The Role of Ambient Particulate Matter Air Pollution in Cutaneous Malignant Melanoma and Non-Melanoma Skin Cancer in the Women's Health Initiative

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Abstract

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Introduction: The incidence rates of non-melanoma skin cancer (NMSC) and cutaneous malignant melanoma are rapidly increasing. While inhaled particulate matter (PM) has been classified as a lung carcinogen, the associations between ambient PM (either $PM_{2.5}$ and PM_{10}) and skin cancers have not been studied thoroughly. This study evaluated the associations between $PM_{2.5}$ and PM_{10} and incidence of cutaneous malignant melanoma and NMSC of postmenopausal women in the Women's Health Initiative Observational Study.

Methods: Annual particulate matter exposure levels for the subjects were estimated previously from geostatistical spatial correlation models using data from the EPA Air Quality System national monitoring network and the IMPROVE network along with 171 GIS-based geographic covariates. Participants were excluded if they were non-Caucasian, had a previous history of melanoma or NMSC at baseline, had missing air pollution predictions, had missing covariate data, had missing follow-up time, were cases of melanoma or NMSC prior to the first 4 years of follow-up, or were lost to follow-up prior to the first 4 years. Cox proportional hazards models controlling for various sets of covariates, including daily ultraviolet (UV)-B radiation (wavelengths 280 - 315 nm) through watts, were generated to evaluate the

relationships between PM and the skin cancers. Sensitivity analyses were conducted to test the robustness of results by using 5-, 7-, and 10 year-PM averages and adjusting for all sun-related covariates.

Results: Study participants had a mean follow-up time of 16 years, with a maximum of 23 years. There were 787 adjudicated cases of first occurrence of cutaneous melanoma and 5419 self-reported cases of first occurrence of NMSC. After adjusting for multiple covariates, an increased risk of NMSC by 20% (95% CI: 7 – 36) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ was observed. All other effect estimates were consistent with no association of ambient PM air pollution and increased risk of skin cancer. The findings were robust to the multiple sensitivity analyses conducted.

Discussion: This epidemiological study is the first study to examine the role of ambient PM air pollution in skin cancer incidence in the United States. With its validated exposure predictions and large sample size, the study findings add to the evidence that $PM_{2.5}$ exposure may increase the risk for cancers other than lung cancer. However, biases may remain due to potential confounding, exposure measurement error, and self-reporting of NMSC. Further studies are necessary to determine the impacts of co-pollutants, improve estimation of exposure to UV radiation, and examine the effects of PM on NMSC and melanoma incidence in younger women.

INTRODUCTION

Skin Cancers

Cutaneous malignant melanoma (CM) is a skin cancer arising from a melanocyte. Melanocytes are located in the stratum basale of the epidermis and produce melanin through melanogenesis. Melanin is responsible for pigmentation of the skin and also for the protection of the hypodermis against damage from ultraviolet (UV)-B radiation (wavelengths 280 - 315 nm) and UV-A radiation (315 – 400 nm)[1]. Due to this, highly pigmented skin is protected from UV-induced carcinogenesis by approximately 500 to 1000 fold[2]. Melanocytes are also considered as immune cells as they share similarities with dendritic cells such as phagocytic capabilities, production and release of cytokines, and presentation of antigens to T cells[1]. Cutaneous melanoma is the main cause of death from skin cancer, however, if detected early, is easily diagnosed and treated through skin biopsy and surgical management with wide local excision[3].

Cutaneous melanoma was reported in 2018 as the 21st most common cancer in the world[4]. Furthermore, each year, the incidence rate of melanoma has been rising 1.5% over the previous 10 years and the number of melanoma related deaths has been steadily increasing in the United States[5] with an age-standardized mortality rate of 1.2 per 100,000 for women and 2.6 per 100,000 for men in North America based on 2012 statistics[6]. The National Society for Cutaneous Medicine's report from 2016 estimates the current lifetime risk of developing invasive or in situ melanoma in the US as 1 in 28[7]. The incidence rate of melanoma increases with age. Other significant risk factors for developing melanoma include being of male sex, lighter skin pigmentation, family history of melanoma, history of sunburns, indoor tanning use, exposure to UV radiation, and childhood sun exposure[8]. Due to melanin's protective factor, melanoma is much more common among Caucasians with incidence rates of 33.0 per 100,000 men and 20.2 per 100,000 women compared to African Americans with incidence rates of 1.2 per 100,000 men and 1.0 per 100,000 women[9]. Approximately 100,350 new cases of cutaneous melanoma are

estimated to occur in 2020 with the median age at diagnosis being 65 and median age of death due to CM being 71.[5]

Non-melanoma skin cancer (NMSC) encompasses multiple cancers such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), Merkel cell carcinoma, and cutaneous T-cell lymphoma. However, 70% of NMSC cases are BCC and 25% of NMSC cases are SCC. Basal cell carcinoma is a slow growing tumor, arising from the abnormal growth of long-term keratinocyte progenitor cells of the epidermis. The majority of the keratinocyte mutations (approximately 76%)[10] that cause tumorigenesis are UV-B radiation induced. Squamous cell carcinoma is also a slow growing tumor with a relatively low rate of metastases, but it originates from epidermal keratinocytes or pilosebaceous units and eccrine glands. Similar to BCC, SCC often arises from UV radiation induced mutations but an infection with human papillomavirus may also induce squamous cell tumors. It is believed that for both SCC and BCC, mutations occur in epidermal p53 genes, leading to the inhibition of apoptosis of abnormal cells[11].

NMSCs are very common (at a prevalence of 0.7% in the United States) but have good prognoses when detected at early stages. Risk factors for NMSC include genetic susceptibility, male gender after age 45, previous diagnosis of NMSC, and skin reaction to sun; however, the most important risk factor is UV radiation and sun exposure[12]. The risk of developing a subsequent BCC or SCC within 3 years of initial diagnosis of NMSC is quite high, up to 41 to 45% in the Caucasian population[11].It is estimated that treatment costs for 5 million NMSC patients averaged $8.1 billion per year in the years 2007 to 2011[13].

With annual increases in the incidence rates of both CM and NMSC, it is expected that the economic burden of the two cancers will rise as well. Although outdoor sun exposure is the most important risk factor for both cancers, it is important to determine whether other ambient environmental exposures may also be playing a significant role in the growing incidence of these cancers.

Ambient Particulate Matter Air Pollution

Air pollution is the presence of harmful pollutants in the atmosphere, such as particles and gaseous compounds. The adverse health effects of air pollution have become an alarming public health concern with increases in exposure associated with higher burden of disease. Through damage to the cardiovascular and respiratory systems, air pollution is estimated to cause two million deaths globally per year. Particulate matter (PM) in air pollution is classified by aerodynamic diameter. PM with an aerodynamic diameter of 10 μm or under is PM_{10} and PM with an aerodynamic diameter of 2.5 μm or under is $PM_{2.5}$. PM_{10} and $PM_{2.5}$ are commonly emitted from traffic due to suspended road dust and vehicle exhaust. They are also abundantly emitted from industrial sources (mining, construction, solid-fuel combustion) and natural sources (volcanoes, forest fires, storms)[14].

Trends in ambient air pollution data have shown that the average annual $PM_{2.5}$ and PM_{10} levels in the United States have been decreasing with an approximate 39%[15] and 31%[16] decrease between 2000 to 2018. However, recent research has indicated that wildfires may be causing an increase in $PM_{2.5}$[17] and PM_{10}[16] concentrations within the Northwestern US. This will have adverse health implications in the future as human-caused climate change continues to drive wildfires in the western US. Approximately 4.2 million hectares of forest fire area between 1984 and 2015 have been attributed to anthropogenic climate change[18]. With annually growing wildfire-affected areas and lengthening wildfire seasons, it will be important to continue to analyze adverse health effects that may be associated with particulate matter air pollution.

Pathophysiologic and Immune Effects of Particulate Matter

Inhalation exposure to PM has been shown to induce inflammation. Epidemiologic studies have indicated strong associations of PM with pulmonary and cardiovascular inflammatory diseases such as chronic obstructive pulmonary disease (COPD), asthma, pneumonia, ischemic heart disease, congestive

heart failure, and stroke[19]. Moreover, inflammatory biomarkers such as increased neutrophils and IL-8 levels have been characterized in nasal or bronchoalveolar lavage for pulmonary PM-induced respiratory diseases. PM can also elicit a systemic inflammatory state in the body, as evidenced by increases in C-reactive protein levels[20], cytokine levels (IL-6, IL-8, IFN-γ, TNF-α), and white blood cells[21] after acute and chronic PM exposures.

The adverse impacts of PM on the cardiovascular and respiratory systems have been fervently researched over multiple decades; however, the health effects of PM on the skin have just started to be examined thoroughly. It is proposed that there are two pathways in which particulate matter can penetrate the epidermis: 1) through the hair follicle and sweat glands and 2) across the stratum corneum through intercellular or transcellular movement[22]. In barrier-disrupted skin, it is believed that particles may penetrate passively as well as break down the barrier further by disrupting essential tight junctions[23] and down-regulating filaggrin in keratinocytes[24]. Additionally, studies suggest that when particles are inhaled, ultrafine particles ($PM_{0.1}$) may diffuse through the alveolar-capillary membrane to be transported via the bloodstream to the whole body, carrying great potential for systemic, including dermatologic, and immune toxicity[25].

Furthermore, $PM_{2.5}$ has been surmised to be an activator of the aryl hydrocarbon receptor (AhR). A review by Peng et al. examined the potential role of $PM_{2.5}$ in melanogenesis[26] and hypothesized that through activation by PM, AhR mediated the maturation of the melanoblast to melanocyte. Similarly, lentigines, also known as pigment spots, are thought to be associated with particulate matter through AhR signaling leading to melanocyte maturation, proliferation, and activation[27]. Along the same lines, Hidaka et al.[28] in 2017 proposed that the mechanism behind air pollution-induced atopic dermatitis was AhR activation in keratinocytes.

In an *in vitro* study with urban particulate matter air pollution, the researchers found that the uptake of PM in human primary keratinocytes was mostly in vesicles proposed to be secondary lysosomes, but not in the mitochondria[22]. The keratinocytes produced the cytokines IL-8 and MMP-1, mediated by reactive oxygen species (ROS). Additionally, in their counterpart *in vivo* study with barrier-intact and barrier-disrupted mouse dorsal skin, they found that PM could penetrate into the hair follicles and the intercellular space of the epidermis in barrier-disrupted skin. With a 5-day exposure, findings such as the thickening of the epidermis and neutrophil infiltration in the dermis were observed[22]. Studies have indicated that neutrophils play a predominant role in PM-induced inflammation in the respiratory tract[29]. With outdoor physical activity, it is likely that both inhalation and dermal exposure to PM may be playing a role in increasing inflammation and altering immune surveillance in the skin.

The skin has a complex and robust immune surveillance system in which its dysregulation can lead to various skin disorders and tumors. In primary immune surveillance, antigens that are encountered in the skin induce innate mechanisms that can lead to activation of Antigen Presenting Cells (APC)s such as dendritic cells in the dermis. In an *in vitro* study conducted with myeloid dendritic cells and traffic-related urban particulate matter, PM was found to act not only as an adjuvant to antigens, but also as an antigen itself; inducing an immune cascade suggestive of an antigen-dependent mechanism[30].

The dendritic cells travel through the lymphatic system to the draining lymph nodes and present the antigen to naïve and central memory T-cells. In secondary immune surveillance, the T cells are activated to become T effector cells that are antigen-specific with homing receptors for the original site. Although effector memory T-cells are recruited back to the site in an antigen non-specific manner, the T cells that express receptors for the original cognate antigen help induce local inflammatory response whereas the ones that do not have the antigen-specific receptors return back to the general circulation. In tertiary immune surveillance, central memory T cells that are formed after the original antigen encounter

can circulate through different lymph nodes in the body. In the lymph nodes, they seek the cognate antigen expressed by dendritic cells that can be from other tissues, such as the lungs, gut, and muscles. This ensures that a rapid and effective response can occur, even if the antigen is seen elsewhere than in the skin. In mice chronically exposed to ambient $PM_{2.5}$ through inhalation, $PM_{2.5}$ was shown to have significantly increased T cell infiltration, effector memory T cell activation, central memory T cell populations[31]. Common skin conditions such as psoriasis, atopic dermatitis, and vitiligo are thought to be due to faulty cutaneous immune surveillance, specifically related to T-cells[32].

Although the pathogenesis of melanoma and NMSC is multi-factorial and still debated, the role of the immune system in each skin cancer can be speculated through their respective immune treatments. The typical treatment for cutaneous melanoma is surgical excision of the localized primary cancer, which leads to a 92% overall 5-year survival rate. However, when melanoma metastasizes, many patients undergo chemotherapy and/or radiation therapy. Additionally, immune checkpoint inhibitors such as those for CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) and PD-1 (programmed cell death protein-1) are used to increase the probability of survival for advanced melanoma patients. CTLA-4 inhibits T-cell activation by working through an intrinsic inhibitory feedback mechanism. For melanoma, CTLA-4 inhibition through ipilimumab has shown to improve 5-year overall survival and 5-year recurrence-free survival in Phase III studies. The mechanism of action of ipilimumab is through increasing IFN-γ production by T-cells and enhancing T-cell-mediated antitumor immunity by binding to CTLA-4 on effector T-cells and diminishing Treg cells. Like CTLA-4, PD-1 also inhibits T-cell activity and is expressed by activated T-cells. However, the mechanism of inhibition is different, and PD-1 also regulates T-cell receptor (TCR)-signaling events. Nivolumab binds to PD-1, preventing it from inhibiting T-cell activity and through Phase III trials, it has shown to improve 1-year overall survival and objective response rate compared to the control treatment for patients with advanced melanoma[6].

Surgical excision is the most common therapy for SCC and BCC treatment as most cases of these cancers do not become metastatic or progress further. For the cases that do progress, radiotherapy and platinum-based chemotherapy are frequently used. However, when chemotherapy is not an option, epidermal growth factor receptor (EGFR) inhibitors such as cetuximab are used, albeit not having promising results. Immune checkpoint inhibitors such as inhibitors for PD-1 are promising immunotherapies for metastatic SCC with Phase II studies showing promising results for overall response rate and disease control rate[33]. Patients undergoing immunosuppressive therapy have been shown to have increased risks of all skin cancers, including SCC, BCC, melanoma, Merkel cell carcinoma, and Kaposi sarcoma. In solid organ transplant recipients, there is approximately a 65 to 250-fold increase in incidence of cutaneous SCC, 10-fold increase in incidence of BCC, and 0 to 8-fold increase in incidence of melanoma[34]. With increasing evidence that the immune system is involved in both skin cancers, it is possible that particulate matter dermal exposure or inhalation exposure, or both, may increase cancer risk through inducing immunological effects.

Particulate Matter and Dermatological Diseases

There have been multiple epidemiological investigations on the effects of ambient air pollution on skin diseases such as atopic dermatitis and acne. Studies have strongly suggested that an increased concentration of ambient PM is associated with the progression and exacerbation of symptoms of atopic dermatitis in children[35,36]. Higher concentrations of ambient $PM_{2.5}$, PM_{10}, and NO_2 were significantly associated with increased numbers of outpatient visits for acne vulgaris in Beijing[37]. With more burgeoning research, it has become apparent that PM is also significantly increasing the symptoms of extrinsic skin aging through mechanisms of oxidative stress and inflammatory reactions. A study[38] of 400 elderly European Caucasian women conducted in 2008 and 2009 showed that an increase in particles from traffic per 475 kg • y^{-1} • km^{-2} was associated with a 16% (95% CI: 6 -27%) and 17% (95% CI: 8-27%) increase, respectively, in pigments spots on the forehead and cheeks. The Taizhou cohort study[39]

also demonstrated that per IQR increase of indoor $PM_{2.5}$, there were approximately 12.5% (95% CI: 0.7 – 24.3%) more pigment spots on the forehead and 7.7% (95% CI: 1.1 – 14.2%) more wrinkles on the upper lip. Additionally, a study[40] conducted in Nanjing showed that a 10 μg/m^3 increase in $PM_{2.5}$ concentration was significantly associated with a 0.65% (95% CI: 0.42-0.87%) change in relative risk (RR) in dermatology related hospital visits. In the study[40], compared to the 18-64-year age group with a percent change of 0.65 (95% CI: 0.38-0.91), the dermatology related population that was aged 65 or older was more vulnerable with a percent change in RR of 1.18 (95% CI: 0.72 – 1.65).

Particulate Matter and Skin Carcinogenesis

In 2013, outdoor air pollution and particulate matter from outdoor air pollution was classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1)[41]. To assess the harm from air pollution, the IARC Working Group reviewed hundreds of studies that examined the association between levels of polluted air, specifically outdoor PM and NO_2 concentrations, and an increased risk of lung cancer. Overall, the classification was based on strong mechanistic evidence and sufficient evidence of carcinogenicity in experimental animals through animal bioassays and humans through epidemiological studies.

Currently, a few studies suggest that PM may contribute to skin carcinogenesis. A study[42] conducted in Sao Paulo, Brazil between the years of 1997 and 2005 found that PM_{10} levels were significantly correlated (correlation coefficients ranging from 0.6- 0.8) with skin cancer incidence. Another study[43] conducted an epidemiological analysis on health care data from 1.9 million people in Saxony who were cancer-free in 2008 and 2009, following their incident cancer cases from 2010 to 2014. Their exposures of interest were PM_{10}, NO_2, and green space. They reported an association between an increase of PM_{10} of 10 μg/m^3 and a 52% (95% CI: 35-75%) increase in the relative risk of NMSC. An occupational study[44] of exposure to carbon black dust (a component of particulate matter) reported a

standardized incidence ratio of 355 (95% CI: 130-772) for melanoma, although this may have been due to work performed outside with high exposures to sunlight, which was not taken into account.

In all the aforementioned studies, the authors conclude that polycyclic aromatic hydrocarbons (PAHs) in the particulate phase may be a significant factor in skin carcinogenesis. Often derived from incomplete combustion of organic matter, PAHs are most commonly emitted from the exhaust fumes of transportation vehicles, the burning of oil, gas, wood, and coal, and the processing of aluminum[45]. Murine models[46] and multiple occupational studies[47,48] have demonstrated development of squamous cell carcinoma and melanoma after high levels of exposure to PAHs. PAHs are often bound to $PM_{2.5}$ and PM_{10}, with most on the finer ambient $PM_{2.5}$ particles rather than PM_{10} particles[49,50].

Aims and Rationale

This analysis evaluates the associations between $PM_{2.5}$ and PM_{10} on melanoma and non-melanoma skin cancer incidence rates in the Women's Health Initiative (WHI) study. The central hypothesis that higher concentrations of ambient air pollution particulate matter are associated with higher incidence rates of NMSC and melanoma will be examined through the following specific aims:

Aim 1) Describe relevant demographic, clinical, and lifestyle characteristics in study participants with melanoma, with NMSC and in non-cases

Aim 2) Investigate the association of long-term ambient particulate matter concentration with risk of NMSC and melanoma in a national cohort of post-menopausal women.

As the previous evidence linking PM_{10} and particulate PAHs with skin cancers derives either from observational studies performed outside the US or from occupational and mouse model studies,

there is limited generalizability to the United States population. Additionally, overall, there are very few studies that have been conducted on air pollution and skin cancer. There is a need for an epidemiological study with greater statistical power and sample size, and good estimates of exposure, to robustly examine the effects of ambient air pollution on skin cancer incidence rates. This study includes a large, geographically diverse population of post-menopausal women with a wide range of ages in the United States. With this study, in addition to advancing understanding of the role of PM exposure in skin cancer, we hope to advance the methodologic approaches to studying air pollution exposure and skin cancer. Findings from this study may also help guide future public health policies and motivate focused preventative measures.

METHODS

Study Population

The subjects were postmenopausal women (age 50-79) enrolled in the Women's Health Initiative (WHI) Observational Study (OS) cohort. The study recruited, in 24 states and the District of Columbia, a total of 93,676 women from 40 different clinics across the United States between October 1, 1993 and December 31, 1998[51]. All necessary informed consent was obtained before enrollment in the study and WHI protocols and procedures were approved by review boards at participating institutions. To determine eligibility, women were screened through telephone calls and then followed up by baseline screening visits to collect demographic characteristics, physical measurements, history of exposures, and lifestyle factors. Exclusion criteria included having a medical condition with predicted survival of less than 3 years and have issues with adherence or retention to the study (alcohol or drug dependency, mental illness, dementia, active participation in other studies). A self-completed questionnaire related to sun exposure was completed at year 4 of follow up. Participants in this cohort were followed for a range between 8 to 12 years. Additionally, participants were invited to join the WHI Extension Study for an additional 5

years of follow-up in March 2005 up to 2010. If they agreed and were current participants, they were invited to continue for supplementary follow up to 2020.

Outcomes

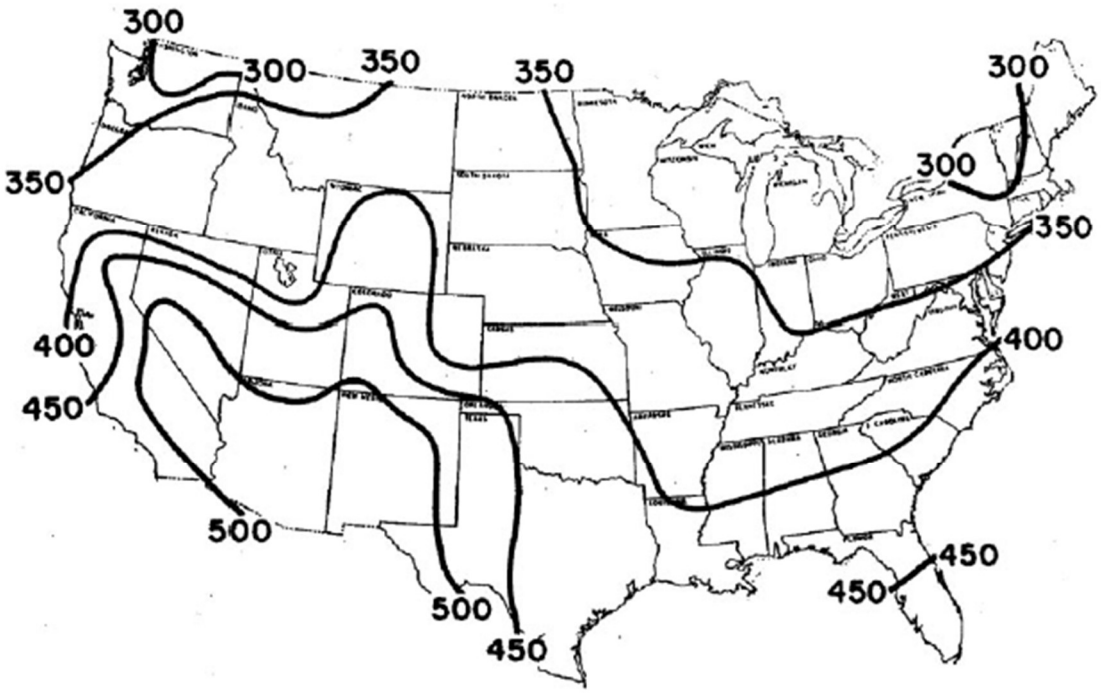
Data on cancers, including non-melanoma skin cancer (NMSC) and melanoma skin cancer, were obtained through medical questionnaires that were administered annually to participants. Melanoma skin cancer cases were adjudicated through physicians who used standardized criteria to confirm or deny the diagnoses. To become physician adjudicators, they completed a training process that included important readings, participating in conferences calls, and reviewing study protocol and procedures. Non-melanoma skin cancer cases were self-reported in which the participant would report a WHI-defined outcome and would be contacted by mail or phone to complete an additional form to obtain more information on the new outcome.

Covariate Data

Covariate data on factors that have either been identified in the literature, or suspected to be, associated with either particulate matter air pollution or skin cancer were obtained from the questionnaires at baseline as well as the Year 4 follow-up questionnaire. The year 4 follow-up questionnaire included variables such as skin reaction to sun; time spent outdoors during the summer during childhood, teenage years, thirties, and the current year; sunscreen usage; usual sunscreen Sun Protection Factor (SPF); and energy expenditure from recreational physical activity (MET-hours/week). The baseline questionnaire included important demographic characteristics such as age, smoking history, alcohol history, education, household income, body mass index (BMI), waist to hip ratio (WHR), dietary vitamin D intake, dietary caffeine intake, and Watts ((J/s) per m^2) and Langleys (g-cal per cm^2) of UV irradiation. The Langleys were obtained from a publication[52] in the 1980s that calculated the mean annual total solar irradiance reaching the ground for different states in the US. They were computed by selecting the solar radiation

contour that passed through the state or selecting the closest contours and taking their mean (Figure 1). The solar radiation data was originally from the US Weather Bureau and encompasses all solar wavelengths. The Watts were determined in 1989[53], from the NASA Total Ozone Mapping Spectrometer and Earth Radiation Budget Experiment. This measurement entails the daily UVB flux reaching the earth, within the solar wavelength required for Vitamin D synthesis (290-315 nm), and considers factors such as ozone abundance, cloud cover, surface reflectivity, and surface elevation. Both Langleys and Watts were determined at the time of enrollment for the participants.

Figure 1: Annual mean daily solar radiation levels (gm*cal/cm^2) in the United States[33]



A specific neighborhood socio-economic status (NSES) variable created for the WHI OS cohort from Ancillary Study #220[54] was included as a covariate. This NSES index was measured using an index of 6 variables: 1) the percentage of adults with less than a high school education older than 25, 2) the percentage of unemployed males, 3) the percentage of households with income below the poverty line, 4) the percentage of households receiving public assistance, 5) the percentage of households with children

headed by a woman, and 6) median household income. The index, ranging from 0 to 100 with higher scores representing more advantaged census tracts, was assigned to participants based on their residence.

Only women with a complete data set for these sun exposures and other skin cancer risk factors were included. As a result, many women with melanoma and NMSC were excluded; these exclusions were justified because it was deemed that these specific demographic and sun related factors were critical to the analysis. No attempt was made to impute missing data. Given the low incidence rates of skin cancer in non-Caucasians, the primary analysis was limited to Caucasian women. Women with previous history of NMSC or cutaneous melanoma were also excluded from analyses.

Exposure Variables

Exposure models and predictions of particulate matter (ug/m^3), PM_{10} and $PM_{2.5}$, for the WHI OS were previously generated under Ancillary Study #150 and #251[55]. Briefly, spatial models with exposure predicted by year were developed using monitoring data from the EPA Air Quality System national monitoring network and the IMPROVE network. A land-use regression approach together with partial least squares (PLS) regression for dimension reduction of 171 GIS-based geographic covariates in a universal kriging framework was used to develop the models. Because many of the GIS-based covariates were highly correlated, PLS regression was used to simplify and reduce the number of predictors to a small number of composite covariate scores while maintaining high quality predictions. The universal kriging framework accomplishes spatial smoothing of the PLS regression residuals.

The geographic covariates included 1) population, 2) total emissions of CO, NO_x, PM_{10}, $PM_{2.5}$, and SO_2 (tons per year), 3) percentages of land according to 12 land use categories, 4) summaries of the distribution of the satellite-based MODIS Normalized Difference Vegetation Index (NDVI), 5) measures of impervious surfaces, 6) indirect measures of traffic influences provided by distances to major roads,

and 7) distances to commercial zones, airports, smalls shipping ports, railroads, and railway yards. Annual predictions from the start of enrollment in the study employing the same set of geographic covariates were made at the residential address, incorporating changes in address. The predictions of annual average $PM_{2.5}$ concentrations had good predictive accuracy, as reflected by a high cross validated R^2 value ($R^2 = 0.88$). $PM_{2.5}$ concentration predictions were generated from the first reported address onwards, which may have preceded enrollment into the study. The earliest time point was at 4.8 years before enrollment.

Statistical Analysis

All statistical analyses were performed using R (version 3.6.0, R Core Team, R Foundation for Statistical Computing, Vienna, Austria) through RStudio. R packages included *survival* (version 2.44.1.1)*, survminer* (version 0.4.6)*, ggplot2* (version 3.2.1)*, and powerSurvEpi* (version 0.1.0).

Descriptive Analyses

Aim 1: Descriptive statistics for categorical covariate data included number and percent for cases and non-cases of NMSC and melanoma. For continuous covariates, the mean and standard deviation in cases and non-cases of NMSC and melanoma were calculated. The distribution of exposure levels of $PM_{2.5}$ and PM_{10} air pollution was summarized by mean, standard deviation, and interquartile range.

Inferential Analyses

Aim 2: The relationships between melanoma skin cancer and particulate matter air pollution ($PM_{2.5}$ and PM_{10}) and the relationships between NMSC and $PM_{2.5}$ and PM_{10} were analyzed using Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals (CI). Models including and not including covariate adjustment were generated. All Cox models used age as the time axis. The adjusted model was a data-driven extended confounder model which included only variables that altered the

regression coefficient for PM by at least 10%. This approach was motivated by the lack of information on potential confounders of the skin cancer and air pollution association. The proposed potential confounders are listed in the table below.

In the primary analyses, PM exposures were averages of predicted $PM_{2.5}$ and PM_{10} concentration from the first 4 years after enrollment. Due to restrictions on access to data on calendar time and year of the WHI participants, it was not possible to calculate time-varying PM concentrations. Average PM concentrations over the initial 4 years resulted in less exclusion of participants than longer averaging times, since many participants had already been excluded as a result of missing covariate data at the Year-4 follow-up. Cases of melanoma and NMSC and participants that had their last follow-up date prior to the first 4 years (either due to death, dropping out of the study, or missing information) were also excluded from the study.

The Cox model is as follows:

Model: $h(t) = h_0(t) * e\text{^}(\beta_1 X_1 + \beta_2 X_2 + \ \ldots \ \beta_p X_p)$

Where h(t) is the expected hazard at time t, $h_0(t)$ is the baseline hazard when predictors and variables are equal to zero, β_1 is the regression coefficient for the exposure ($PM_{2.5}$ or PM_{10}), X_1 is the exposure measure of interest which is the 4-year average of $PM_{2.5}$ or PM_{10}, β_{2-p} are regression coefficients for the covariates, and X_{2-p} are the measures of the covariates in the model

Null hypothesis: HR = 1 or $\beta_1 = 0$

Alternative hypothesis: HR $\neq$ 1 or $\beta_1 \neq 0$

Covariates

Type	Variables
Demographic (OS and Ancillary Study 220)	1. Education (Categories: none-some grade school (5-8 years), some high school – high school/GED, vocational – some college/associates degree, college graduate and beyond) 2. Watts of solar irradiance (0.4-0.5, 0.7, 1.0, 1.4, 1.5-1.9) 3. Langleys of solar irradiance (300-325, 350, 375-380, 400-430, 475-500) 4. Neighborhood socioeconomic status 5. Household Family Income (0 - 19,999, 20 - 34,999, 35 - 49,999, 50 - 74,999, 75 - 99,999, 100,000 and greater)
Anthropometric data at baseline (Form 80)	6. Body mass index (kg/m^2) 7. Waist to hip ratio
Lifestyle data at baseline (Form 34)	8. Smoking status (Never, Past, Current) 9. Alcohol status ((Non-drinker, Past drinker, <1 drink per month, at least 1 drink per month to <1 drink per week, 1 to <7 drinks per week, 7+ drinks per week)
Vitamin D intake and caffeine consumption (Form 60)	10. Dietary Vitamin D use (mcg) 11. Dietary caffeine (mcg)
Melanoma/NMSC risk factors (Form 144) (OS only at follow up year 4)	12. Skin reaction to sun (No change in skin color, Tans but does not burn, Burns then tans, Burns then tans a minimal amount, Burns but does not tan) 13. Usually use sunscreen outdoors (Yes/No) 14. Usual sunscreen SPF (2-9, 10-14, 15-24, 25 or more) 15. Summer sun exposure as a child, teen, in thirties, this year (<30 min, 30 min to 2 hours, 2+hours) 16. Energy expenditure from recreational physical activity (MET-hours/week)

Sensitivity Analyses

Sensitivity analyses were calculated testing different numbers of years of averaging particulate matter air pollution. Averages were calculated for 5, 7, and 10 years after enrollment. These averages were applied to each of the adjusted Cox models to test whether it would change the hazard ratios. Additionally, logistic regression models were used to examine the robustness of results for the NMSC Cox proportional hazards models as the NMSC outcome was self-reported. A fully adjusted model was created to adjust for all sun exposure related covariates.

RESULTS

Participant Characteristics

After exclusions were applied, there were 787 adjudicated cases of first occurrence of cutaneous melanoma out of a sample size of 52,205 women. For NMSC, there were 5,419 self-reported cases out of a sample size of 46,141 women. Originally starting with 161,808 women, participants were excluded if they were non-Caucasian (133,541 women remaining), had missing covariate or outcome data (53,548 women remaining), had a previous history of melanoma or NMSC at baseline (52,785 women remaining for melanoma, 48,505 women remaining for NMSC), had missing air pollution predictions and follow-up time (52,423 women remaining for melanoma, 48,188 women remaining for NMSC), were cases of melanoma or NMSC prior to the first 4 years of follow-up, or were lost to follow-up prior to the first 4 years (n= 52,205 for melanoma, n=46,141 for NMSC). The mean follow-up time for the study participants was 16 years, with the maximum being 23 years.

The demographic, clinical, and lifestyle characteristics of the study subjects are described in Tables 1,2, and 3. Characteristics in Table 1 that show differences in percent frequency between cutaneous melanoma cases and non-cases included education level (College graduate and beyond: 58% to 44% in cases and non-cases, respectively), income level (100,000 and above: 37% to 23%), and skin

reaction to sun (Tans but does not burn: 19% to 30%). Similar differences in percent frequency between NMSC cases and non-cases were seen in Table 2 for education level (College graduate and beyond: 51% to 43%) and income level (100,000 and above: 28% to 21%). The averages of characteristics shown in Table 3 were quite similar between cutaneous melanoma cases and non-cases as well as between NMSC cases and non-cases. Slight differences were observed in age for melanoma and physical activity for both skin cancers. In both the CM study population and the NMSC study population, the median predicted PM_{10} concentration was 22.4 ug/m^3, ranging from 7.7 to 49.3 ug/m^3 (IQR of 5.2 ug/m^3) whereas the median $PM_{2.5}$ was 13.3 ug/m^3, ranging from 2.5 to 23.9 ug/m^3 (IQR of 3.5 ug/m^3).

Table 1: Frequency distribution of characteristics in cutaneous melanoma cases (n=787) and non-cases (n=51,418)

Characteristics	**Cases**	%	**Non-cases**	**%**
Alcohol				
Non-drinker	49	6	4545	9
Past Drinker	95	12	8411	16
<1 Drink per month	78	10	5920	12
<1 Drink per week	160	20	10647	21
1 to <7 Drinks per week	260	33	14601	28
7+ Drinks per week	139	18	7294	14
Smoking				
Never Smoked	364	46	25776	50
Past Smoker	403	51	22808	44
Current Smoker	20	3	2834	6
Education				
None - Some Grade school (5-8 years)	1	0	260	1
Some high school - High school/GED	82	10	9777	19
Vocational - some college/associates degree	246	31	18530	36
College grad - beyond	458	58	22851	44
Income				
0 - 19,999	43	5	6179	12
20 - 34,999	120	16	11707	26
35 - 49,999	156	25	10449	31

50 - 74,999	196	42	10657	46
75 - 99,999	106	20	5075	14
100,000 and above	166	37	7351	23
SPF/Sunscreen Usage				
No Sunscreen	267	34	24459	48
2 to 9	17	2	834	2
10 to 14	35	4	1746	3
14 to 24	289	37	15571	30
25 or more	179	23	8808	17
Skin Reaction to Sun				
No change in skin color	29	4	3065	6
Tans but does not burn	146	19	15515	30
Burns, then tans	224	28	13049	25
Burns, then tans a minimal amount	281	36	13945	27
Burns but does not tan	107	14	5844	11
Summer Sun Exposure as a Child				
Less than 30 minutes	20	3	1103	2
30 minutes to 2 hours	166	21	13248	26
More than 2 hours	601	76	37067	72
Summer Sun Exposure as a Teen				
Less than 30 minutes	27	3	1588	3
30 minutes to 2 hours	261	33	18700	36
More than 2 hours	499	63	31130	61
Summer Sun Exposure in their 30s				
Less than 30 minutes	88	11	6326	12
30 minutes to 2 hours	401	51	28720	56
More than 2 hours	298	38	16372	32
Summer Sun Exposure at Year 4 follow-up				
Less than 30 minutes	188	24	15523	30
30 minutes to 2 hours	407	52	25844	50
More than 2 hours	192	24	10021	20
Watts (J/s per m^2)				
0.4 - 0.5	223	28	11721	23
0.7	192	24	13563	26
1	136	17	10380	20
1.4	170	22	10625	21
1.5 - 1.9	66	8	5129	10

Langleys (g-cal per cm^2)				
300 - 325	268	34	17733	34
350	172	22	10401	20
375- 380	88	11	6252	12
400 - 430	135	17	9019	18
475 - 500	124	16	8013	16

Table 2: Frequency distribution of characteristics in NMSC cases (n=5419) and non-cases (n=40,722)

Characteristics	**Cases**	%	**Non-cases**	**%**
Alcohol				
Non-drinker	373	7	3700	9
Past Drinker	801	15	6782	17
<1 Drink per month	571	11	4813	12
<1 Drink per week	1094	20	8480	21
1 to <7 Drinks per week	1671	31	11383	28
7+ Drinks per week	909	17	5564	14
Smoking				
Never Smoked	2682	49	20410	50
Past Smoker	2480	46	17970	44
Current Smoker	257	5	2342	6
Education				
None - Some Grade school (5-8 years)	19	0	219	1
Some high school - High school/GED	854	16	8111	20
Vocational - some college/associates degree	1802	33	14845	36
College grad - beyond	2744	51	17547	43
Income				
0 - 19,999	580	11	4977	12
20 - 34,999	1090	23	9381	26
35 - 49,999	1083	29	8261	31
50 - 74,999	1161	44	8420	47
75 - 99,999	608	16	3961	13
100,000 and above	897	28	5722	21
SPF/Sunscreen Usage				
No Sunscreen	2187	40	20626	51
2 to 9	104	2	684	2
10 to 14	192	4	1420	3

14 to 24	1852	34	11617	29
25 or more	1084	20	6375	16
Skin Reaction to Sun				
No change in skin color	252	5	2478	6
Tans but does not burn	1382	26	12938	32
Burns, then tans	1429	26	10448	26
Burns, then tans a minimal amount	1628	30	10687	26
Burns but does not tan	728	13	4171	10
Summer Sun Exposure as a Child				
Less than 30 minutes	94	2	903	2
30 minutes to 2 hours	1396	26	10531	26
More than 2 hours	3929	73	29288	72
Summer Sun Exposure as a Teen				
Less than 30 minutes	140	3	1338	3
30 minutes to 2 hours	1924	36	14904	37
More than 2 hours	3355	62	24480	60
Summer Sun Exposure in their 30s				
Less than 30 minutes	602	11	5165	13
30 minutes to 2 hours	3001	55	22735	56
More than 2 hours	1816	34	12822	31
Summer Sun Exposure at Year 4 follow-up				
Less than 30 minutes	1468	27	12271	30
30 minutes to 2 hours	2814	52	20436	50
More than 2 hours	1137	21	8015	20
Watts (J/s per m^2)				
0.4 - 0.5	1224	23	9463	23
0.7	1311	24	11157	27
1	1056	19	8237	20
1.4	1182	22	8078	20
1.5 - 1.9	646	12	3787	9
Langleys (g-cal per cm^2)				
300 - 325	1726	32	14535	36
350	1049	19	8423	21
375- 380	674	12	4868	12
400 - 430	965	18	7012	17
475 - 500	1005	19	5884	14

Table 3: Descriptive statistics (mean and SD) of cutaneous melanoma cases and non-cases and NMSC cases and non-cases

Characteristic	Melanoma cases		Non-melanoma cases		NMSC cases		Non-NMSC cases	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
BMI (kg/m^2)	26.2	5.4	26.9	5.6	26.4	5.3	27.1	5.6
WHR (no units)	0.8	0.1	0.8	0.1	0.8	0.1	0.8	0.1
Age (years)	61.6	6.8	63.6	7.2	63.8	6.9	63.2	7.2
Physical Activity (MET-hours/week)	16.7	15.5	13.5	13.7	14.9	13.9	13.3	13.7
NSES (no units)	78.6	6.8	77.5	6.8	78.1	6.7	77.4	6.8
Vitamin D intake (mcg)	4.6	2.9	4.5	3.1	4.6	3.2	4.4	3.1
Caffeine intake (mcg)	169.0	120.0	169.0	131.0	168.0	128.0	170.0	132.0

Cox Proportional Hazards Analysis

Covariates selected for inclusion in the data-driven extended models are listed in the Table 4. In Cox proportional hazards models of only predicted PM_{10} or $PM_{2.5}$ (Table 5), or with addition of the full suite of covariates, the risk of melanoma was not associated with either PM_{10} or $PM_{2.5}$. Additionally, the risk of NMSC in Cox proportional hazards models of only predicted PM_{10} or $PM_{2.5}$ was similarly not associated with either PM_{10} or $PM_{2.5}$ (Table 6). However, in the covariate-adjusted model, higher predicted $PM_{2.5}$ concentration was associated with a higher risk of NMSC (HR per 10 $\mu g/m^3$ $PM_{2.5}$ increase: 1.20; 95% CI: 1.07 – 1.36). The addition of the solar radiation covariate (in Watts) was responsible for the large change in HR; with $PM_{2.5}$ and Watts included as the only independent variables, the HR was 1.14 (95% CI: 1.01 – 1.29) per 10 $\mu g/m^3$ $PM_{2.5}$ increase. The association between PM_{10} and risk of NMSC, on the other hand, was not changed substantially with adjustment for covariates.

Table 4: Covariates adjusted for in the multiple data-driven extended models

Models	Covariates included
PM_{10} and NMSC	Watts, NSES, Education, Income, Smoking, SPF Usage, Skin Reaction to Sun
$PM_{2.5}$ and NMSC	Watts, NSES, Education, SPF Usage, Summer Sun at 30s
PM_{10} and CM	Watts, NSES, Education, Summer Sun at Year-4 Follow-up
$PM_{2.5}$ and CM	Watts, NSES, Education, Summer Sun at 30s, Summer Sun at Year-4 Follow-up

Table 5: Hazard ratios (HR) from unadjusted models of cutaneous melanoma and NMSC for a particulate matter concentration increase of 10 µg/m^3

Exposure Variable	Unadjusted NMSC HR (95% CI)	Unadjusted NMSC p-value	Unadjusted CM HR (95% CI)	Unadjusted CM p-value
PM_{10}	1.04 (0.99 – 1.09)	0.16	0.91 (0.79 – 1.06)	0.23
$PM_{2.5}$	1.00 (0.91 – 1.12)	0.93	0.90 (0.69 – 1.17)	0.43

Table 6: Hazard ratios from covariate-adjusted models of cutaneous melanoma and NMSC for a particulate matter concentration increase of 10 µg/m^3

Exposure Variable	Adjusted NMSC HR (95% CI)	Adjusted NMSC p-value	Adjusted CM HR (95% CI)	Adjusted CM p-value
PM_{10}	1.00 (0.94 – 1.06)	0.94	0.94 (0.80 – 1.11)	0.48
$PM_{2.5}$	1.20 (1.07 – 1.36)	0.002	0.80 (0.58 – 1.11)	0.19

Sensitivity analyses were conducted to test the robustness of the main finding. In a logistic regression analysis using the same population, exposure levels, and covariates as the Cox model for NMSC and $PM_{2.5}$, the result was still statistically significant (p-value: 0.01) with an odds ratio of 1.02 (95% CI: 1.00-1.03) per 10 ug/m^3 increase in $PM_{2.5}$. Additionally, multiple Cox proportional hazards models were conducted with varying years of average exposure of $PM_{2.5}$ (5, 7, and 10 years). Once again, these models were calculated using the same covariates as the Cox model for NMSC and $PM_{2.5}$. The number of subjects included in each model decreased with every year (cases and non-cases) because cases that occurred before that particular year and participants lost to follow-up or death before that particular year had to be excluded. Each model resulted in a statistically significant finding that was similar to and

contained the original hazard ratio within its 95% confidence interval. As the Cox models that were analyzed in this study were built using a data-driven extended covariate model approach, a Cox model including all important sun-related covariates was run as a sensitivity analysis. The model included watts of solar irradiance, NSES, education, household income, smoking, alcohol, summer sun exposure at 30 years of age, SPF status, skin reaction to sun, BMI, outdoor physical activity, caffeine intake, and vitamin D intake. With a 4-year average of exposure to $PM_{2.5}$, the fully adjusted model had a statistically significant HR of 1.18 (95% CI: 1.04 – 1.33) per 10 ug/m^3. These results are displayed in Table 7.

Table 7: Hazard ratios of sensitivity analysis models of NMSC in association with a 10 µg/m^3 increase in $PM_{2.5}$

	n	n cases	Adjusted NMSC HR (95% CI)	Adjusted NMSC p-value
5 years average	45084	4791	1.20 (1.06 – 1.37)	0.005
7 years average	40873	3594	1.21 (1.05 – 1.41)	0.011
10 years average	32316	1901	1.27 (1.03 – 1.57)	0.027
Including all covariates	46141	5419	1.18 (1.04 – 1.33)	0.008

DISCUSSION

A significant association between non-melanoma skin cancer and ambient $PM_{2.5}$ was observed in the study after adjusting for watts of solar irradiance, neighborhood socioeconomic status, education level, SPF usage and summer sun exposure when participants were in their thirties. Risk of NMSC increased by 20% (95% CI: 7 – 36%) per 10 µg/m^3 increase in $PM_{2.5}$. In a recent meta-analysis[56] of dermatological diseases and particulate matter, it was noted that $PM_{2.5,}$ concentrations of approximately 26 ug/m^3 (95% CI: 20 – 31) could adversely affect the human skin. The authors calculated a combined estimate of 1.60 % excess risk (95% CI: 0.45 – 2.48) of skin disease per 10 ug/m^3 increase in $PM_{2.5.}$ The 95% confidence intervals presented in this meta-analysis overlap with those from our study. As these estimates are not based on skin cancer and are instead based on conditions such as atopic dermatitis, skin

itching, eczema, and skin aging, it is unclear how relevant they are to the estimates reported here. Nevertheless, they are the only estimates available given that there are no published research findings on $PM_{2.5}$ and skin cancer risk.

After adjusting for covariates, there was quite a large difference noted between the estimates of association of the logistic regression sensitivity analysis and the Cox proportional hazards model for $PM_{2.5}$ and NMSC. All assumptions of both models were tested using diagnostic tests and each of the models adhered to the assumptions. As both regression analyses adjusted for the same variables, the divergence in effect estimates was most likely due to accounting for time to event in the Cox model. Differences between the measures of risk have been shown occur with more common outcomes and increasing length of follow-up time[57]. For cohort studies, it has been shown that the Cox model generates more precise effect estimates[58]. With NMSC being the leading cause of cancer in the world and the median years of follow-up in this study being 16 years (ranging up to 23 years), the logistic regression estimates are likely to be less reliable than the hazard ratios from the proportional hazards model.

As the first study of its kind, this study has many strengths. The WHI OS cohort allowed for the first and largest assessment of particulate matter air pollution and skin cancer incidence with good power for assessing effects on both CM and NMSC. The WHI cohort data include extensive information on many potential risk factors including sun and UV exposure-related covariates.

Although men have a higher risk of CM and NMSC, research on skin cancer in women is nevertheless surprisingly limited in light of the increasing rates in young women, especially in younger women under age 45 who are developing skin cancer from use of indoor tanning beds. An observational study[59] conducted in the Netherlands using data from 1973 to 2009 found that in women under age 40 years, the incidence in BCC increased from 1.8 to 22.2 per 100,000 person-years. In contrast, the

incidence in BCC in men only increased from 2.4 to 9.9 per 100,000 person-years in that same time frame. Another population-based study[60] in Minnesota using data from 2000 to 2010 observed that the incidence rates for both BCC and SCC were higher for younger (<49 years old) women than for younger men. With women younger than 45 years accounting for approximately 60% of all tanning bed users, it has also been shown that "ever-use" tanning bed exposure in that age group increases the risk of cutaneous melanoma with an odds ratio of 3.22 (95% CI: 1.01 - 11.46)[61]. As the incidences of CM and NMSC grow in this age group, it is essential to understand the role that environmental factors such as particulate matter may be playing.

Another advantage of this study was the use of highly validated geospatial models of ambient particulate matter air pollution. The models calculated highly accurate exposure concentrations at homes using up to 171 GIS-based geographic covariates combined with high quality monitoring data, combining them efficiently using PLS regression. Compared to the other two epidemiological studies on skin cancer and air pollution, this study had the most precise average exposure data for each participants' home. In the Yanagi et al. study[42], the authors utilized ecological air quality exposure data for 11 districts within the city provided by the São Paulo State Environmental Company (Companhia Ambiental do Estado de São Paulo – CETESB). The ecological exposure data represented mean exposure levels over a wide area rather than predicted values for individuals. Additionally, the study could not control for crucial confounders such as sun-related variables, smoking, alcohol consumption, outdoor physical activity, and age as this information was absent in the dataset. In comparison, the Datzmann et al. study[43] used similar land-use regression models based on over 1500 EuroAirnet monitoring sites. The predictor variables they utilized for the models of PM_{10} and NO_2 included population density, distance to sea, road length, land use characteristics, altitude and satellite-derived ground level $PM_{2.5}$ data[62]. Model development used a stepwise selection to derive a multiple linear regression model by including predictor variables that produced the highest increase in adjusted R^2 in the prespecified effect direction. The partial adjusted-R^2

for the PM_{10} model was at best 0.48 when including the predictor variables such as industry, ports, urban green, seminatural land, residential, and continuous and discontinuous urban fabric, together with satellite data[62]. In contrast, the R^2 for the $PM_{2.5}$ model used in this study was 0.88 for the fully regional model, indicating much better model performance.

With both CM and NMSC incidence being heavily influenced by UV radiation, one of the limitations of the study was the relatively limited spatial resolution of the solar and UV radiation data due to restricted access to participant locations. Watts of solar irradiance at enrollment was used in this study as a primary confounder because it was more strongly associated with the outcomes of melanoma and NMSC than Langleys. Furthermore, Watts were calculated using physical measurements from the NASA Total Ozone Mapping Spectrometer and Earth Radiation Budget Experiment rather than using extrapolation along contours like the Langleys calculations. However, both variables were limited to ambient baseline exposure and to broad categories of exposure. The intensity of UV radiation could have varied substantially from baseline to the years following. Without being able to link residential history to solar irradiance, the time spent outdoors before enrollment could have occurred in a different geographical location in the US. Because we did not have access to either latitude or clinic location data in WHI, both Watts and Langleys were categorized into rough categories rather than precise individual exposures. This raises concern about residual potential confounding by this important risk factor.

An additional limitation was that the WHI data for NMSC did not differentiate between SCC, BCC, and other dermal carcinomas; therefore, this study was constrained to analyzing NMSC without stratification by subtype. Consequently, specific risk factors such as previous HPV infection for SCC could not be adjusted for in the analysis which may have led to residual confounding and bias. Furthermore, there was no data on the location of the respective cancers on the body of the participants. Had this data been available, further analysis would have been conducted with stratification by cancer

location, as it would give indication as to whether PM effects on skin cancer are from inhalation exposure or dermal exposure. There was also, unlike for CM, no formal adjudication for NMSC cases, as these were self-reported. Subsequently, there may have been a lag between the time of NMSC reporting and actual disease onset as participants may have delayed reporting until the next follow-up. The results of the sensitivity analysis using the logistic regression model rather than the Cox model provide some assurance that if this was in fact the case, the study conclusions would have remained the same.

Another limitation is that while the post-menopausal exposures predictions for PM air pollution were well-validated, data on pre-menopausal exposure to PM was not available for the study. Participants may have resided in different addresses with different exposure levels prior to menopause and study enrollment. Furthermore, only ambient PM predictions were available for analysis. No data from indoor settings or other microenvironments where the study participants spent most of their time was available. Participants may have had occupations with high exposures to air pollution or spent long periods of time away from their main residential address. These potential exposure measurement errors, which if nondifferential, would most likely have resulted in a bias to the null.

With the exposure period designated as the first 4 years of the study after enrollment, the study was left truncated as women who were cases of NMSC or melanoma during the 4 years were excluded from the study which may have resulted in bias. More importantly, with an average PM exposure period of only 4 years, the study may be mischaracterizing the time of the most relevant PM exposure. For instance, the latency period between first exposure of radiation and development of NMSC has been shown to be 20-30 years[63]. Similarly, the latency period between extensive exposure to sunlight and the development of cutaneous melanoma has been thought to be at least 10 years[8]. With PM_{10} in the United States decreasing 25% from 1989 to 1998, it is possible that the hazard ratios from this analysis may be related to past higher exposures of PM_{10}. $PM_{2.5}$ concentrations between 1989 and 1998 did not show a

clear trend, fluctuating depending on whether they were measured at Eastern IMPROVE sites or Western IMPROVE sites. If the latency period for $PM_{2.5}$ and NMSC is similar to that of radiation and NMSC, it is possible that the findings may be related to a $PM_{2.5}$ exposure from 20-30 years prior to event. Data on NMSC subtype may have helped gain insight into the most important time period of exposure.

A further limitation in the dataset that played a role in this was the lack of data regarding actinic keratoses (AK). Actinic keratoses are precancerous lesions that usually develop on sun-exposed areas of the skin. The prevalence of AK is extremely high (~40%) in the adult population and it is a precursor to invasive SCC. Not all AKs progress into SCC with many remaining dormant in the same stage. It is proposed that AKs develop through multiple stages to evolve into invasive SCC. AKs with atypical keratinocytes first progress to lesions with atypical keratinocytes in the lower sections of the epidermis then finally progress to lesions with full thickness epidermal neoplasia, leading to the formation of invasive SCC[64]. The mean time for progression of AK to SCC was found to be 25 months (95% CI: 21-28 months), depending on location of the AK[65]. The progression has been attributed to p53 mutations caused by UV-induced damage to DNA[65]. An analysis looking at average PM exposure during the progression from AK to SCC would begin to clarify whether there is a relationship between higher PM exposure levels and SCC progression.

Finally, the impact of co-pollutants was not considered in this study. Had co-pollutants such as ozone been included, the estimated $PM_{2.5}$ hazard ratios may have been different. In a study by Xu et al.[66], increased levels of ozone were not significantly associated with increases in skin conditions when including PM_{10}, SO_2, and NO_2 as covariates. Future studies should investigate the effects of adding co-pollutants as covariates to the relationship of PM and dermatological cancers. However, because the evidence that pollutants other than PM are carcinogenic is weak, it is unlikely that the findings of this study were confounded by co-pollutant effects.

With its large sample size and high quality exposure predictions, the results of this study provide the strongest evidence to date that post-menopausal women with exposure to higher concentrations of $PM_{2.5}$ are at increased of non-melanoma skin cancer: specifically, a 20% higher risk per 10 ug/m^3 long-term increase in residential ambient $PM_{2.5}$ concentration. As the first of its kind in the United States, the present epidemiological study adds to the evidence that $PM_{2.5}$ exposure increases risk for cancers other than those of the lung. The main finding was robust in all sensitivity analyses that were conducted. However, residual biases may still be present due to exposure measurement error, potential confounding due to less than ideal estimation of historical UV exposure and due to self-reporting of NMSC. Future studies are warranted that also include improved estimation of both post- and pre-menopausal exposure to UV radiation and particulate matter air pollution, as well as investigating the effects of particulate matter on NMSC and melanoma in younger women.

REFERENCES

1. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;445(7130):843-850. doi:10.1038/nature05660

2. Kollias N, Sayre RM, Zeise L, Chedekel MR. New trends in photobiology: Photoprotection by melanin. *J Photochem Photobiol B*. 1991;9(2):135-160. doi:10.1016/1011-1344(91)80147-A

3. Hartman RI, Lin JY. Cutaneous Melanoma—A Review in Detection, Staging, and Management. *Hematol Oncol Clin North Am*. 2019;33(1):25-38. doi:10.1016/j.hoc.2018.09.005

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

5. Melanoma of the Skin - Cancer Stat Facts. SEER. Accessed April 30, 2020. https://seer.cancer.gov/statfacts/html/melan.html

6. Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia,PA, USA, Ward WH, Farma JM, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia,PA, USA, eds. *Cutaneous Melanoma: Etiology and Therapy*. Codon Publications; 2017. doi:10.15586/codon.cutaneousmelanoma.2017

7. Glazer AM, Winkelmann RR, Farberg AS, Rigel DS. Analysis of Trends in US Melanoma Incidence and Mortality. *JAMA Dermatol*. 2017;153(2):225. doi:10.1001/jamadermatol.2016.4512

8. Ali Z, Yousaf N, Larkin J. Melanoma epidemiology, biology and prognosis. *Eur J Cancer Suppl*. 2013;11(2):81-91. doi:10.1016/j.ejcsup.2013.07.012

9. Mahendraraj K, Sidhu K, Lau CSM, McRoy GJ, Chamberlain RS, Smith FO. Malignant Melanoma in African–Americans. *Medicine (Baltimore)*. 2017;96(15). doi:10.1097/MD.0000000000006258

10. Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS. Mutational Landscape of Basal Cell Carcinomas by Whole-Exome Sequencing. *J Invest Dermatol*. 2014;134(1):213-220. doi:10.1038/jid.2013.276

11. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol*. 2000;136(12):1524-1530. doi:10.1001/archderm.136.12.1524

12. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. *Dermatol Pract Concept*. 2017;7(2). doi:10.5826/dpc.0702a01

13. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002−2006 and 2007−2011. *Am J Prev Med*. 2015;48(2):183-187. doi:10.1016/j.amepre.2014.08.036

14. Kim K-H, Kabir E, Kabir S. A review on the human health impact of airborne particulate matter. *Environ Int*. 2015;74:136-143. doi:10.1016/j.envint.2014.10.005

15. US EPA O. Particulate Matter (PM2.5) Trends. US EPA. Published July 19, 2016. Accessed April 30, 2020. https://www.epa.gov/air-trends/particulate-matter-pm25-trends

16. US EPA O. Particulate Matter (PM10) Trends. US EPA. Published July 19, 2016. Accessed April 30, 2020. https://www.epa.gov/air-trends/particulate-matter-pm10-trends

17. McClure CD, Jaffe DA. US particulate matter air quality improves except in wildfire-prone areas. *Proc Natl Acad Sci U S A*. 2018;115(31):7901-7906. doi:10.1073/pnas.1804353115

18. Abatzoglou JT, Williams AP. Impact of anthropogenic climate change on wildfire across western US forests. *Proc Natl Acad Sci U S A*. 2016;113(42):11770-11775. doi:10.1073/pnas.1607171113

19. Wu W, Jin Y, Carlsten C. Inflammatory health effects of indoor and outdoor particulate matter. *J Allergy Clin Immunol*. 2018;141(3):833-844. doi:10.1016/j.jaci.2017.12.981

20. Li Y, Rittenhouse-Olson K, Scheider WL, Mu L. Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. *Rev Environ Health*. 2012;27(2-3):133-149. doi:10.1515/reveh-2012-0012

21. Delfino RJ, Staimer N, Tjoa T, et al. Associations of Primary and Secondary Organic Aerosols With Airway and Systemic Inflammation in an Elderly Panel Cohort. *Epidemiol Camb Mass*. 2010;21(6). doi:10.1097/EDE.0b013e3181f20e6c

22. Jin S-P, Li Z, Choi EK, et al. Urban particulate matter in air pollution penetrates into the barrier-disrupted skin and produces ROS-dependent cutaneous inflammatory response in vivo. *J Dermatol Sci*. 2018;91(2):175-183. doi:10.1016/j.jdermsci.2018.04.015

23. Pan T-L, Wang P-W, Aljuffali IA, Huang C-T, Lee C-W, Fang J-Y. The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption. *J Dermatol Sci*. 2015;78(1):51-60. doi:10.1016/j.jdermsci.2015.01.011

24. Lee C-W, Lin Z-C, Hu SC-S, et al. Urban particulate matter down-regulates filaggrin via COX2 expression/PGE2 production leading to skin barrier dysfunction. *Sci Rep*. 2016;6:27995. doi:10.1038/srep27995

25. Schraufnagel DE, Balmes JR, Cowl CT, et al. Air Pollution and Noncommunicable Diseases. *Chest*. 2019;155(2):409-416. doi:10.1016/j.chest.2018.10.042

26. Peng F, Tsuji G, Zhang J, Chen Z, Furue M. Potential role of PM2.5 in melanogenesis. *Environ Int*. 2019;132:105063. doi:10.1016/j.envint.2019.105063

27. Nakamura M, Morita A, Seité S, Haarmann-Stemmann T, Grether-Beck S, Krutmann J. Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. *Exp Dermatol*. 2015;24(6):407-411. doi:10.1111/exd.12690

28. Hidaka T, Ogawa E, Kobayashi EH, et al. The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. *Nat Immunol*. 2017;18(1):64-73. doi:10.1038/ni.3614

29. Potey PM, Rossi AG, Lucas CD, Dorward DA. Neutrophils in the initiation and resolution of acute pulmonary inflammation: understanding biological function and therapeutic potential. *J Pathol*. 2019;247(5):672-685. doi:10.1002/path.5221

30. Matthews NC, Pfeffer PE, Mann EH, et al. Urban Particulate Matter–Activated Human Dendritic Cells Induce the Expansion of Potent Inflammatory Th1, Th2, and Th17 Effector Cells. *Am J Respir Cell Mol Biol*. 2016;54(2):250-262. doi:10.1165/rcmb.2015-0084OC

31. Deiuliis JA, Kampfrath T, Zhong J, et al. Pulmonary T cell activation in response to chronic particulate air pollution. *Am J Physiol - Lung Cell Mol Physiol*. 2012;302(4):L399-L409. doi:10.1152/ajplung.00261.2011

32. Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. *Nat Rev Immunol*. 2004;4(3):211-222. doi:10.1038/nri1310

33. Ascierto PA, Schadendorf D. Immunotherapy in non-melanoma skin cancer: updates and new perspectives. *Drugs Context*. 2019;8. doi:10.7573/dic.212583

34. Rangwala S, Tsai KY. Roles of the Immune System in Skin Cancer. *Br J Dermatol*. 2011;165(5):953-965. doi:10.1111/j.1365-2133.2011.10507.x

35. Song S, Lee K, Lee Y-M, et al. Acute health effects of urban fine and ultrafine particles on children with atopic dermatitis. *Environ Res*. 2011;111(3):394-399. doi:10.1016/j.envres.2010.10.010

36. Kim J, Kim E-H, Oh I, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol*. 2013;132(2):495-498.e1. doi:10.1016/j.jaci.2013.04.019

37. Liu W, Pan X, Vierkötter A, et al. A Time-Series Study of the Effect of Air Pollution on Outpatient Visits for Acne Vulgaris in Beijing. *Skin Pharmacol Physiol*. 2018;31(2):107-113. doi:10.1159/000484482

38. Vierkötter A, Schikowski T, Ranft U, et al. Airborne Particle Exposure and Extrinsic Skin Aging. *J Invest Dermatol*. 2010;130(12):2719-2726. doi:10.1038/jid.2010.204

39. Ding A, Yang Y, Zhao Z, et al. Indoor PM 2.5 exposure affects skin aging manifestation in a Chinese population. *Sci Rep*. 2017;7(1):1-7. doi:10.1038/s41598-017-15295-8

40. Wang C, Zhu G, Zhang L, Chen K. Particulate matter pollution and hospital outpatient visits for endocrine, digestive, urological, and dermatological diseases in Nanjing, China. *Environ Pollut*. 2020;261:114205. doi:10.1016/j.envpol.2020.114205

41. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013;14(13):1262-1263. doi:10.1016/s1470-2045(13)70487-x

42. Yanagi Y, Assunção JV de, Barrozo LV. The impact of atmospheric particulate matter on cancer incidence and mortality in the city of São Paulo, Brazil. *Cad Saúde Pública*. 2012;28(9):1737-1748. doi:10.1590/S0102-311X2012000900012

43. Datzmann T, Markevych I, Trautmann F, Heinrich J, Schmitt J, Tesch F. Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. *BMC Public Health*. 2018;18(1):715. doi:10.1186/s12889-018-5615-2

44. Puntoni R, Ceppi M, Gennaro V, et al. Occupational Exposure to Carbon Black and Risk of Cancer. *Cancer Causes Control*. 2004;15(5):511-516. doi:10.1023/B:CACO.0000036446.29787.94

45. Guo X, Wang J. The chemical behaviors of microplastics in marine environment: A review. *Mar Pollut Bull*. 2019;142:1-14. doi:10.1016/j.marpolbul.2019.03.019

46. Siddens LK, Larkin A, Krueger SK, et al. Polycyclic aromatic hydrocarbons as skin carcinogens: Comparison of benzo[a]pyrene, dibenzo[def,p]chrysene and three environmental mixtures in the FVB/N mouse. *Toxicol Appl Pharmacol*. 2012;264(3):377-386. doi:10.1016/j.taap.2012.08.014

47. Pukkala E, Martinsen JI, Weiderpass E, et al. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med*. 2014;71(6):398-404. doi:10.1136/oemed-2013-101803

48. Mehlman MA. Causal Relationship from Exposure to Chemicals in Oil Refining and Chemical Industries and Malignant Melanoma. *Ann N Y Acad Sci*. 2006;1076(1):822-828. doi:10.1196/annals.1371.005

49. Pehnec G, Jakovljević I. Carcinogenic Potency of Airborne Polycyclic Aromatic Hydrocarbons in Relation to the Particle Fraction Size. *Int J Environ Res Public Health*. 2018;15(11). doi:10.3390/ijerph15112485

50. Zhu J, Hsu C-Y, Chou W-C, et al. PM2.5- and PM10-bound polycyclic aromatic hydrocarbons (PAHs) in the residential area near coal-fired power and steelmaking plants of Taichung City, Taiwan: In vitro-based health risk and source identification. *Sci Total Environ*. 2019;670:439-447. doi:10.1016/j.scitotenv.2019.03.198

51. Hays J, Hunt JR, Hubbell FA, et al. The women's health initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9, Supplement):S18-S77. doi:10.1016/S1047-2797(03)00042-5

52. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*. 2006;35(2):217-220. doi:10.1093/ije/dyi229

53. Lubin D, Jensen EH, Gies HP. Global surface ultraviolet radiation climatology from TOMS and ERBE data. *J Geophys Res Atmospheres*. 1998;103(D20):26061-26091. doi:10.1029/98JD02308

54. Dubowitz T, Ghosh-Dastidar B, Eibner C, et al. The Women's Health Initiative: the Food Environment, Neighborhood Socioeconomic Status, Body Mass Index and Blood Pressure. *Obes Silver Spring Md*. 2012;20(4):862-871. doi:10.1038/oby.2011.141

55. Bergen S, Sheppard L, Sampson PD, et al. A National Prediction Model for PM $_{2.5}$ Component Exposures and Measurement Error–Corrected Health Effect Inference. *Environ Health Perspect*. 2013;121(9):1017-1025. doi:10.1289/ehp.1206010

56. Ngoc L, Park D, Lee Y, Lee Y-C. Systematic Review and Meta-Analysis of Human Skin Diseases Due to Particulate Matter. *Int J Environ Res Public Health*. 2017;14(12):1458. doi:10.3390/ijerph14121458

57. Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis*. 1983;36(10):715-723. doi:10.1016/0021-9681(83)90165-0

58. Staley JR, Jones E, Kaptoge S, et al. A comparison of Cox and logistic regression for use in genome-wide association studies of cohort and case-cohort design. *Eur J Hum Genet*. 2017;25(7):854-862. doi:10.1038/ejhg.2017.78

59. Flohil SC, Seubring I, van Rossum MM, Coebergh J-WW, de Vries E, Nijsten T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. *J Invest Dermatol*. 2013;133(4):913-918. doi:10.1038/jid.2012.431

60. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: A population-based study in Olmsted County, Minnesota, 2000–2010. *Mayo Clin Proc*. 2017;92(6):890-898. doi:10.1016/j.mayocp.2017.02.015

61. Ting W, Schultz K, Cac NN, Peterson M, Walling HW. Tanning bed exposure increases the risk of malignant melanoma. *Int J Dermatol*. 2007;46(12):1253-1257. doi:10.1111/j.1365-4632.2007.03408.x

62. Vienneau D, de Hoogh K, Bechle MJ, et al. Western European Land Use Regression Incorporating Satellite- and Ground-Based Measurements of NO2 and PM10. *Environ Sci Technol*. 2013;47(23):13555-13564. doi:10.1021/es403089q

63. Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA, Greenberg ER. Therapeutic Ionizing Radiation and the Incidence of Basal Cell Carcinoma and Squamous Cell Carcinoma. *Arch Dermatol*. 2000;136(8):1007-1011. doi:10.1001/archderm.136.8.1007

64. Didona D, Paolino G, Bottoni U, Cantisani C. Non Melanoma Skin Cancer Pathogenesis Overview. *Biomedicines*. 2018;6(1):6. doi:10.3390/biomedicines6010006

65. Fuchs A, Marmur E. The Kinetics of Skin Cancer: Progression of Actinic Keratosis to Squamous Cell Carcinoma. *Dermatol Surg*. 2007;33(9):1099-1101. doi:10.1111/j.1524-4725.2007.33224.x

66. Xu F, Yan S, Wu M, et al. Ambient ozone pollution as a risk factor for skin disorders. *Br J Dermatol*. 2011;165(1):224-225. doi:10.1111/j.1365-2133.2011.10349.x