00 (0.89–1.13)	0.98 (0.88–1.09)	1.00 (0.87–1.15)
African Americans	#cases	170	157	125	111
	HR (95% CI)	0.98 (0.86–1.11)	0.96 (0.82–1.12)	1.00 (0.85–1.15)	0.97 (0.81–1.17)
Latin Americans	#cases	168	103	119	68
	HR (95% CI)	1.07 (0.91–1.26)	1.13 (0.93–1.38)	1.02 (0.82–1.27)	1.07 (0.81–1.42)
Japanese Americans	#cases	30	14	28	13
	HR (95% CI)	0.87 (0.45–1.70)	1.34 (0.77–2.34)	0.88 (0.45–1.71)	1.22 (0.65–2.29)
European Americans	#cases	52	27	43	22
	HR (95% CI)	0.98 (0.75–1.27)	0.96 (0.66–1.40)	1.00 (0.77–1.39)	1.04 (0.71–1.53)
$P_{heter(race)}$		0.82	0.43	0.66	0.88

[a]All models were stratified by age at entry (in 1 year category) and adjusted for sex, education, baseline and current neighborhood SES, and race/ethnicity for analyses in all subjects combined. Race/ethnicity was excluded in analyses stratified by race/ethnicity.

[b]The IQRs of UFP (particle/cm^3) were 5280 for any address in grid, 5390 all addresses in grid, 6300 any address in impact zone and 6490 all addresses in impact zone.

Table 4.

Risk[a] of brain cancer in association with per interquartile range (IQR) [b] of ultrafine particle (UFP) exposure (particle/cm^3) and kriging gaseous and particulate matter pollutants in all subjects combined

#Brain cancers/cohort	Any address in grid 155/75936 HR (95% CI)	Any address in impact zone 113/55088 HR (95% CI)
UFP (per IQR)	1.12 (0.98–1.27)	1.08 (0.91–1.29)
NOx (per 50ppb) [c]	1.20 (0.50–2.92)	1.03 (0.34–2.09)
UFP (per IQR)	1.12 (0.98–1.28)	1.07 (0.89–1.29)
NO_2 (per 20ppb) [c]	1.10 (0.37–3.25)	0.77 (0.20–2.96)
UFP (per IQR)	1.12 (0.98–1.27)	1.09 (0.91–1.30)
CO (per 1000ppb) [c]	1.64 (0.42– 6.38)	1.39 (0.27–7.20)
UFP (per IQR)	1.12 (0.99–1.28)	1.10 (0.92–1.31)
Ozone (per 10ppb) [c]	0.68 (0.24–1.91)	0.63 (0.17–2.29)
UFP (per IQR)	**1.14 (1.00–1.30)**	1.08 (0.90–1.29)
PM_{10} (per 10 μg/m^3) [c]	1.54 (0.77–3.10)	0.94 (0.37–2.40)
UFP (per IQR)	**1.14 (1.00–1.30)**	1.08 (0.90–1.30)
$PM_{2.5}$ (per 10 μg/m^3) [c]	3.31 (0.56–19.5)	1.05 (0.12–9.50)
UFP (per IQR)	1.12 (0.99–1.28)[d]	1.09 (0.92–1.31)[d]
Benzene (1ppb) [c]	1.42 (0.76–2.66)	1.36 (0.60–3.10)

[a] All models were stratified by age at entry (in 1 year category) and adjusted for sex, education, baseline and current neighborhood SES, and race/ethnicity.

[b] The IQRs of UFP (particle/cm^3) were 5280 for any address in grid and 6300 any address in impact zone.

[c] The distributions (mean, range) for co-pollutants are: NOx (66.6, 31.1–188.7), NO_2 (30.1, 17.8–54.4), CO (1003.4, 461.9–2951.4), ozone(22.1, 6.6–39.0), PM_{10}(35.8, 25.5–57.4), $PM_{2.5}$ (16.9, 11.3–24.6), and benzene (0.96, 0.33–4.51)

[d] Any address in grid analysis was based on 154 brain cancers/75561 cohort and any address in impact zone analysis was based on 113 brain cancers/55088 cohort because we considered as valid benzene data if they were derived from air monitors within 20 km from residential addresses (Wu et al., Ref 10).