UC Irvine

UC Irvine Previously Published Works

Title

Dioxin exposure and breast cancer risk in a prospective cohort study

Permalink

https://escholarship.org/uc/item/3kk70383

Authors

VoPham, Trang
Bertrand, Kimberly A
Jones, Rena R
et al.

Publication Date

2020-07-01

DOI

10.1016/j.envres.2020.109516

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Environ Res. 2020 July ; 186: 109516. doi:10.1016/j.envres.2020.109516.

Dioxin exposure and breast cancer risk in a prospective cohort study

Trang VoPham[1,2,3], **Kimberly A. Bertrand**[4], **Rena R. Jones**[5], **Nicole C. Deziel**[6], **Natalie C. DuPré**[2,3,7], **Peter James**[8], **Ying Liu**[9,10], **Verónica M. Vieira**[11], **Rulla M. Tamimi**[3,12], **Jaime E. Hart**[2,13], **Mary H. Ward**[5], **Francine Laden**[2,3,13]

[1]Epidemiology Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[4]Slone Epidemiology Center at Boston University, Boston, Massachusetts, USA

[5]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA

[6]Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut, USA

[7]Department of Epidemiology and Population Health, University of Louisville School of Public Health and Information Sciences, Louisville, KY, USA

[8]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA

Address correspondence to Trang VoPham, PhD MS, Epidemiology Program, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N M4-C805, Seattle, WA 98109, USA. Telephone: (206) 667-2642. tvopham@fredhutch.org.

Credit Author Statement

Trang VoPham: methodology, software, formal analysis, investigation, writing – original draft, writing – review and editing, visualization. Kimberly Bertrand, Rena Jones, Nicole Deziel, Natalie DuPré, Peter James, Ying Liu, Veronica Vieira, Rulla Tamimi, Jaime Hart: formal analysis, investigation, writing – review and editing. Mary Ward, Rena Jones: conceptualization, data curation, writing – review and editing. Francine Laden: conceptualization, data curation, writing – review and editing, supervision, funding acquisition.

Authors' contributions: Trang VoPham: methodology, software, formal analysis, investigation, writing – original draft, writing – review and editing, visualization. Kimberly Bertrand, Rena Jones, Nicole Deziel, Natalie DuPré, Peter James, Ying Liu, Veronica Vieira, Rulla Tamimi, Jaime Hart: formal analysis, investigation, writing – review and editing. Mary Ward, Rena Jones: conceptualization, data curation, writing – review and editing. Francine Laden: conceptualization, data curation, writing – review and editing, supervision, funding acquisition.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Competing financial interests: The authors declare they have no financial interests.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[9]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, USA

[10]Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital, St. Louis, Missouri, USA

[11]Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of California, Irvine, California, USA

[12]Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA

[13]Exposure, Epidemiology, and Risk Program, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Abstract

Background: Dioxins are persistent organic pollutants generated from industrial combustion processes such as waste incineration. To date, results from epidemiologic studies of dioxin exposure and breast cancer risk have been mixed.

Objectives: To prospectively examine the association between ambient dioxin exposure using a nationwide spatial database of industrial dioxin-emitting facilities and invasive breast cancer risk in the Nurses' Health Study II (NHSII).

Methods: NHSII includes female registered nurses in the US who have completed self-administered biennial questionnaires since 1989. Incident invasive breast cancer diagnoses were self-reported and confirmed by medical record review. Dioxin exposure was estimated based on residential proximity, duration of residence, and emissions from facilities located within 3, 5, and 10 km around geocoded residential addresses updated throughout follow-up. Cox regression models adjusted for breast cancer risk factors were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: From 1989 to 2013, 3,840 invasive breast cancer cases occurred among 112,397 participants. There was no association between residential proximity to any dioxin facilities (all facilities combined) and breast cancer risk overall. However, women who resided within 10 km of any municipal solid waste incinerator (MSWI) compared to none had increased breast cancer risk (adjusted HR = 1.15, 95% CI: 1.03, 1.28), with stronger associations noted for women who lived within 5 km (adjusted HR = 1.25, 95% CI: 1.04, 1.52). Positive associations were also observed for longer duration of residence and higher dioxin emissions from MSWIs within 3, 5, and 10 km. There were no clear differences in patterns of association for ER+ vs. ER- breast cancer or by menopausal status.

Discussion: Results from this study support positive associations between dioxin exposure from MSWIs and invasive breast cancer risk.

Keywords

dioxin; environmental exposure; breast cancer; epidemiology

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

1. Introduction

Dioxins, a class of structurally and chemically related compounds that includes polychlorinated dibenzo- *p*-dioxins (PCDD or dioxins) and polychlorinated dibenzofurans (PCDF or furans) (hereafter referred to as dioxins) (Schecter et al. 2006; Srogi 2008), are persistent organic pollutants primarily generated during industrial combustion processes such as waste incineration, production of chlorophenols and chlorophenoxy herbicides, processing of metals, bleaching of paper pulp with free chlorine, and production and use of dioxin-like polychlorinated biphenyls (PCBs) (International Agency for Research on Cancer 2012). As dioxins are highly lipophilic and environmentally persistent, they accumulate in adipose tissues (International Agency for Research on Cancer 2012). Human exposure mainly occurs through dietary ingestion of meat, milk, eggs, and fish as well as through inhalation and dermal absorption (International Agency for Research on Cancer 2012). Humans can also be exposed through occupation, accidental releases, and from ambient air emissions as a result of dispersion, transport, and deposition from industrial point sources (e.g., municipal solid waste incinerators, MSWIs) into the surrounding environment (Jones et al. 2018; Srogi 2008). Populations residing near industrial sources may experience higher ambient exposures as elevated PCDD/F have been detected in soil samples near MSWIs and in residential dust concentrations sampled from homes near industrial facilities (<3-12 km) (Deziel et al. 2012; Deziel et al. 2017; Floret et al. 2006).

The International Agency for Research on Cancer (IARC) classified 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most biologically active congener, as a Group 1 human carcinogen primarily based on evidence from all cancers combined in occupationally exposed populations (International Agency for Research on Cancer 1997). Further, 2,3,4,7,8-pentachlorodibenzofuran and 3,3’,4,4’,5-pentachlorobiphenyl were also classified as Group 1 human carcinogens (International Agency for Research on Cancer 2012). Experimental evidence has shown that dioxins may impact breast carcinogenesis through mechanisms related to binding and activation of the aryl hydrocarbon receptor (AhR), which is associated with cell growth, proliferation, and apoptosis (Birnbaum and Fenton 2003). Mixed results from epidemiologic studies of dioxin exposure and breast cancer risk, which have shown positive, inverse, and null associations, may reflect limitations associated with small sample sizes, differences in outcome definitions (e.g., incidence vs. mortality), occupational vs. non-occupational study populations, residual confounding, and differences in exposure assessment (Consonni et al. 2008; Dai and Oyana 2008; Danjou et al. 2015; Danjou et al. 2019; Hardell et al. 1996; Kogevinas et al. 1997; Manuwald et al. 2012; Pesatori et al. 2009; Revich et al. 2001; Reynolds et al. 2005; Viel et al. 2008; Warner et al. 2002; Warner et al. 2011). Further, although emissions may be important in non-occupational settings (Jones et al. 2018), to our knowledge, only two studies have investigated dioxin exposures that are not related to occupational exposures or industrial accidents and breast cancer risk, showing null and inverse associations (Danjou et al. 2019; Viel et al. 2008). However, these studies were limited by the small number of cases living close to dioxin-emitting sources, lack in exposure variability, as well as a relatively small total number of breast cancer cases (Danjou et al. 2019; Viel et al. 2008), making it difficult to interpret the results. The objective of the present analysis was to prospectively examine the association between ambient exposure to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

dioxins from industrial sources using a comprehensive nationwide spatial database of dioxin-emitting facilities and invasive breast cancer risk.

2. Materials and Methods

2.1 Study population

The Nurses' Health Study II (NHSII) is an ongoing US nationwide prospective cohort study of 116,429 female registered nurses aged 25-42 years at baseline in 1989 (Bao et al. 2016). Participants (originally residents of California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas) have lived in all 50 states and Washington, D.C. as of the mid-1990's. Participants completed self-administered questionnaires every two years to ascertain information regarding incident disease, medical history, diet, lifestyle, and health behaviors. Response rates for each questionnaire cycle exceed 90% (Bao et al. 2016). We excluded women who were missing exposure information (e.g., missing addresses throughout follow-up) or with prior diagnoses of other cancers (except non-melanoma skin cancer). The study protocol was approved by the institutional review board of the Brigham and Women's Hospital and the human subjects committee of the Harvard T.H. Chan School of Public Health, and those of participating registries as required. Participants provided implied consent through returning questionnaires and written informed consent for release of medical records and collection of tissue specimens.

2.2 Outcome assessment

Invasive breast cancer cases were primarily identified through self-report on biennial questionnaires. Deaths were ascertained from family members, US Postal Service, or National Death Index. A medical record review confirmed breast cancer cases and provided information on tumor characteristics. As 99% of reported breast cancer cases were confirmed through medical record review, self-reported cases not confirmed by medical records were also included in the analysis. We examined breast cancer subtypes defined by hormone receptor status based on tissue microarrays (TMAs) constructed at the Dana-Farber/Harvard Cancer Center Tissue Microarray Core Facility. Three 0.6 mm diameter cores from tumor tissue samples were inserted into TMA blocks. Immunohistochemical staining for markers (e.g., estrogen receptor [ER]) was performed on 5 μm paraffin sections cut from TMA blocks. Immunostained TMA sections were reviewed under a microscope and visually scored for ER positivity as determined by any nuclear staining (≥1%) (Sisti et al. 2016; Tamimi et al. 2008). If TMA information was unavailable, hormone receptor status was determined using the medical record or pathology report.

2.3 Exposure assessment

Biennially updated residential address histories for each participant beginning in 1989 were geocoded to the street or ZIP Code level (Figure 1a). To estimate ambient airborne dioxin exposure, we used a nationwide database of industrial facilities emitting PCDD/F (Figure 1b) from the US Environmental Protection Agency (USEPA) (Jones et al. 2018; US Environmental Protection Agency 2006). This database included information on the facility name, latitude and longitude of the smokestack location, city, county, state, and estimated air

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

emissions of PCDD/F (ng toxic equivalency quotient [TEQ]/year) in 1987 for two facility types MSWIs and secondary copper smelters and in 1995 for ten facility types: cement kilns (hazardous), cement kilns (non-hazardous), coal-fired power plants, hazardous waste incinerators, industrial boilers, iron ore sintering plants, medical waste incinerators, MSWIs, secondary copper smelters, and sewage sludge incinerators (Table S1, Supplementary data). These ten types of facilities accounted for more than 85% of PCDD/F air emissions in the 1990s in the US (US Environmental Protection Agency 2006). In addition, we included information from an ESRI (Redlands, CA) database of hospital locations presumed to have medical waste incinerators; smokestack locations were identified using multiple spatial data sources (Jones et al. 2018) and emissions were estimated based on methods detailed below.A re-review, conducted by Jones et al. (2018), of randomly selected facilities was conducted to determine how consistently facility locations could be identified compared to the original review that created the dioxin database (Jones et al. 2018). A total of n = 240 facilities were examined, including 200 locations that were verified and 40 that were not verified in the original review. Agreement in verification (location confirmed or not) and distances between verified locations (verification error) were estimated. Overall agreement in verification was high (84.2%) and verification errors were small (median = 84 meters) (Jones et al. 2018).

Using a geographic information system (GIS), we created three time-varying dioxin exposure metrics considering facilities located within 3, 5, and 10 km around each participant's geocoded residential address updated every two years over the study time period: (1) residential proximity, (2) duration of residence, and (3) emissions. We assumed all facilities were operational during the study time period. The selected distances were based on prior evidence suggesting that they are relevant to human exposures (Deziel et al. 2012; Deziel et al. 2017) and health outcomes (Danjou et al. 2019; Pronk et al. 2013). For example, an emission index (calculated using methods applied in this analysis) that incorporated residential proximity to and emissions from industrial dioxin facilities within 5 km was associated with higher carpet dust concentrations of PCDD/F congeners (e.g., TCDD) in 100 homes in the US (Deziel et al. 2017). Another study of 40 homes in the US showed that residential proximity within 3 and 5 km of cement kilns was associated with higher PCDD/F carpet dust concentrations such as for TCDD (Deziel et al. 2012).

(1) Residential proximity (yes, no) was defined as living within the specified distance (i.e., 3, 5, or 10 km) of any (≥1) dioxin-emitting facilities. (2) Duration of residence (years) was defined as the number of years living within the specified distance of any (≥1) dioxin-emitting facilities. (3) The emission index was calculated using estimated air emissions (ng TEQ/year) for each facility in the database. Emissions expressed in units of ng TEQ/year incorporate the potency of each PCDD/F compound relative to TCDD; higher emission values indicate higher toxicity (International Agency for Research on Cancer 1997). If a facility was missing air emissions data, the average of the estimated air emissions for the facility type in 1995 was used for imputation (Pronk et al. 2013). To estimate changes in air emissions for each facility and each year over the study time period, we used the average emission levels for each facility type in 1987, 1995, 2000, and 2012 obtained from a USEPA national survey of dioxin-emitting facilities and an updated dioxin inventory (Dwyer and Themelis 2015; US Environmental Protection Agency 2006). The linear rate of change in emissions between 1987 and 1995, 1995 and 2000, and 2000 and 2012 was estimated by

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

facility type (Pronk et al. 2013). For each year, we calculated each facility's estimated emissions by multiplying the rate of change by the facility's emission levels separately in 1995 and 2000. An inverse distance weighting calculation was applied to emissions from each facility within 3, 5, or 10 km of a residence (i.e., facilities located closer to a residence were weighted more); weighted emissions were summed across all facilities near each residence for each year (Pronk et al. 2013). A time-varying cumulative average emission index was calculated, where the emission index from previous years was averaged and updated every two years over the course of follow-up.

For each specified distance, the duration of residence and emission metrics were defined as three-level categorical variables with categories for no exposure, exposure greater than zero and less than or equal to the median value among participants who ever resided near any dioxin-emitting facility over follow-up, and exposure greater than the median value (Pronk et al. 2013). Overall (referred to as all facilities combined) and facility-specific metrics for residential proximity and duration of residence were examined. We *a priori* examined emission metrics for all facilities combined and for any facility type showing statistically significant positive associations with breast cancer risk in multivariable models using the residential proximity and duration of residence metrics. Only the MSWI facility type satisfied this criterion. All spatial analyses were conducted using ArcMap 10.5.1 (Esri, Redlands, CA).

2.4 Statistical analysis

Cox proportional hazards regression models were fit to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each of the time-varying dioxin exposure metrics (residential proximity, duration of residence, and emission index) and invasive breast cancer risk. All models were stratified by age and questionnaire period. Person-time accrued from June 1989 until the end of follow-up in May 2013, incidence of invasive breast cancer, in situ breast cancer, or other cancer (excluding non-melanoma skin cancer), death, or loss to follow-up, whichever occurred first. We *a priori* determined that the following established and suspected breast cancer risk factors would be included in multivariable models, which were collected from biennial questionnaires (or every other questionnaire for diet and physical activity) or ascertained by linking each participant's locational information with US Census Bureau data: age (years), race (white, non-white), family history of breast cancer (yes, no), personal history of biopsy-confirmed benign breast disease (BBD) (yes, no), age at menarche (years), parity and age at first birth (nulliparous, 1-2 children and <25 years, 1-2 children and ≥25-30, 1-2 children and ≥30, 3+ children and <25, 3+ children and ≥25-30, 3+ children and ≥30), lactation (never, ever), menopausal status and hormone use (among postmenopausal women only) (never, past, current), height (in), body mass index (BMI) at age 18 (kg/m^2), change in BMI since age 18 (kg/m^2), physical activity (MET hours/week), smoking status (never, past, current), adult alcohol consumption (g/day), individual-level socioeconomic status (SES) (i.e., personal income [> $100,000, ≤$100,000], marital status [married, not married], and living arrangements [living alone, not living alone]), area-level SES (i.e., Census tract median home value [$10,000] and Census tract median income [$]), and population density ($population/mi^2$). We present results from a basic model adjusted for age and race and a fully adjusted model adjusting for

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the other aforementioned covariates. We also considered a model that additionally adjusted for oral contraceptive (OC) use (never, past, current), screening mammography (yes, no), animal fat intake (g/day), total fat intake (g/day), alcohol consumption at age 15 and 18 (g/day), Alternate Healthy Eating Index (AHEI) diet score (continuous) (Chiuve et al. 2012), fine particulate matter (PM) air pollution <2.5 μm in diameter ($PM_{2.5}$, $\mu g/m^3$), and coarse PM air pollution between 2.5 and 10 μm in diameter ($PM_{2.5-10}$, $\mu g/m^3$) (Yanosky et al. 2014). Population density and PM were proxies for high-traffic areas as other sources of airborne dioxin exposure include combustion of gasoline- and diesel-fueled engines (Dopico and Gomez 2015). However, as these variables did not change the effect estimate for dioxin exposure (≥10% change in HR), they were not included in the final model.

We examined potential effect modification by race, menopausal status, BMI, physical activity, animal fat intake, total fat intake, $PM_{2.5}$, $PM_{2.5-10}$, and US Census Bureau region of residence (i.e., Northeast, Midwest, West, and South). Differential associations with either dioxin or population subgroups with higher risk or susceptibility for breast cancer have been observed according to these variables (Breivik et al. 2004; DeSantis et al. 2014; International Agency for Research on Cancer 2012; Kaupp et al. 1994; Stavraky and Emmons 1974). Tests for interaction were performed by adding interaction terms to the model and using likelihood ratio tests to determine statistical significance. We also conducted sensitivity analyses according to residential mobility (movers, non-movers) to assess the potential impact of exposure measurement error. The missing indicator method was used to account for any missing covariates. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

Population characteristics for the 112,397 participants included in the analysis overall and by residential proximity to any dioxin-emitting facilities are shown in Table 1. Over follow-up, participants were on average aged 44.9 ± 8.2 years, mostly white (96%), premenopausal (70%), married (93%), never-smokers (65%), with an average BMI of 25.4 ± 4.9 kg/m^2, average animal fat intake of 33.9 ± 8 g/day, and living in areas with an average Census tract median income of $63,929 ± 23,634. Participants living near any dioxin-emitting facilities (3, 5, or 10 km) were more likely to be nulliparous, less likely to be married, and more likely to live in more densely populated areas as well as in the Northeast and Midwest regions of the US.

From 1989 to 2013 (2,302,566 person-years of follow-up), 3,840 invasive breast cancers occurred. Of these cases, there were 2,332 ER+ cases and 585 ER− cases. Residential proximity to any dioxin-emitting facilities (all facilities combined) within 3 km (adjusted HR = 1.03, 95% CI: 0.93, 1.13), 5 km (adjusted HR = 1.04, 95% CI: 0.97, 1.12), and 10 km (adjusted HR = 1.07, 95% CI: 1.00, 1.14) compared to none was not associated with invasive breast cancer risk (Table 2). Similar null associations were observed for ER+ and ER− breast cancers (Table 2) and among premenopausal (Table S2, Supplementary data) and postmenopausal women (Table S3, Supplementary data). Results from the basic model adjusted for age and race did not substantially differ after adjustment for breast cancer risk factors, individual- and area-level SES, and population density in fully adjusted models.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

However, there were statistically significant positive associations between dioxin emissions from MSWIs and invasive breast cancer risk (Table 2). Residential proximity to MSWIs within 3 km (adjusted HR = 1.20, 95% CI: 0.86, 1.68), 5 km (adjusted HR = 1.25, 95% CI: 1.04, 1.52), and 10 km (adjusted HR = 1.15, 95% CI: 1.03, 1.28) was associated with invasive breast cancer risk. Longer duration of residence (>6 years compared to 0 years) near MSWIs within 3 km (adjusted HR = 1.39, 95% CI: 1.00, 1.93), 5 km (adjusted HR = 1.27, 95% CI: 1.05, 1.54), and 10 km (adjusted HR = 1.11, 95% CI: 0.99, 1.24) was associated with invasive breast cancer risk. Higher levels of emissions from MSWIs within 3 km (>4.70 ng TEQ/year per km^2 compared to 0 ng TEQ/year per km^2: adjusted HR = 1.40, 95% CI: 1.03, 1.92), 5 km (>1.95 ng TEQ/year per km^2 compared to 0 ng TEQ/year per km^2: adjusted HR = 1.21, 95% CI: 0.98, 1.48), and 10 km (>0.48 ng TEQ/year per km^2 compared to 0 ng TEQ/year per km^2: adjusted HR = 1.16, 95% CI: 1.03, 1.32) were associated with invasive breast cancer risk. In general, positive associations were observed for both ER+ and ER− breast cancer, although effect estimates were less precise due to small numbers in stratified analyses and results were not consistent by exposure metric (Table 2). Positive associations were observed among premenopausal (Table S2, Supplementary data) and postmenopausal women (Table S3, Supplementary data). Dioxin exposure from other facility types was not associated with breast cancer risk (data not shown).

There were no statistically significant interactions between dioxin exposure and race, menopausal status, BMI, physical activity, animal fat intake, total fat intake, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and region of residence (data not shown). In sensitivity analyses, similar results were observed among participants who did not move (data not shown).

4. Discussion

We did not observe an association between proximity-, duration-, and emissions-based metrics for exposures to any dioxin-emitting facilities (all facilities combined) and risk of invasive breast cancer in the NHSII prospective cohort. However, we observed statistically significant positive associations between dioxin emissions from MSWIs located within 3, 5, and 10 km of residences and invasive breast cancer risk. There were no clear differences in patterns of associations by ER status or menopausal status. To our knowledge, this is the first epidemiologic study to prospectively examine the association between ambient dioxin exposure from industrial sources and breast cancer risk in a non-occupationally exposed US population.

Given that regulation of particular dioxin-emitting facilities (e.g., MSWIs, medical waste incinerators, and hazardous waste incinerators) was not promulgated in the US until the late 1990s (Institute of Medicine 2003) and the estimated half-life for TCDD is 7 to 11 years among humans (Pirkle et al. 1989), ambient exposures from residential proximity to industrial sources of PCDD/F may represent an important source for individuals living nearby via direct releases or migration of dioxins in the air or through contact with polluted soil (Jones et al. 2018). Higher levels of particular PCDD/F congeners were observed in carpet dust from homes near industrial dioxin facilities in the US (Deziel et al. 2012; Deziel et al. 2017). A doubling of the emission index (on the arithmetic scale) incorporating facilities within 5 km of homes was associated with a 4.4 (for 1,2,3,4,6,7,8-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

heptachlorodibenzodioxin) to 7.9% (for TCDD) increase in PCDD/F carpet dust concentrations (Deziel et al. 2017). Higher MSWI- and medical waste incinerator-specific emission indices (≥median compared to 0) were associated with increased carpet dust concentrations for PCDD/F congeners (e.g., TCDD and octachlorodibenzodioxin) (Deziel et al. 2017). Further, average emissions from MSWI were among the highest of any facility type in the US (87.42 ng TEQ/year in 1987 and 19.88 ng TEQ/year in 1995) (Pronk et al. 2013). Several studies have shown that living near industrial facilities is associated with higher levels of dioxins measured in blood among non-occupationally exposed populations. For example, individuals living within 5 km compared to >5 km of a chemical plant in Russia producing chlorinated compounds had higher serum dioxin levels (Akhmedkhanov et al. 2002; Burns et al. 2009). Other studies in the Czech Republic, Spain, and Taiwan have shown similar associations (Cerna et al. 2007; Lee et al. 2006; Zubero et al. 2009). However, some studies have shown no association between residential proximity to incinerators and dioxins measured in blood or breast milk, although results may have been influenced by small sample sizes, not accounting for time spent outdoors, operational status of the facilities, and/or differences in stack emissions by facility type (De Felip et al. 2008; Deml et al. 1996; Gonzalez et al. 2000; Schuhmacher et al. 1999; Tajimi et al. 2005; Zubero et al. 2017).

PCDD/F are endocrine disrupting compounds, showing high affinity towards binding and activation of the aryl hydrocarbon receptor, an important mediator of cell growth, proliferation, and anti-apoptosis pathways (Birnbaum and Fenton 2003; Gray et al. 2017; International Agency for Research on Cancer 2012). TCDD has been shown to delay proliferation and differentiation of the mammary gland in rats by increasing the number of terminal end buds, lengthening the window of sensitivity to potential carcinogens (Birnbaum and Fenton 2003; Brown et al. 1998; Lewis et al. 2001). In M13SV1 human breast epithelial cells, TCDD exposure induced alterations in the expression of genes involving ERK2 and AKT signal transduction pathways associated with cell proliferation and survival (Ahn et al. 2005). TCDD may also promote breast carcinogenesis through inhibiting p53 tumor suppressor mechanisms and by inducing estrogenic signaling (Seifert et al. 2009). Thus, the observed associations between dioxin exposure and breast cancer risk are biologically plausible.

Results from previous epidémiologic studies examining dioxin exposure and breast cancer risk have been mixed. A prospective study in the Etude Epidemiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort in France showed no association between dietary dioxin exposure (assessed by combining a food frequency questionnaire with food dioxin contamination data) and breast cancer risk (n = 3,465 cases, adjusted HR = 0.96, 95% CI: 0.85, 1.09) (Danjou et al. 2015). An ecological study in the US showed that ZIP Code-level soil dioxin levels were associated with elevated odds for breast cancer in several ZIP Codes in Michigan (n = 4,604 cases) (Dai and Oyana 2008). In two hospital-based retrospective case-control studies in Sweden (n = 22 cases) and the US (n= 79 cases), PCDD/F measured in breast adipose tissue at diagnosis was not associated with breast cancer risk (Hardell et al. 1996; Reynolds et al. 2005). The most recent epidemiologic studies following the Seveso accident in Italy, where an industrial explosion at a chemical plant producing trichlorophenol in 1976 released TCDD into the environment, showed an

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

increase in breast cancer incidence but not mortality after 20-25 years of follow-up (Consonni et al. 2008; Pesatori et al. 2009). There was an increased risk of breast cancer in females living in the most contaminated area in the 15 years following the accident (adjusted RR = 2.57, 95% CI: 1.07, 6.20), although these results were based on only 5 cases (Pesatori et al. 2009). In the retrospective Seveso Women's Health Study (SWHS), serum TCDD levels (most were measured from 1976-1977) were associated with an increased risk for breast cancer (n = 15 cases; HR = 2.1, 95% CI: 1.0, 4.6) (Warner et al. 2002). However, results from an analysis of the SWHS with longer follow-up through 2008 showed that serum TCDD levels were no longer associated with breast cancer risk (n = 33 cases; adjusted HR = 1.44, 95% CI: 0.89, 2.33) (Warner et al. 2011).

Several occupational studies have shown inconsistent results. There was an increased risk for breast cancer mortality among residents of Chapaevsk, Russia, the location of a chemical plant that produced lindane and other chemicals, compared to residents of the Samara Region (n = 58 cases; SMR = 2.1, 95% CI: 1.6, 2.7) (Revich et al. 2001). In the IARC international cohort of individuals occupationally exposed to phenoxy herbicides, there was a suggestive positive association with breast cancer mortality (n = 9 cases; SMR = 2.16, 95% CI: 0.99, 4.10) (Kogevinas et al. 1997). Breast cancer cases for this IARC study were from a Hamburg, Germany cohort of workers employed at a chemical plant that produced herbicides (e.g., lindane) contaminated with TCDD (Manz et al. 1991). In a subsequent study of the Hamburg cohort with 23 years of follow-up after plant closure, the elevation in breast cancer mortality became statistically significant (n = 19 cases; SMR = 1.86, 95% CI: 1.12, 2.91) (Manuwald et al. 2012).

To date, two non-occupational epidemiologic studies (unrelated to industrial accidents) have examined the association between individual-level dioxin exposure from ambient air and breast cancer risk (Danjou et al. 2019; Viel et al. 2008). In a prospective case-control study nested in the E3N cohort, dioxin exposure was estimated using geocoded residential address histories (1990–2008) and dioxin air emissions predicted for facilities located within 10 km using information including stack height and wind direction (Danjou et al. 2019). There was no association between dioxin exposure and breast cancer risk (n = 439 cases; adjusted OR = 1.12, 95% CI: 0.69, 1.82); similar null results were observed for breast cancer subtypes defined by hormone receptor status and menopausal status (Danjou et al. 2019). In a retrospective case-control study in France, there were null and inverse associations between emissions from a MSWI (estimated using a validated dispersion model linked to residential blocks at diagnosis) and breast cancer risk (n = 434 cases) (Viel et al. 2008). Mixed results may be due to small sample sizes, examining breast cancer incidence compared to mortality, and/or investigating occupational exposures that are higher compared to the general population and in which studies generally did not adjust for potential confounders. Further, there were differences in the exposure assessment, for example, using food frequency questionnaires, biomonitoring, and area-level geographic variables at diagnosis.

Our findings of positive associations between ambient dioxin exposures from MSWIs with breast cancer risk are consistent with MSWIs as historically the largest contributor of dioxin emissions in the US (Thomas and Spiro 1995; US Environmental Protection Agency 2006). Municipal solid waste is comprised of the nonhazardous solid portion of waste generated by

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

households, commercial establishments, public and private institutions, and government agencies (National Research Council 2000). Approximately 36 million tons of municipal solid waste is combusted each year (National Research Council 2000). Average emissions from MSWIs were between 1.5 and 2,913 times higher compared to other facilities in 1987 and 1995 (i.e., cement kilns, coal-fired power plants, hazardous waste incinerators, industrial boilers, iron ore sintering plants, medical waste incinerators, and sewage sludge incinerators with emissions ≤8.10 ng TEQ/year in 1987 and 1995) (Pronk et al. 2013). Further, higher MSWI-specific emission indices were associated with increased carpet dust concentrations for PCDD/F congeners including TCDD, octachlorodibenzodioxin, 2,3,7,8-tetrachlorodibenzofuran, 1,2,3,7,8-pentachlorodibenzofuran, 1,2,3,4,7,8-hexachlorodibenzofuran, and 1,2,3,4,6,7,8-heptachlorodibenzofuran (Deziel et al. 2017). In particular, we observed positive associations when examining dioxin exposure according to residential proximity, residential duration, and emissions, although results using the emission metrics showed relatively stronger associations. Further, the strength of the associations was stronger at distances closer to residential locations (3 and 5 km), although positive associations persisted up to 10 km. The emission index may be a relatively better indicator of the burden of airborne dioxin exposure to which an individual is exposed compared to considering general proximity. Results using the 5 and 10 km vs. 3 km exposure metrics were consistently positive and generally statistically significant, reflecting the relatively larger sample size of exposed.

This study had several potential limitations. The generalizability of our findings may be limited as participants of the NHSII were mostly white, although there is no evidence to suggest that the association would differ by race. However, as industrial facilities are more commonly found near environmental justice communities and our population of registered nurses is less likely to live in these areas, we may have been limited in capturing the highest levels of exposure (Mohai et al. 2009). We were not able to directly assess dioxin exposure using biological samples. The locations of the dioxin-emitting facilities are subject to errors from multiple reviewers and data sources. However, a re-review of randomly selected facilities showed good agreement and small verification errors (Jones et al. 2018). The dioxin exposure measures for residential proximity, duration of residence, and emissions are surrogates for airborne exposure that do not account for complex dispersion patterns or environmental fate and transport. There may be exposure misclassification due to imputed emissions data as emissions were available only in 1995 for all facilities except for MSWIs and secondary copper smelters, which were available in 1987 and 1995. We did not have information regarding each facility's years of operation. We examined dioxin exposure during adulthood; early-life exposures during critical windows of susceptibility to carcinogens may be warranted (Gray et al. 2017). Although we cannot rule out that other compounds associated with the industrial facilities may have adversely impacted breast cancer risk, the positive association between dioxin exposure and breast cancer risk is supported by strong biological plausibility demonstrated in experimental evidence (Birnbaum and Fenton 2003; Gray et al. 2017; International Agency for Research on Cancer 1997, 2012). Further, adjustment for proxies for high-traffic areas (e.g., population density, $PM_{2.5}$) did not change results. As MSWIs emit other carcinogenic chemicals (Goria et al. 2009), it is possible that other pollutants may have contributed to the positive associations.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

This study had several strengths. Our exposure assessment included geocoded residential address histories updated biennially since 1989 as well as a nationwide spatial database of dioxin-emitting facilities, representing a comprehensive assessment of PCDD/F air emissions sources appropriate for assessing general population exposure (Jones et al. 2018). We were able to account for residential mobility over time; thus, women who developed breast cancer before living near a facility were categorized as unexposed as we used their address prior to diagnosis to assign exposure. We used GIS to derive objective measures of ambient dioxin exposure used in previous epidemiologic studies (Danjou et al. 2019; Pronk et al. 2013). We were able to examine exposures from specific industrial facility types, including MSWIs, characterized by different emissions profiles. We were also able to examine a large number of breast cancer cases and breast cancer subtypes defined by ER status. Using information collected from questionnaires and from geocoded addresses linked with databases such as the US Census Bureau, we were able to evaluate potential confounding and effect modification using time-varying information on an extensive number of breast cancer risk factors.

5. Conclusions

In summary, results from this large nationwide prospective non-occupationally exposed cohort study of US women showed a positive association between ambient dioxin exposures from MSWIs and invasive breast cancer risk, which was similar by ER status and menopausal status. Future research assessing dioxin exposure using biological samples to confirm these results and evaluating exposures relevant to contemporary dioxin emission levels (given changes in regulations over time) may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This work was supported by the National Institutes of Health (NIH) National Cancer Institute (NCI) Training Program in Cancer Epidemiology (T32 CA009001), R00 CA201542, UM1 CA176726, P30 ES000002, and R01 ES017017, and Susan G. Komen for the Cure® (IIR13264020). K.A.B. was supported in part by the Dahod Breast Cancer Research Program at the Boston University School of Medicine. We would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

References

Ahn NS, Hu H, Park JS, Park JS, Kim JS, An S, et al. 2005 Molecular mechanisms of the 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced inverted U-shaped dose responsiveness in anchorage independent growth and cell proliferation of human breast epithelial cells with stem cell characteristics. Mutation research 579:189–199. [PubMed: 16051281]

Akhmedkhanov A, Revich B, Adibi JJ, Zeilert V, Masten SA, Patterson DG Jr., et al. 2002 Characterization of dioxin exposure in residents of Chapaevsk, Russia. Journal of exposure analysis and environmental epidemiology 12:409–417. [PubMed: 12415489]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bao Y, Bertoia ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, et al. 2016 Origin, Methods, and Evolution of the Three Nurses' Health Studies. American journal of public health 106:1573–1581. [PubMed: 27459450]

Birnbaum LS, Fenton SE. 2003 Cancer and developmental exposure to endocrine disruptors. Environmental health perspectives 111:389–394. [PubMed: 12676588]

Breivik K, Alcock R, Li YF, Bailey RE, Fiedler H, Pacyna JM. 2004 Primary sources of selected POPs: regional and global scale emission inventories. Environmental pollution 128:3–16. [PubMed: 14667716]

Brown NM, Manzolillo PA, Zhang JX, Wang J, Lamartiniere CA. 1998 Prenatal TCDD and predisposition to mammary cancer in the rat. Carcinogenesis 19:1623–1629. [PubMed: 9771934]

Burns JS, Williams PL, Sergeyev O, Korrick S, Lee MM, Revich B, et al. 2009 Predictors of serum dioxins and PCBs among peripubertal Russian boys. Environmental health perspectives 117:1593–1599. [PubMed: 20019911]

Cerna M, Kratenova J, Zejglicova K, Brabec M, Maly M, Smid J, et al. 2007 Levels of PCDDs, PCDFs, and PCBs in the blood of the non-occupationally exposed residents living in the vicinity of a chemical plant in the Czech Republic. Chemosphere 67:S238–246. [PubMed: 17207843]

Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. 2012 Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 142:1009–1018. [PubMed: 22513989]

Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M, et al. 2008 Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. American journal of epidemiology 167:847–858. [PubMed: 18192277]

Dai D, Oyana TJ. 2008 Spatial variations in the incidence of breast cancer and potential risks associated with soil dioxin contamination in Midland, Saginaw, and Bay Counties, Michigan, USA. Environmental health : a global access science source 7:49. [PubMed: 18939976]

Danjou AM, Fervers B, Boutron-Ruault MC, Philip T, Clavel-Chapelon F, Dossus L. 2015 Estimated dietary dioxin exposure and breast cancer risk among women from the French E3N prospective cohort. Breast cancer research : BCR 17:39. [PubMed: 25849111]

Danjou AMN, Coudon T, Praud D, Leveque E, Faure E, Salizzoni P, et al. 2019 Long-term airborne dioxin exposure and breast cancer risk in a case-control study nested within the French E3N prospective cohort. Environment international 124:236–248. [PubMed: 30658268]

De Felip E, Abballe A, Casalino F, di Domenico A, Domenici P, Iacovella N, et al. 2008 Serum levels of PCDDs, PCDFs and PCBs in non-occupationally exposed population groups living near two incineration plants in Tuscany, Italy. Chemosphere 72:25–33. [PubMed: 18407315]

Deml E, Mangelsdorf I, Greim H. 1996 Chlorinated dibenzodioxins and dibenzofurans (PCDD/F) in blood and human milk of non occupationally exposed persons living in the vicinity of a municipal waste incinerator. Chemosphere 33:1941–1950. [PubMed: 8930103]

DeSantis C, Ma J, Bryan L, Jemal A. 2014 Breast cancer statistics, 2013. CA: a cancer journal for clinicians 64:52–62. [PubMed: 24114568]

Deziel NC, Nuckols JR, Colt JS, De Roos AJ, Pronk A, Gourley C, et al. 2012 Determinants of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in house dust samples from four areas of the United States. The Science of the total environment 433:516–522. [PubMed: 22832089]

Deziel NC, Nuckols JR, Jones RR, Graubard BI, De Roos AJ, Pronk A, et al. 2017 Comparison of industrial emissions and carpet dust concentrations of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in a multi-center U.S. study. The Science of the total environment 580:1276–1286. [PubMed: 28017415]

Dopico M, Gomez A. 2015 Review of the current state and main sources of dioxins around the world. J Air Waste Manag Assoc 65:1033–1049. [PubMed: 26068294]

Dwyer H, Themelis NJ. 2015 Inventory of U.S. 2012 dioxin emissions to atmosphere. Waste management 46:242–246. [PubMed: 26297638]

Floret N, Viel JF, Lucot E, Dudermel PM, Cahn JY, Badot PM, et al. 2006 Dispersion modeling as a dioxin exposure indicator in the vicinity of a municipal solid waste incinerator: a validation study. Environmental science & technology 40:2149–2155. [PubMed: 16646446]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Gonzalez CA, Kogevinas M, Gadea E, Huici A, Bosch A, Bleda MJ, et al. 2000 Biomonitoring study of people living near or working at a municipal solid-waste incinerator before and after two years of operation. Archives of environmental health 55:259–267. [PubMed: 11005431]

Goria S, Daniau C, de Crouy-Chanel P, Empereur-Bissonnet P, Fabre P, Colonna M, et al. 2009 Risk of cancer in the vicinity of municipal solid waste incinerators: importance of using a flexible modelling strategy. International journal of health geographics 8:31. [PubMed: 19476608]

Gray JM, Rasanayagam S, Engel C, Rizzo J. 2017 State of the evidence 2017: an update on the connection between breast cancer and the environment. Environmental health : a global access science source 16:94. [PubMed: 28865460]

Hardell L, Lindstrom G, Liljegren G, Dahl P, Magnuson A. 1996 Increased concentrations of octachlorodibenzo-p-dioxin in cases with breast cancer--results from a case-control study. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation 5:351–357.

Institute of Medicine. 2003 Dioxins and Dioxin-like Compounds in the Food Supply: Strategies to Decrease Exposure. . (Committee on the Implications of Dioxin in the Food Supply). Washington, D.C.: National Academies Press.

International Agency for Research on Cancer. 1997 Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans (volume 69). (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans). Lyon, France.

International Agency for Research on Cancer. 2012 Chemical Agents and Related Occupations. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No 100F). Lyon, France.

Jones RR, VoPham T, Sevilla B, Airola M, Flory A, Deziel NC, et al. 2018 Verifying locations of sources of historical environmental releases of dioxin-like compounds in the U.S.: implications for exposure assessment and epidemiologic inference. Journal of exposure science & environmental epidemiology.

Kaupp H, Towara J, McLachlan M. 1994 Distribution of polychlorinated dibenzo-p-dioxins and dibenzofurans in atmospheric particulate matter with respect to particle size. Atmospheric environment 28:585–593.

Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, et al. 1997 Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. American journal of epidemiology 145:1061–1075. [PubMed: 9199536]

Lee CC, Lin WT, Liao PC, Su HJ, Chen HL. 2006 High average daily intake of PCDD/Fs and serum levels in residents living near a deserted factory producing pentachlorophenol (PCP) in Taiwan: influence of contaminated fish consumption. Environmental pollution 141:381–386. [PubMed: 16213641]

Lewis BC, Hudgins S, Lewis A, Schorr K, Sommer R, Peterson RE, et al. 2001 In utero and lactational treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin impairs mammary gland differentiation but does not block the response to exogenous estrogen in the postpubertal female rat. Toxicological sciences : an official journal of the Society of Toxicology 62:46–53. [PubMed: 11399792]

Manuwald U, Velasco Garrido M, Berger J, Manz A, Baur X. 2012 Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure. Occupational and environmental medicine 69:636–642. [PubMed: 22767868]

Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. 1991 Cancer mortality among workers in chemical plant contaminated with dioxin. Lancet 338:959–964. [PubMed: 1681339]

Mohai P, Lantz PM, Morenoff J, House JS, Mero RP. 2009 Racial and socioeconomic disparities in residential proximity to polluting industrial facilities: evidence from the Americans' Changing Lives Study. American journal of public health 99 Suppl 3:S649–656. [PubMed: 19890171]

National Research Council. 2000 Waste Incineration & Public Health. National Research Council (US) Committee on Health Effects of Waste Incineration. Washington, D.C.:National Academies Press (US).

Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. 2009 Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environmental health : a global access science source 8:39. [PubMed: 19754930]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Pirkle JL, Wolfe WH, Patterson DG, Needham LL, Michalek JE, Miner JC, et al. 1989 Estimates of the half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Vietnam Veterans of Operation Ranch Hand. Journal of toxicology and environmental health 27:165–171. [PubMed: 2733058]

Pronk A, Nuckols JR, De Roos AJ, Airola M, Colt JS, Cerhan JR, et al. 2013 Residential proximity to industrial combustion facilities and risk of non-Hodgkin lymphoma: a case-control study. Environmental health : a global access science source 12:20. [PubMed: 23433489]

Revich B, Aksel E, Ushakova T, Ivanova I, Zhuchenko N, Klyuev N, et al. 2001 Dioxin exposure and public health in Chapaevsk, Russia. Chemosphere 43:951–966. [PubMed: 11372889]

Reynolds P, Hurley SE, Petreas M, Goldberg DE, Smith D, Gilliss D, et al. 2005 Adipose levels of dioxins and risk of breast cancer. Cancer causes & control : CCC 16:525–535. [PubMed: 15986107]

Schecter A, Birnbaum L, Ryan JJ, Constable JD. 2006 Dioxins: an overview. Environmental research 101:419–428. [PubMed: 16445906]

Schuhmacher M, Domingo JL, Llobet JM, Kiviranta H, Vartiainen T. 1999 PCDD/F concentrations in milk of nonoccupationally exposed women living in southern Catalonia, Spain. Chemosphere 38:995–1004. [PubMed: 10028656]

Seifert A, Taubert H, Hombach-Klonisch S, Fischer B, Navarrete Santos A. 2009 TCDD mediates inhibition of p53 and activation of ERalpha signaling in MCF-7 cells at moderate hypoxic conditions. International journal of oncology 35:417–424. [PubMed: 19578757]

Sisti JS, Collins LC, Beck AH, Tamimi RM, Rosner BA, Eliassen AH. 2016 Reproductive risk factors in relation to molecular subtypes of breast cancer: Results from the nurses' health studies. International journal of cancer 138:2346–2356. [PubMed: 26684063]

Srogi K 2008 Levels and congener distributions of PCDDs, PCDFs and dioxin-like PCBs in environmental and human samples: a review. Environmental Chemistry Letters 6:1–28.

Stavraky K, Emmons S. 1974 Breast cancer in premenopausal and postmenopausal women. Journal of the National Cancer Institute 53:647–654. [PubMed: 4412246]

Tajimi M, Uehara R, Watanabe M, Oki I, Ojima T, Nakamura Y. 2005 Correlation coefficients between the dioxin levels in mother's milk and the distances to the nearest waste incinerator which was the largest source of dioxins from each mother's place of residence in Tokyo, Japan. Chemosphere 61:1256–1262. [PubMed: 15922405]

Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, et al. 2008 Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast cancer research : BCR 10:R67. [PubMed: 18681955]

Thomas VM, Spiro TG. 1995 An estimation of dioxin emissions in the United States. Toxicological & Environmental Chemistry 50:1–37.

US Environmental Protection Agency. 2006 An inventory of sources and environmental releases of dioxin-like compounds in the United States for the years 1987, 1995, and 2000. National Center for Environmental Assessment. Office of Research and Development Available: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=159286 (accessed 2 Apr 2019).

Viel JF, Clement MC, Hagi M, Grandjean S, Challier B, Danzon A. 2008 Dioxin emissions from a municipal solid waste incinerator and risk of invasive breast cancer: a population-based case-control study with GIS-derived exposure. International journal of health geographics 7:4. [PubMed: 18226215]

Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, et al. 2002 Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environmental health perspectives 110:625–628.

Warner M, Mocarelli P, Samuels S, Needham L, Brambilla P, Eskenazi B. 2011 Dioxin exposure and cancer risk in the Seveso Women's Health Study. Environmental health perspectives 119:1700–1705. [PubMed: 21810551]

Yanosky J, Paciorek C, Laden F, Hart J, Puett R, Liao D, et al. 2014 Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environmental health : a global access science source 13:63. [PubMed: 25097007]

Zubero MB, Ibarluzea JM, Aurrekoetxea JJ, Rivera J, Parera J, Abad E, et al. 2009 Serum levels of polychlorinated dibenzodioxins and dibenzofurans and PCBs in the general population living near

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

an urban waste treatment plant in Biscay, Basque Country. Chemosphere 76:784–791. [PubMed: 19482333]

Zubero MB, Eguiraun E, Aurrekoetxea JJ, Lertxundi A, Abad E, Parera J, et al. 2017 Changes in serum dioxin and PCB levels in residents around a municipal waste incinerator in Bilbao, Spain. Environmental research 156:738–746. [PubMed: 28482295]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- Dioxins are persistent organic pollutants from industrial combustion processes
- Epidemiologic studies of dioxin and breast cancer risk have been mixed
- No associations were shown for any dioxin facilities (all facilities combined)
- Positive associations were observed for municipal solid waste incinerators

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

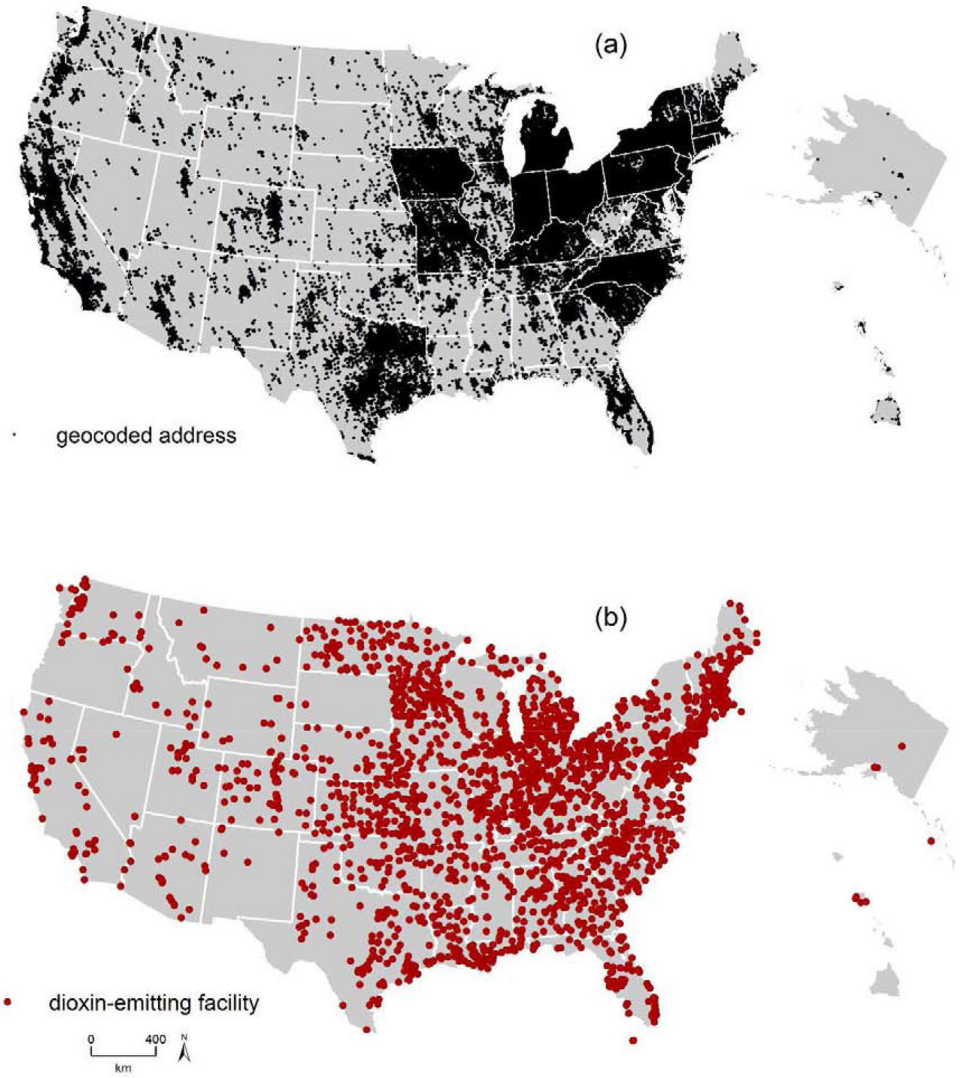

Figure 1.

(a) Geocoded residential addresses for NHSII participants (1989-2011) and (b) industrial dioxin-emitting facilities across the US. The scale bar is associated with the continental US.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Environ Res. Author manuscript; available in PMC 2021 July 01.

Table 1.

Age-adjusted characteristics of 112,397 NHSII women over follow-up from 1989-2013 by residential proximity to dioxin-emitting facilities

		Residential proximity to any (≥1) dioxin-emitting facilities					
		3 km		5 km		10 km	
Variable	**Overall**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Person-years (*n*)	2,302,566	1,995,939	306,627	1,693,295	609,271	1,055,170	1,247,396
Age (years) (mean ± SD)	44.9 ± 8.2	45.1 ± 8.2	44.1 ± 8.4	45.2 ± 8.2	44.2 ± 8.4	45.4 ± 8.2	44.5 ± 8.3
White (%)	96	96	95	96	95	96	96
Family history of breast cancer (%)	11	11	11	11	11	11	11
Personal history of biopsy-confirmed benign breast disease (BBD) (%)	17	17	17	17	17	17	17
Menopausal status and hormone use (%)							
Premenopausal	70	70	70	70	70	70	70
Never users	5	5	6	5	6	5	6
Past users	10	10	10	10	10	10	10
Current users	8	8	8	8	8	9	8
Missing	6	6	7	6	7	6	7
Age at menarche (years) (mean ± SD)	12.4 ± 1.4	12.4 ± 1.4	12.4 ± 1.5	12.4 ± 1.4	12.4 ± 1.4	12.4 ± 1.4	12.4 ± 1.4
Parity and age at first birth (%)							
Nulliparous	18	18	23	17	21	16	20
1-2 children <25	15	15	14	15	14	16	14
1-2 children ≥25-30	20	21	19	21	19	21	20
1-2 children ≥30	14	14	13	13	14	13	14
3+ children <25	12	12	11	12	10	13	11
3+ children ≥25-30	10	10	9	10	10	10	10
3+ children ≥30	2	2	2	2	3	2	3
Missing	9	9	9	9	9	9	9
Breastfeeding (%)							
Never	12	13	13	13	13	13	14
Ever	57	58	52	58	53	59	55
Missing	9	9	9	9	9	9	9
Oral contraceptive (OC) use (%)							

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

		Residential proximity to any (≥1) dioxin-emitting facilities					
		3 km		5 km		10 km	
Variable	**Overall**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Never	12	12	14	12	14	11	13
Past	75	76	73	76	74	77	74
Current	7	7	7	7	7	7	7
Missing	5	5	6	5	6	5	6
Height (in) (mean ± SD)	64.9 ± 2.6	64.9 ± 2.6	64.8 ± 2.6	64.9 ± 2.6	64.8 ± 2.6	64.9 ± 2.6	64.8 ± 2.6
Body mass index (BMI) (kg/m^2) at age 18 (mean ± SD)	21.2 ± 3.1	21.2 ± 3.1	21.4 ± 3.3	21.2 ± 3.1	21.3 ± 3.2	21.2 ± 3.1	21.2 ± 3.2
Current BMI (kg/m^2) (mean ± SD)	25.4 ± 4.9	25.4 ± 4.9	25.4 ± 5.0	25.4 ± 4.9	25.4 ± 4.9	25.4 ± 4.9	25.4 ± 4.9
Smoking status (%)							
Never	65	66	63	66	63	67	64
Past	25	25	26	24	26	24	26
Current	9	9	11	9	10	9	10
Alternate Healthy Eating Index (AHEI) (mean ± SD)	53.4 ± 11.2	53.4 ± 11.2	53.6 ± 11.2	53.4 ± 11.2	53.5 ± 11.1	53.3 ± 11.3	53.5 ± 11.1
Cumulative average total fat intake (g/day)	62.5 ± 9.6	62.5 ± 9.6	62.2 ± 9.7	62.6 ± 9.6	62.2 ± 9.6	62.8 ± 9.6	62.3 ± 9.5
Cumulative average animal fat intake (g/day)	33.9 ± 8.0	34.0 ± 8.0	33.7 ± 8.1	34.0 ± 8.0	33.7 ± 8.0	34.1 ± 8.1	33.8 ± 7.9
Adult alcohol consumption (g/day) (mean ± SD)	3.2 ± 5.3	3.2 ± 5.3	3.4 ± 5.5	3.2 ± 5.3	3.3 ± 5.4	3.2 ± 5.4	3.3 ± 5.3
Physical activity (MET hours/week) (mean ± SD)	20.1 ± 28.0	20.0 ± 27.8	20.7 ± 28.9	20.0 ± 27.8	20.4 ± 28.4	19.9 ± 27.8	20.2 ± 28.1
Census tract median home value ($10,000) (mean ± SD)	16.4 ± 12.2	16.5 ± 11.6	15.9 ± 15.1	16.4 ± 11.4	16.3 ± 14.0	16.2 ± 11.6	16.6 ± 12.6
Census tract median income ($) (mean ± SD)	63,929 ± 23,634	64,367 ± 23,231	61,133 ± 25,926	64,133 ± 22,972	63,421 ± 25,387	61,761 ± 22,388	65,789 ± 24,503
Individual-level income >$100,000 (%)	23	23	22	23	23	22	24
Married (%)	93	93	89	94	90	94	91
Living alone (%)	8	7	11	7	10	6	9
Region of residence (%)							
Northeast	33	33	39	31	39	26	40
Midwest	33	31	42	30	40	27	37
West	15	17	6	19	6	25	6
South	19	20	13	20	15	21	17
Cumulative average $PM_{2.5}$ (10 μg/m^3) (mean ± SD)	1.5 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	1.5 ± 0.3	1.6 ± 0.3
Cumulative average $PM_{2.5\text{-}10}$ (10 μg/m^3) (mean ± SD)	1.1 ± 0.5	1.1 ± 0.5	1.0 ± 0.4	1.1 ± 0.5	1.0 ± 0.4	1.1 ± 0.6	1.0 ± 0.4
Population density (population/mi^2) (mean ± SD)	3,788 ± 10,916	3,001 ± 7,338	8,850 ± 22,511	2,616 ± 5,870	7,008 ± 18,349	1,905 ± 2,957	5,359 ± 14,332

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Variable	Residential proximity to any (≥1) dioxin-emitting facilities							
	Overall	3 km		5 km		10 km		
		No	Yes	No	Yes	No	Yes	
Ever-moved Census tract (%)	78	78	79	78	78	78	79	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Associations between dioxin exposure and invasive breast cancer risk in NHSII (1989-2013) (n=112,397)

	Invasive breast cancer			ER+			ER−		
Exposure metric	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**
1. Residential proximity									
All facilities									
3 km									
No	3349/1995939	Referent	Referent	2026/1997202	Referent	Referent	506/1998553	Referent	Referent
Yes	491/306627	1.01 (0.92, 1.11)	1.03 (0.93, 1.13)	306/306804	1.04 (0.92, 1.17)	1.05 (0.93, 1.19)	69/307025	0.90 (0.70, 1.16)	0.92 (0.71, 1.19)
5 km									
No	2834/1693295	Referent	Referent	1713/1694352	Referent	Referent	429/1695479	Referent	Referent
Yes	1006/609271	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)	619/609654	1.06 (0.97, 1.16)	1.05 (0.96, 1.16)	146/610099	0.97 (0.80, 1.17)	0.98 (0.81, 1.19)
10 km									
No	1729/1055170	Referent	Referent	1052/1055809	Referent	Referent	269/1056502	Referent	Referent
Yes	2111/1247396	1.09 (1.02, 1.16)	1.07 (1.00, 1.14)	1280/1248197	1.09 (1.00, 1.18)	1.06 (0.98, 1.16)	306/1249076	0.98 (0.83, 1.15)	0.98 (0.83, 1.16)
Municipal solid waste incinerators (MSWIs)									
3 km									
No	3804/2283160	Referent	Referent	2312/2284582	Referent	Referent	570/2286142	Referent	Referent
Yes	36/19406	1.20 (0.86, 1.67)	1.20 (0.86, 1.68)	20/19424	1.09 (0.70, 1.69)	1.08 (0.69, 1.68)	5/19436	1.06 (0.44, 2.56)	1.11 (0.46, 2.72)
5 km									
No	3720/2238551	Referent	Referent	2261/2239945	Referent	Referent	556/2241472	Referent	Referent
Yes	120/64015	1.23 (1.02, 1.48)	1.25 (1.04, 1.52)	71/64061	1.19 (0.94, 1.50)	1.19 (0.93, 1.52)	19/64106	1.26 (0.79, 1.99)	1.35 (0.84, 2.19)
10 km									
No	3428/2069456	Referent	Referent	2086/2070747	Referent	Referent	523/2072141	Referent	Referent
Yes	412/233110	1.14 (1.03, 1.26)	1.15 (1.03, 1.28)	246/233259	1.12 (0.98, 1.28)	1.11 (0.96, 1.27)	52/233436	0.91 (0.69, 1.22)	0.94 (0.70, 1.27)
2. Duration of residence (years)[c]									

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Exposure metric	Invasive breast cancer			ER+			ER−		
	Cases/ person-years	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)	Cases/ person-years	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)	Cases/ person-years	Basic[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
All facilities									
3 km									
0	3000/1803070	Referent	Referent	1823/1804184	Referent	Referent	453/1805402	Referent	Referent
1-6	387/286292	0.98 (0.88, 1.09)	0.96 (0.87, 1.07)	228/286447	0.97 (0.85, 1.12)	0.95 (0.82, 1.09)	68/286593	1.06 (0.82, 1.38)	1.08 (0.84, 1.40)
>6	453/213204	1.01 (0.91, 1.11)	1.02 (0.92, 1.12)	281/213375	1.04 (0.92, 1.18)	1.05 (0.92, 1.19)	54/213583	0.89 (0.67, 1.18)	0.92 (0.69, 1.22)
5 km									
0	2365/1427586	Referent	Referent	1424/1428469	Referent	Referent	362/1429408	Referent	Referent
1-6	569/438551	1.01 (0.92, 1.11)	0.98 (0.89, 1.08)	353/438754	1.06 (0.94, 1.20)	1.02 (0.91, 1.15)	91/438991	0.95 (0.75, 1.20)	0.95 (0.75, 1.21)
>6	906/436428	1.00 (0.92, 1.08)	0.99 (0.91, 1.07)	555/436783	1.04 (0.94, 1.15)	1.02 (0.92, 1.13)	122/437178	0.99 (0.80, 1.22)	1.00 (0.81, 1.24)
10 km									
0	1291/807759	Referent	Referent	785/808239	Referent	Referent	208/808745	Referent	Referent
1-6	620/584944	0.99 (0.89, 1.09)	0.95 (0.86, 1.05)	386/585157	1.04 (0.91, 1.18)	0.99 (0.87, 1.13)	112/585397	0.91 (0.71, 1.16)	0.90 (0.70, 1.15)
>6	1929/909863	1.08 (1.01, 1.16)	1.05 (0.97, 1.13)	1161/910610	1.09 (0.99, 1.20)	1.05 (0.96, 1.16)	255/911436	0.99 (0.81, 1.20)	0.98 (0.81, 1.20)
MSWIs									
3 km									
0	3767/2266905	Referent	Referent	2293/2268310	Referent	Referent	564/2269856	Referent	Referent
1-6	36/23027	1.10 (0.79, 1.53)	1.07 (0.77, 1.49)	18/23043	0.94 (0.59, 1.49)	0.90 (0.56, 1.43)	7/23055	1.37 (0.65, 2.90)	1.39 (0.65, 2.98)
>6	37/12634	1.39 (1.01, 1.93)	1.39 (1.00, 1.93)	21/12653	1.30 (0.84, 2.00)	1.28 (0.83, 1.98)	4/12667	1.12 (0.42, 3.00)	1.20 (0.44, 3.23)
5 km									
0	3636/2196373	Referent	Referent	2214/2197728	Referent	Referent	546/2199227	Referent	Referent
1-6	91/62258	1.09 (0.88, 1.34)	1.05 (0.85, 1.29)	51/62296	1.02 (0.77, 1.35)	0.96 (0.73, 1.27)	14/62326	1.06 (0.62, 1.81)	1.11 (0.65, 1.90)
>6	113/43934	1.26 (1.05, 1.52)	1.27 (1.05, 1.54)	67/43982	1.23 (0.97, 1.57)	1.22 (0.95, 1.57)	15/44025	1.26 (0.75, 2.12)	1.34 (0.79, 2.29)
10 km									
0	3259/1977088	Referent	Referent	1985/1978302	Referent	Referent	497/1979638	Referent	Referent

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Exposure metric	Invasive breast cancer Cases/ person-years	Invasive breast cancer Basic[a] HR (95% CI)	Invasive breast cancer Fully adjusted[b] HR (95% CI)	ER+ Cases/ person-years	ER+ Basic[a] HR (95% CI)	ER+ Fully adjusted[b] HR (95% CI)	ER− Cases/ person-years	ER− Basic[a] HR (95% CI)	ER− Fully adjusted[b] HR (95% CI)
1-6	207/159640	1.06 (0.91, 1.22)	1.01 (0.88, 1.17)	118/159733	1.01 (0.84, 1.22)	0.96 (0.80, 1.16)	39/159796	1.17 (0.84, 1.62)	1.19 (0.85, 1.66)
>6	374/165838	1.12 (1.01, 1.25)	1.11 (0.99, 1.24)	229/165971	1.14 (0.99, 1.31)	1.12 (0.97, 1.29)	39/166143	0.85 (0.61, 1.18)	0.87 (0.62, 1.23)
3. Emission index (ng TEQ/ year per km^2)[c]									
All facilities									
3 km									
0	3007/1809819	Referent	Referent	1827/1810937	Referent	Referent	455/1812156	Referent	Referent
0-0.09	418/246917	1.01 (0.91, 1.12)	0.99 (0.90, 1.10)	251/247085	1.02 (0.89, 1.16)	0.99 (0.87, 1.13)	64/247244	1.05 (0.81, 1.37)	1.07 (0.83, 1.40)
>0.09	415/245830	0.99 (0.89, 1.10)	1.00 (0.90, 1.11)	254/245984	1.02 (0.89, 1.16)	1.02 (0.89, 1.17)	56/246179	0.90 (0.68, 1.19)	0.93 (0.70, 1.23)
5 km									
0	2386/1437286	Referent	Referent	1434/1438182	Referent	Referent	366/1439122	Referent	Referent
0-0.05	702/433082	0.96 (0.88, 1.05)	0.94 (0.86, 1.02)	446/433335	1.04 (0.94, 1.16)	1.01 (0.90, 1.12)	96/433659	0.88 (0.70, 1.10)	0.88 (0.70, 1.10)
>0.05	752/432198	1.03 (0.95, 1.12)	1.03 (0.94, 1.12)	452/432489	1.05 (0.94, 1.17)	1.04 (0.93, 1.15)	113/432797	1.04 (0.84, 1.29)	1.06 (0.86, 1.32)
10 km									
0	1305/816691	Referent	Referent	796/817173	Referent	Referent	209/817689	Referent	Referent
0-0.03	1284/744208	1.06 (0.98, 1.14)	1.02 (0.94, 1.10)	786/744681	1.08 (0.98, 1.20)	1.04 (0.94, 1.15)	177/745230	0.93 (0.76, 1.13)	0.91 (0.74, 1.12)
>0.03	1251/741667	1.06 (0.98, 1.14)	1.02 (0.94, 1.11)	750/742153	1.06 (0.96, 1.17)	1.02 (0.92, 1.13)	189/742658	1.01 (0.83, 1.24)	1.02 (0.83, 1.25)
MSWIs									
3 km									
0	3768/2267786	Referent	Referent	2294/2269191	Referent	Referent	564/2270737	Referent	Referent
0-4.70	30/17418	1.06 (0.74, 1.52)	1.04 (0.72, 1.49)	18/17430	1.07 (0.67, 1.70)	1.04 (0.65, 1.65)	2/17444	0.49 (0.12, 1.98)	0.49 (0.12, 1.98)
>4.70	42/17362	1.41 (1.04, 1.92)	1.40 (1.03, 1.92)	20/17385	1.13 (0.72, 1.75)	1.09 (0.69, 1.70)	9/17396	2.03 (1.05, 3.95)	2.24 (1.13, 4.47)
5 km									
0	3645/2198722	Referent	Referent	2220/2200080	Referent	Referent	546/2201582	Referent	Referent

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Invasive breast cancer			ER+			ER−		
Exposure metric	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**	**Cases/ person-years**	**Basic[a] HR (95% CI)**	**Fully adjusted[b] HR (95% CI)**
0-1.95	92/52164	1.09 (0.89, 1.34)	1.06 (0.86, 1.30)	50/52203	0.99 (0.74, 1.31)	0.94 (0.71, 1.25)	14/52230	1.16 (0.68, 1.97)	1.17 (0.68, 1.99)
>1.95	103/51680	1.20 (0.99, 1.46)	1.21 (0.98, 1.48)	62/51723	1.21 (0.94, 1.55)	1.18 (0.90, 1.54)	15/51766	1.21 (0.72, 2.02)	1.33 (0.77, 2.30)
10 km									
0	3264/1981883	Referent	Referent	1987/1983100	Referent	Referent	497/1984440	Referent	Referent
0-0.48	275/161251	1.05 (0.93, 1.19)	1.01 (0.89, 1.15)	160/161362	1.02 (0.87, 1.20)	0.98 (0.83, 1.15)	39/161472	1.01 (0.73, 1.40)	1.01 (0.72, 1.40)
>0.48	301/159431	1.16 (1.03, 1.31)	1.16 (1.03, 1.32)	185/159544	1.19 (1.02, 1.38)	1.18 (1.00, 1.38)	39/159666	1.00 (0.72, 1.38)	1.06 (0.75, 1.50)

[a] Adjusted for age, race.

[b] Additionally adjusted for family history of breast cancer, personal history of biopsy-confirmed BBD, age at menarche, parity, age at first birth, lactation, menopausal status and hormone use (among postmenopausal women only), height, BMI at age 18, change in BMI since age 18, physical activity, smoking status, adult alcohol consumption, Census tract median home value, Census tract median income, marital status, living arrangements, individual-level income, population density.

[c] For each specified distance of 3, 5, and 10 km, the duration of residence and emission metrics were defined as three-level categorical variables with categories for no exposure, exposure greater than zero and less than or equal to the median value among participants who ever resided near any dioxin-emitting facility over follow-up, and exposure greater than the median value.

Environ Res. Author manuscript; available in PMC 2021 July 01.