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Pesticide exposure and hepatocellular carcinoma risk: a case-control study using a geographic information system (GIS) to link SEER-Medicare and California pesticide data

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Abstract

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Human subjects research

The SEER-Medicare data used in this study are considered exempt from human subjects' regulation. The University of Pittsburgh Institutional Review Board approved this study in 2013 as an exemption under section 45 CFR 46.101(b)(4).

[2]Abbreviations: ANOVA, analysis of variance; CDPR, California Department of Pesticide Regulation; CDWR, California Department of Water Resources; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; ESRD, end-stage renal disease; GIS, geographic information system; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HMO, health maintenance organization; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; IQR, interquartile range; LUS, land use survey; MAUP, modifiable areal unit problem; NLCD, National Land Cover Database; OR, odds ratio; pctl, percentile; PLSS, Public Land Survey System; PUR, Pesticide Use Report; RUCC, Rural-Urban Continuum Codes; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; ZCTA, ZIP Code Tabulation Area.

Background—Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is associated with low survival. U.S. studies examining self-reported pesticide exposure in relation to HCC have demonstrated inconclusive results. We aimed to clarify the association between pesticide exposure and HCC by implementing a novel data linkage between Surveillance, Epidemiology, and End Results (SEER)-Medicare and California Pesticide Use Report (PUR) data using a geographic information system (GIS).

Methods—Controls were frequency-matched to HCC cases diagnosed between 2000 and 2009 in California by year, age, race, sex, and duration of residence in California. Potential confounders were extracted from Medicare claims. From 1974 to 2008, pounds (1 pound represents 0.45 kg) of applied organophosphate, organochlorine, and carbamate pesticides provided in PURs were aggregated to the ZIP Code level using area weighting in a GIS. ZIP Code exposure estimates were linked to subjects using Medicare-provided ZIP Codes to calculate pesticide exposure. Agricultural residents were defined as living in ZIP Codes with a majority area intersecting agricultural land cover according to the 1992, 2001, and 2006 National Land Cover Database (NLCD) rasters. Multivariable conditional logistic regression was used to estimate the association between pesticide exposure and HCC.

Results—Among California residents of agriculturally intensive areas, previous annual ZIP Code-level exposure to over 14.53 kg/km^2 of organochlorine pesticides (75th percentile among controls) was associated with an increased risk of HCC after adjusting for liver disease and diabetes (adjusted odds ratio [OR] 1.87, 95% confidence interval [CI] 1.17, 2.99; p=0.0085). ZIP Code-level organochlorines were significantly associated with an increased risk of HCC among males (adjusted OR 2.76, 95% CI 1.58, 4.82; p=0.0004), but not associated with HCC among females (adjusted OR 0.83, 95% CI 0.35, 1.93; p=0.6600) (interaction p=0.0075).

Conclusions—This is the first epidemiologic study to use GIS-based exposure estimates to study pesticide exposure and HCC. Our results suggest that organochlorine pesticides are associated with an increase in HCC risk among males but not females.

Keywords

liver cancer; pesticide; geographic information system; epidemiology; case-control study

1. Introduction

Pesticides, an environmental exposure comprised of widely used chemicals designed to treat pests (e.g., insects), have been associated with adverse human health outcomes such as cancers (Alavanja et al., 2004; Blair et al., 2015). Pesticide use, particularly among herbicides, rapidly increased between 1960 and 1981 in the U.S., and has since experienced fluctuations in use due to changes in planted acreage, pest infestation, and Integrated Pest Management (e.g., crop rotation) (Fernandez-Cornejo et al., 2014). In the U.S., pesticides are commonly used in agriculture and horticulture and exposure occurs most frequently via diet (Dich et al., 1997; Ritz and Rull, 2008). Additional sources of exposure include occupation (e.g., pest control) and very importantly, residential proximity to agricultural pesticide applications. Applied pesticides can drift from their intended sites through the air and ground via spray drift and post-application volatilization (Rull and Ritz, 2003). Vulnerable populations include rural residents and farming families (Ward et al., 2000), as

pesticides can enter homes through drift and from clothing (Ritz and Rull, 2008). Gunier et al. (2011) demonstrated that residential proximity within 1,250 m of pesticide-treated crops in California was significantly correlated with pesticide concentrations in sampled carpet dust. Pesticides are less likely to degrade within homes due to the absence of moisture, sunlight, and microorganisms (Gunier et al., 2011; Ritz and Rull, 2008), and humans can be subsequently exposed via dermal contact and ingestion (Gunier et al., 2001).

Epidemiologic studies have shown that pesticide exposure may increase the risk of hepatocellular carcinoma (HCC). Primary liver cancer is the sixth most common cancer in the world and the second leading cause of cancer-related death (Ferlay et al., 2013), and between 70 and 85% of primary liver cancer cases are HCC (Jemal et al., 2011). U.S. HCC incidence, adjusted to the 2000 U.S. Standard Population, significantly increased 29% from 4.4 per 100,000 (2000 to 2004) to 5.7 per 100,000 (2005 to 2009) (rate ratio 1.29, 95% confidence interval [CI] 1.27, 1.32) (National Cancer Institute, 2014a). In the U.S., HCC is more common among males and among individuals of Asian descent (Altekruse et al., 2009). The mean age at diagnosis is 64 years (median 63) (National Cancer Institute, 2014b). Many HCC cases are diagnosed at a regional or distant stage (49% between 2000 and 2009) (National Cancer Institute, 2014b), which contributes to the low five-year 16.6% relative survival rate in the U.S. (National Cancer Institute, 2014c). Predominant HCC risk factors in most high-risk areas, such as parts of Asia, include chronic hepatitis B virus (HBV) infection and consumption of aflatoxin-contaminated foods (Yu and Yuan, 2004). Chronic hepatitis C virus (HCV) infection and heavy alcohol consumption (>50 to 70 g per day) are major risk factors in low-risk areas such as the U.S. Approximately 64.5% (95% CI 63.3, 65.6) of all HCC cases occurring in the U.S. population aged 68 years and older are attributed to HCV, HBV, alcoholic liver disease (e.g., alcoholic cirrhosis of liver), rare metabolic disorders (e.g., hemochromatosis), and diabetes and/or obesity (Welzel et al., 2013). Most of these risk factors contribute to the formation and progression of cirrhosis, or scarring of the liver (El-Serag, 2011). Between 70 and 90% of all HCC cases occur within an established background of chronic liver disease and cirrhosis (El-Serag, 2011; Sanyal et al., 2010). Very importantly, although HCV, HBV, and heavy alcohol consumption are the major risk factors for cirrhosis among HCC cases in the U.S., between 15 and 50% of all HCC cases have no established risk factors (Carr, 2010; El-Serag, 2007).

Pesticides are hypothesized to contribute to liver carcinogenesis through mechanisms of genotoxicity, tumor promotion, immunotoxicity, and hormonal action (Dich et al., 1997; Gomaa et al., 2008). Several case-control studies conducted in China demonstrated statistically significant increased risks for HCC (McGlynn et al., 2006; Persson et al., 2012; Zhao et al., 2011). Persson et al. (2012) showed that the highest quintile of serum dichlorodiphenyltrichloroethane (DDT) (≥810 ng/g fat), an organochlorine pesticide, compared to ≤261 ng/g fat significantly increased HCC risk after adjusting for risk factors including age, hepatitis B surface antigen (HBsAg), and alcohol consumption (adjusted odds ratio [OR] 2.96, 95% CI 1.19, 7.40). However, some studies have shown inconclusive results. In the U.S., three studies reported non-significant increased risks for HCC among those employed in farming (Austin et al., 1987; Brownson et al., 1989; Suarez et al., 1989). However, farming in New Jersey conferred significantly higher risk for HCC compared to

no employment in this occupation (adjusted OR 3.20, 95% CI 1.11, 9.21) (Stemhagen et al., 1983).

To clarify the relationship between pesticide exposure and HCC in the U.S., we conducted a population-based case-control study in California, the most agriculturally productive state in the U.S. (U.S. Department of Agriculture, 2010). Cases and controls, in addition to claims used to identify comorbidities, were derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Pesticide exposure was estimated using California Pesticide Use Reports (PURs). We implemented a novel data linkage between SEER-Medicare and PUR data using Medicare-provided ZIP Codes in a geographic information system (GIS), calculating an ecologic metric of exposure. Individuals with the opportunity for exposure to agricultural pesticides were selected according to residence within ZIP Codes mostly occupied by agricultural land cover using National Land Cover Database (NLCD) rasters.

2. Methods

2.1. Study population

SEER-Medicare represents a data linkage between SEER cancer data and Medicare claims (Engels et al., 2011). SEER is a National Cancer Institute program collecting individual person-level information on cancer incidence and survival from 18 population-based cancer registries covering 28% of the U.S. Medicare is a U.S. federal health insurance program for qualifying individuals ≥65 years old, covering 97% of this age group, in addition to those <65 years with end-stage renal disease (ESRD) or medical disability. All Medicare beneficiaries are entitled to Part A (hospital insurance), approximately 96% enroll in Part B (medical insurance), 24% enroll in Medicare Advantage or a managed care plan (e.g., health maintenance organization [HMO]), and 38% enroll in Part D prescription drug coverage (Engels et al., 2011; The Kaiser Family Foundation, 2007). Part C does not process bills through Medicare. The SEER-Medicare data linkage includes all SEER cancer cases also in the Medicare Enrollment Database. Medicare claims are linked to cases via personal identifiers, e.g., Social Security number. The 2012 data linkage includes SEER cases from 1991 to 2009 and Medicare claims from 1991 to 2010. The SEER-Medicare linkage is 94% successful among those 65 years and older (3% of elderly do not receive Medicare and 3% have insufficient linkage information). SEER cancer data for the entire state of California has been available since 2000 (National Cancer Institute, 2015).

2.2. Case and control ascertainment

Study participants were eligible for inclusion into this study if they were of known race and ≥66-year-old California residents with at least 13 months of continuous Parts A and B, non-HMO coverage and at least one California ZIP Code (used for mail delivery in the U.S.) available by the time of diagnosis/selection. The case file only included liver cancer cases. Cases were defined using the following criteria: International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography code C22.0 (primary liver cancer) and ICD-O-3 histology codes 8170 to 8175 (Fritz et al., 2000); diagnostic confirmation (e.g., positive histology) excluding clinical diagnosis only (Davila et al., 2005); sequence number 00 or 01;

reported to a California cancer registry; diagnosed between 2000 and 2009; and not reported via autopsy or death certificate only. Controls were selected from a 5% random sample of Medicare beneficiaries residing in SEER geographic areas. Only the liver cancer case file and the 5% random sample of non-cancer individuals were utilized during control selection (Davila et al., 2005; Welzel et al., 2011). Cases originally included in the 5% random sample (five percent flag) were added back into the random sample to be considered during control selection (Engels et al., 2011). For each year between 2000 and 2009 (the period during which SEER data is available for California), eligible controls who were not a case and alive as of July 1 of that year were enumerated. Eligible controls may have included cases diagnosed after July 1 in the year of selection. Cases and controls were frequency-matched according to age, sex, race (white, black, Asian, other, Hispanic, Native American), and years (duration) of non-continuous California residence (using available Medicare-provided ZIP Codes, categorized using tertiles among cases: 1–5, 6–10, ≥11). At most five controls were matched to cases within each stratum. Controls were sampled with replacement.

2.3. Pesticide exposure

The pesticide exposure time period of interest was 1974 until the year before diagnosis/selection (the year of diagnosis/selection is between 2000 and 2009). Agricultural pesticide exposure was estimated at the ZIP Code level by linking California Department of Pesticide Regulation (CDPR) Pesticide Use Report (PUR) data with available Medicare-provided ZIP Codes in a GIS. PUR data include pounds of applied pesticides (1 pound represents 0.45 kg), chemical name, date, and the specific 2.59 km^2 (1 mi^2) Public Land Survey System (PLSS) section where the pesticides were applied (California Department of Pesticide Regulation, 2014). Agricultural use PURs from 1974 to 2008 were checked for errors (e.g., duplicates). Outlier pesticide use densities (kg/km^2), defined using CDPR flags (e.g., >22,417 kg/km^2 if non-fumigant pesticide) from 1990 to 2008 and as >22,417 kg/km^2 (>112,085 kg/km^2 if fumigant) or 50 times the median use density for all uses of a given pesticide product, crop, unit type, and record type from 1974 to 1989, were replaced with the statewide median use density for that pesticide in that year (Rull and Ritz, 2003). Pounds of active ingredient were recalculated using the PUR number of treated acres (1 acre represents 0.004 km^2).

Pesticide applications belonging to the organophosphate, organochlorine, and carbamate chemical classes, which have been previously associated with HCC, were extracted from PUR records (Supplemental Table 1) (Cordier et al., 1993; Ezzat et al., 2005; Persson et al., 2012). For each year between 1974 and 2008, pounds were matched and summed according to PLSS section and divided by the section area to calculate pesticide use densities (kg/km^2) for each PLSS section (Bell et al., 2001; Clary and Ritz, 2003; Reynolds et al., 2004; Rull and Ritz, 2003). PLSS sections and California TIGER/Line® ZIP Code Tabulation Areas (ZCTAs; used to approximate ZIP Code boundaries for all years between 1974 and 2008) were intersected (U.S. Census Bureau, 2000). PLSS section pesticide use densities were spatially aggregated (i.e., upscaled) to the ZIP Code level to calculate ZIP Code-level pesticide use densities using area weighting in a GIS, where section rates were weighted by the proportion of the ZIP Code area comprised by that section.

Medicare-provided ZIP Codes (last billing ZIP Code in that year) were available for each study subject for each year from 1991 until 2009 depending on age and enrollment in Medicare and were used to determine residence in or outside of California. We assumed that each study subject's earliest available Medicare-provided ZIP Code was their ZIP Code of residence back to 1974 (i.e., carried back). The majority of earliest available Medicare-provided ZIP Codes among cases (86.4%) and controls (85.6%) included in the study were in California and in the TIGER/Line® ZIP Code file. The remainder of earliest available Medicare-provided ZIP Codes among cases and controls were missing (8.6%; 8.9%), a California ZIP Code not found in the TIGER/Line® ZIP Code file (1.8%; 2.1%), or not a California ZIP Code (3.3%; 3.4%).

The ZIP Code-level pesticide use densities (upscaled from PLSS sections) were linked to each study subject's Medicare-provided ZIP Codes from 1974 to the year before diagnosis/selection that were in California and in the TIGER/Line® ZIP Code file. In other words, residence outside of California was not considered in the exposure calculation. Among cases (n=93,849 ZIP Codes from 1974 until the year before diagnosis; includes carried back) and controls (n=463,700 ZIP Codes from 1974 until the year before selection) included in the study, 88.9% (88.3% controls) of all ZIP Codes were found in California and in the TIGER/Line® ZIP Code file, 6.7% (6.9%) were missing, 2.9% (3.0%) were not in California, and 1.6% (1.8%) were in California but not in the TIGER/Line® ZIP Code file. Each study subject's ZIP Code pesticide use densities were summed and divided by the number of years of California residence (i.e., number of years with California ZIP Codes in the TIGER/Line® ZIP Code file) to calculate an average annual pesticide use density (Ritz et al., 2009; Rull and Ritz, 2003; Wang et al., 2011). ZIP Codes in California and in the TIGER/Line® ZIP Code file associated with a 0 kg/km^2 pesticide use density were included in the annual pesticide use density calculation.

2.4. Covariates

The following were extracted from inpatient (Part A), outpatient (Part B), and carrier (e.g., physician) Medicare claims: HCV (ICD-9-CM [Ninth Revision, Clinical Modification] codes 070.41, 070.44, 070.51, 070.54, 070.70, V02.62), HBV (070.22, 070.23, 070.32, 070.33, V02.61), unspecified hepatitis (070.9, 070.59, 070.49, 571.4, 571.8, 571.9), diabetes (250), obesity (278.00, 278.01, 278.02, V77.8, 259.9), alcoholic liver disease (571.0, 571.1, 571.2, 571.3; 571.5 or 571.6 in the presence of 303, 291, 305.0, V11.3, or V79.1), non-specific cirrhosis (571.5 or 571.6 not in the presence of HCV, HBV, unspecified hepatitis, or alcoholic liver disease), rare genetic disorders (α1 antitrypsin deficiency 273.4, hemochromatosis 275.0, porphyria 277.1, tyrosinemia 270.2, Wilson disease 275.1), human immunodeficiency virus (HIV) (042, V08), and smoking (V15.82, 305.1, 989.84; ever-smoking as there is not enough information to identify former smokers) (Davila et al., 2005; Welzel et al., 2013; Welzel et al., 2011). Liver disease is a three-level categorical variable used in statistical modeling, defined as none (no hepatitis, alcoholic liver disease, and non-specific cirrhosis), hepatitis only (hepatitis without alcoholic liver disease and cirrhosis), and cirrhosis (alcoholic liver disease or non-specific cirrhosis with or without hepatitis). In the subgroup analysis, liver disease (yes/no) was defined as having any of the following conditions: hepatitis, alcoholic liver disease, or non-specific cirrhosis. Conditions were

considered present if there was a single Part A diagnosis or two Part B or carrier claim diagnoses separated by at least 30 days (Engels et al., 2011). Due to differential availability of claims data depending on when cases were diagnosed (claims from 1991 to 2010 if diagnosed before 2003; from 1998 to 2010 if diagnosed between 2003 and 2005; from 2000 to 2010 if diagnosed between 2006 and 2007; and from 2002 to 2010 if diagnosed between 2008 and 2009) (National Cancer Institute, 2014d), Medicare claims within the six years preceding diagnosis/selection were examined. Claims within one year preceding diagnosis/selection were excluded due to potential medical detection bias (Engels et al., 2011). As eligible study subjects were required to have at least 13 months of continuous Parts A and B, non-HMO enrollment prior to diagnosis/selection, no Medicare claim diagnosis codes identifying a particular health condition indicated the absence of that condition (i.e., there were no missing variables in our study).

State buy-in, or Medicare Savings Programs where states pay for Medicare premiums, deductibles, and/or coinsurance due to limited income, was used as an indicator for socioeconomic status (Centers for Medicare & Medicaid Services, 2014; Davila et al., 2005). State buy-in was considered present if a subject was enrolled in Parts A or B state buy-in at any time point beginning in the year before diagnosis/selection. The proportion of each ZIP Code's ≥16-year-old population employed in the agriculture industry was provided by the 2000 Census Summary File 3 (U.S. Census Bureau, 2002). The Medicare-provided ZIP Code in or closest to 2000 was matched to Census data.

2.5. Subgroup analysis: California residents of agriculturally intensive areas

In a subgroup analysis, statistical analyses were limited to California residents of agriculturally intensive areas, defined as individuals with the opportunity (i.e., at risk) for exposure to agricultural pesticides by virtue of residing in California ZIP Codes mostly comprised of agricultural land cover. National Land Cover Database (NLCD) raster files from 1992, 2001, and 2006, a standard U.S. land cover data source derived from classified 30 m Landsat images, were used in this study (Homer et al., 2012). California files from 1992 were mosaicked or combined. All NLCD files were subject to a majority filter (3×3 filter) to reduce random noise (Fuller and Brown, 1996; Stow et al., 1989). Each raster file was reclassified to agricultural land cover (NLCD classes 81–85) vs. all other land covers and combined using map algebra. The agricultural raster layer was converted to a vector layer and intersected with California ZIP Codes. Using the ZIP Code occurring most frequently (referred to as the mode ZIP Code), cases and controls residing in ZIP Codes with a majority area (≥50%) intersecting agricultural land cover were selected into this analysis.

2.6. Statistical analysis

Pesticide exposure was examined by combining all pesticide chemical classes (organophosphates, organochlorines, and carbamates) and by each class separately (Gunier et al., 2001; Reynolds et al., 2005). The pesticide chemical classes were highly correlated with each other and were thus not included as predictors in a single statistical model (Spearman correlation for organophosphates and organochlorines 0.90, $p<0.0001$; organophosphates and carbamates 0.92, $p<0.0001$; organochlorines and carbamates 0.88, $p<0.0001$). We initially used random-intercept logistic regression to explore the extent to

which individuals within the same ZIP Code might have similar risk for HCC. After incorporating a random intercept defined as the ZIP Code at diagnosis/selection and the mode ZIP Code, a low intraclass correlation coefficient (0.03) indicated little variability between clusters (ZIP Codes) and that a random intercept was not necessary. Univariable conditional logistic regression using robust variance estimation and stratifying by (conditioning on) the frequency matching factors of year, age, sex, race, and California residence was used to assess the association between each variable and case-control status. Chi-square, one-way analysis of variance (ANOVA), and Kruskal-Wallis tests were used to evaluate the association between each variable and pesticide exposure. Selecting variables that were either significantly associated with HCC or pesticide exposure ($p<0.05$), backward elimination methods ($p>0.20$ removed), confirmed with forward selection ($p<0.20$ to enter), were utilized to build final models. Regression diagnostics (e.g., goodness of fit, collinearity, linearity of the logit, outliers, influential points) were performed on final models. ORs and 95% CIs were estimated using the final multivariable conditional logistic regression models (robust variance estimation) conditioned on the frequency matching factors.

Models were stratified by rural/urban residence using Rural-Urban Continuum Codes (RUCC) codes, which define U.S. counties as metropolitan vs. non-metropolitan using population, worker commuting, and metropolitan adjacency information (U.S. Department of Agriculture, 2013). Counties were assigned the mode RUCC code using 1974, 1983, 1993, and 2009 data; if there was no clear majority, the more urban RUCC code was assigned. After intersecting TIGER/Line© counties and ZIP Codes in a GIS (ZIP Code was matched to county comprising the majority of its area), county RUCC codes were assigned to each study subject according to their mode ZIP Code. RUCC codes were categorized into three groups: urban (RUCC codes 0–3; metropolitan areas of <250,000 to >1 million population), rural ≥20,000 population (4–5), and rural <20,000 population (6–9) (McCall-Hosenfeld et al., 2014). Rural/urban residential status was assumed to be constant regardless of state boundaries. Interactions between pesticide exposure and each covariate and matching factor on the risk of HCC were examined by individually including the cross-product term in the model and testing its significance. When a significant interaction was detected, separate models, stratified by the covariate or factor, were created to estimate the effect of pesticides on HCC risk within stratum. The effect of 10-, 15-, and 20-year lags was examined, where pesticide exposure occurring outside of the lag window (before diagnosis/selection) was considered. Pesticide use densities were categorized using tertiles or the 75th percentile among controls (McGlynn et al., 2006; Reynolds et al., 2005; Rignell-Hydbom et al., 2009). All reported p-values are two-sided. Analyses were conducted in 2014 using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). All spatial data were re-projected to the California Teale Albers (NAD83 datum; meter) coordinate system and all geospatial analyses were conducted in 2014 using ArcGIS (Esri, 2012).

2.7. Spatial analyses: spatial autocorrelation and the modifiable areal unit problem (MAUP)

Potential spatial autocorrelation of residuals from the final multivariable conditional logistic regression model (entire sample; all classes) was examined using the global Moran's I test (considering the mode ZIP Code and diagnosis/selection ZIP Code). Regarding the potential

impact of the MAUP on study results, global Moran's I tests of PLSS section-level pesticide use densities (all classes) were calculated for each year from 1974 to 2008. After intersecting PLSS sections with ZIP Codes, yearly within-ZIP Code PLSS section pesticide use density variability from 1974 to 2008 was examined using average medians and average interquartile ranges (IQRs) of PLSS section use densities within each ZIP Code. Using the mode ZIP Code, global and local spatial autocorrelation of study subject residential locations (proportion of study population residing within each ZIP Code overall and stratified by case-control status) in California was examined using global Moran's I and Anselin Local Moran's I tests.

3. Results

Among 10,408 individuals diagnosed with HCC as a first cancer in California between 2000 and 2009 who were of known race and in the Medicare Enrollment Database, 29% were included in our study. Fig. 1 shows cases excluded from our study according to each eligibility criterion. Thirty-three percent of all considered cases were excluded due to age and 29% due to HMO coverage. A comparison of characteristics for included vs. excluded HCC cases is shown in Table 1. Excluded cases were more likely to be urban-dwelling younger white males of higher socioeconomic status having resided in California for a shorter period of time (reflecting younger age).

Table 2 presents population characteristics of the 3,034 HCC cases and 14,991 frequency-matched controls included in our study (entire sample). Cases were on average 75.1 years old (median 74.0), typically males, of white race, and had resided in California for over 6 years. By design, matching factors did not differ between cases and controls. When considering the time period of six years before diagnosis/selection during which claims were examined for health conditions, most cases (75.1%) and controls (75.1%) contributed between 4.1 and 6.1 years of claims to the study. As expected, a higher proportion of cases were ever-smokers and had previously been diagnosed with HCV, HBV, unspecified hepatitis, alcoholic liver disease, non-specific cirrhosis, diabetes, obesity, or rare genetic disorders. Cases were more likely than controls to be of low socioeconomic status, while controls typically resided in ZIP Codes with a slightly higher percentage of individuals aged 16 years or older employed in agriculture.

From 1974 until the year before diagnosis/selection (exposure time period), a median of 30 (IQR 27, 33) ZIP Codes in California and in the TIGER/Line® ZIP Code file were available for both cases and controls. Among cases and controls, an average of 88.9% (median 100%) and 88.3% (median 100%), respectively, of each study subject's exposure time period (i.e., residential address history) was comprised of ZIP Codes in California and in the TIGER/Line® ZIP Code file. Cases were more likely to reside in an urban area (Table 2). A small proportion of cases (n=77; 2.5%) and controls (n=420; 2.8%) were missing RUCC codes (rural/urban residence) due to the absence of their ZIP Codes in the TIGER/Line® file used to intersect with counties. Of those with non-missing RUCC codes, a small proportion of cases (n=81; 2.7%) and controls (n=433; 3.0%) had ZIP Codes outside of California (i.e., subjects with at least one California ZIP Code eligible for study inclusion but their mode ZIP Code was not in California). The majority of cases (n=2,710; 89.3%) and controls

(n=13,081; 87.3%) resided in ZIP Codes where rural/urban residence did not change over time.

In the unadjusted models conditioning on the frequency matching factors, there was no association between increasing exposure to any of the examined pesticide chemical classes and incidence of HCC in the entire sample or among urban residents (Table 3). However, increasing exposure to pesticides (all classes and organochlorines) was associated with an increased odds of HCC among residents of rural areas with ≥20,000 population. Risks were elevated, but no statistically significant associations were observed among individuals living in rural areas with <20,000 population.

After adjusting for liver disease, diabetes, rare genetic disorders, and state buy-in, ZIP Code-level pesticide exposure was not associated with HCC in the entire sample or among urban residents (Table 3). Risks remained elevated among rural residents, however, after adjustment, only moderate compared to low ZIP Code-level organochlorine pesticide exposure remained statistically significant among individuals residing in rural areas with <20,000 population. Both similar and stronger associations between moderate vs. low organochlorine exposure and HCC were observed among rural <20,000 population residents when accounting for exposure lags: 10-year lag (adjusted OR 5.30, 95% CI 1.73, 16.22; p=0.0035); 15-year lag (adjusted OR 3.59, 95% CI 1.31, 9.86; p=0.0130); and 20-year lag (adjusted OR 5.83, 95% CI 2.02, 16.81; p=0.0011). There were no significant interactions between pesticide exposure and the other variables or the matching factors.

3.1. California residents of agriculturally intensive areas

In a subgroup analysis, 227 cases and 1,437 controls residing in the 201 California ZIP Codes with a majority area intersecting agricultural land cover (according to each study subject's mode ZIP Code) were examined (Fig. 2). Most of the 53,322.27 km^2 of agricultural land cover in California in 1992, 2001, and/or 2006 was present during all three years (28,259.35 km^2; 53%). Approximately 28% of the agricultural land cover was present only in 2001 and 2006, likely attributable to the documented California 1987–1992 drought where agricultural lands lay fallow or were affected by crop failure (California Department of Water Resources, 1993). Among California residents of agriculturally intensive areas, liver disease, diabetes, rare genetic disorders, HIV, and state buy-in were more common among cases (Table 2). ZIP Code-level organophosphate, organochlorine, and carbamate exposure were univariably associated with HCC, where high vs. low exposure was associated with higher risk of HCC (Table 4).

Organochlorines were the only pesticide chemical class remaining significant after adjustment. After accounting for a 10-year exposure lag, high ZIP Code-level organochlorine pesticide exposure compared to low exposure was associated with a 91% increase in HCC risk after adjusting for liver disease and diabetes (Table 5). Among males, ZIP Code-level organochlorine pesticide exposure was significantly associated with an increased risk of HCC, where high exposure compared to low exposure was significantly associated with a 2-fold or greater increased risk of HCC irrespective of lag. Organochlorines were not significantly associated with HCC among females. Significant associations were also observed with no lag and 10- and 20-year lags when using the 75th

percentile among controls to indicate exposure (Table 5). Previous ZIP Code-level exposure (no lag) to ≥14.53 kg/km^2 of applied organochlorine pesticides was significantly associated with an 87% increase in HCC risk after adjustment for liver disease and diabetes (95% CI 1.17, 2.99). The effect of ZIP Code-level organochlorine pesticide exposure on HCC was significantly greater among males compared to females (interaction p=0.0075); exposure to ≥14.53 kg/km^2 of applied organochlorine pesticides was associated with HCC among males (adjusted OR 2.76, 95% CI 1.58, 4.82) but not among females (adjusted OR 0.83, 95% CI 0.35, 1.93). This interaction between organochlorine pesticides and sex was also significant in the 10-year lag model (interaction p=0.0252), but borderline significant in the 15- (interaction p=0.05) and 20-year (interaction p=0.0563) lag models.

Among agricultural residents with no known risk factors for HCC (n=80 cases, n=1,143 controls), previous ZIP Code-level organochlorine pesticide exposure was not associated with HCC (no lag, 75th percentile: OR 1.60, 95% CI 0.74, 3.45; p=0.2331). Sensitivity analyses among 187 cases and 1,259 controls entitled to Medicare due to attaining the age of 65 years (40 cases and 178 controls originally entitled to Medicare due to disability and/or ESRD were excluded) demonstrated both stronger and more significant positive associations between ZIP Code-level organochlorine pesticide exposure and HCC (no lag, 75th percentile: overall adjusted OR 1.97, 95% CI 1.19, 3.26, p=0.0086; males adjusted OR 3.12, 95% CI 1.71, 5.70, p=0.0002; females adjusted OR 0.83, 95% CI 0.35, 1.97, p=0.6694).

3.2. Spatial autocorrelation and the MAUP

No spatial autocorrelation was observed among the residuals of the final multivariable conditional logistic regression model (Moran's I 0.0017 [p=0.42] using mode ZIP Code; Moran's I 0.0021 [p=0.31] using diagnosis/selection ZIP Code). Regarding the MAUP, PLSS section pesticide use densities (kg/km^2) for each year between 1974 and 2008 exhibited statistically significant positive spatial autocorrelation. All yearly Moran's I values were positive and the mean yearly Moran's I value was 0.10 (maximum 0.26). Forty percent of the yearly Moran's I values exceeded 0.10 and 89% were statistically significant (p<0.0001), demonstrating that PLSS sections with similar pesticide use densities were typically close in proximity to each other. For each year from 1974 to 2008, PLSS section pesticide use densities intersecting ZIP Codes exhibited minimal variation reflected in IQRs. In other words, ZIP Codes (via intersection) typically aggregated together similar PLSS section pesticide use densities as opposed to disparately different PLSS section pesticide use densities. For each year between 1974 and 2008, the median value of PLSS section pesticide use densities within each ZIP Code was on average 0.29 kg/km^2, and the average corresponding IQR was 1.31 kg/km^2 (average 75th percentile: 1.37 kg/km^2; average 25th percentile: 0.06 kg/km^2). Using the proportion of the study population residing within each ZIP Code (using each study subject's mode ZIP Code), statistically significant positive spatial autocorrelation was observed in California (Moran's I 0.48, p<0.0001). Comparable results were observed when examining ZIP Code residence among cases (Moran's I 0.46, p<0.0001) and controls (Moran's I 0.45, p<0.0001). Further exploration using Anselin Local Moran's I revealed residential hot spots in the Los Angeles, San Francisco, San Jose, and San Diego metropolitan areas (similar results observed among cases and controls). Apart from these aforementioned geographic areas, a visual inspection of the distribution of case

vs. control ZIP Code residence across California appeared random. PLSS section pesticide use densities within ZIP Codes located in these four urban areas were generally 0 kg/km^2, demonstrating little within-ZIP Code heterogeneity. Accounting for case-control residential locations, pesticide exposure misclassification related to the MAUP and aggregating PLSS section pesticide use densities to the ZIP Code level was likely nondifferential between cases and controls.

4. Discussion

Among California residents of agriculturally intensive areas in the SEER-Medicare population, previous ZIP Code-level exposure to organochlorine pesticides was associated with an increased risk of HCC after adjusting for liver disease and diabetes. ZIP Code-level organochlorines were significantly associated with an increased risk of HCC among males but not associated among females. Implementing exposure lags of 10 and 20 years before diagnosis/selection also demonstrated significant associations between organochlorines and HCC. Complementing the subanalysis results were results observed among rural <20,000 population residents, where moderate compared to low organochlorine exposure increased HCC risk. HCC is a significant public health concern, rising in incidence and associated with low survival in the U.S. As HCC occurs among many individuals with no known risk factors (Carr, 2010; El-Serag, 2007), it is important to explore the role of other exposures that might contribute to liver carcinogenesis.

Several epidemiologic studies have demonstrated that pesticide exposure is significantly associated with an increased risk of HCC (McGlynn et al., 2006; Persson et al., 2012; Zhao et al., 2011). Pesticides are pervasively used chemicals in the U.S. (Alavanja et al., 2004). In 2007, the agricultural sector accounted for approximately 80% of conventional U.S. pesticide usage (e.g., treating insects; 310 million kg) (EPA, 2011). The three specific pesticide chemical classes explored in this study have been previously associated with HCC. Organophosphates and carbamates are mostly insecticides, widely used in the 1980s and 90s after many organochlorines were banned, but have since declined in usage in favor of more environmentally friendly chemicals (Wells, 2011). Some highly toxic organophosphates (e.g., parathion) and carbamates (e.g., aldicarb) have been banned in the U.S. (EPA, 2013; EPA, 2014). Organochlorines are also mostly insecticides, were widely used in the 1940s to 60s, but have largely been banned in the U.S. due to adverse health effects and environmental persistence (CDC, 2009; Longnecker et al., 1997). Animal models have demonstrated that exposure to DDT, an organochlorine pesticide banned in the U.S. in 1972, and its metabolite, dichlorodiphenyldichloroethylene (DDE), lead to the development of HCC and other liver tumors (Rossi et al., 1983; Turusov et al., 1973).

Three case-control studies conducted in China using serum DDT provide the most convincing evidence of an association between pesticides and HCC (McGlynn et al., 2006; Persson et al., 2012; Zhao et al., 2011). In particular, these studies demonstrated a link between HCC and DDT, which belongs to the organochlorine pesticide chemical class demonstrating a significant association with HCC in our study. These studies utilized biomonitoring to estimate pesticide exposure, considered the gold standard method of capturing exposure from specific chemicals via all routes of human exposure (Franklin and

Worgan, 2005). However, these findings may not be generalizable to the U.S. population as China continues to use DDT as an anti-malarial agent (Persson et al., 2012). In the U.S., the 95th percentile of serum DDT levels was 28 ng/g fat between 1999 and 2000 and 19.5 ng/g fat between 2003 and 2004 (CDC, 2009), compared to the Persson et al. (2012) Chinese study population associated with a geometric mean of 468 ng/g fat (18 standard deviation [SD]) DDT among cases and 478 ng/g fat (18 SD) among controls (sera collected in 1992–1993).

Other research examining pesticides in relation to HCC has demonstrated inconclusive results, ranging from significant increases to non-significant deficits in risk (Austin et al., 1987; Badawi and Michael, 1999; Brownson et al., 1989; Cordier et al., 1993; Evans et al., 2002; Ezzat et al., 2005; Hardell et al., 1984; Heinemann et al., 2000; Kauppinen et al., 1992; London et al., 1995; Porru et al., 2001; Soliman et al., 2010; Stemhagen et al., 1983; Suarez et al., 1989). Most studies have relied on self-reported pesticide exposure and occupation, job-exposure matrices, occupational experts, and rural residence. Recall bias may have obscured or inflated study results. Accurately quantifying pesticide exposure, particularly when investigating their role in chronic diseases such as cancer, must consider historical exposures to take into account latency periods, or the time from initial exposure to clinical disease (Alavanja et al., 2004; Rothman et al., 2008). Specific pesticides may be associated with disease, which are not adequately captured with dichotomous (yes/no) classifications. The four case-control studies conducted in the U.S. accounted for few confounders (e.g., age, race, sex) during analysis and/or study design and potentially introduced a selection bias in using other cancer or hospital controls (Austin et al., 1987; Brownson et al., 1989; Stemhagen et al., 1983; Suarez et al., 1989).

We focused on the Medicare population aged 65 years and older in California, which represented a unique opportunity to study HCC as California is the most agriculturally productive state in the U.S. (U.S. Department of Agriculture, 2010) and is characterized by relatively high HCC incidence. California age-adjusted HCC incidence between 2000 and 2009 is 6.3 per 100,000, 24% higher than the overall U.S. rate (National Cancer Institute, 2014a). Furthermore, the California PUR database is the world's most comprehensive pesticide reporting system, collecting agricultural pesticide use since 1974 (California Department of Pesticide Regulation, 2014). Prior to 1990, California farmers were only required to report restricted-use pesticides. As full-use reporting began in 1990, we confirmed that pesticide use densities across all three chemical classes were not significantly different between 1974 to 1989 and 1990 to 2008 (data not shown). We sought to improve upon the limitations of previous HCC U.S. epidemiologic studies by using population-based data sources providing information on HCC cases, controls representative of the same reference population as the cases, comorbidities as potential confounders, and pesticide exposure. PURs allowed for examining specific pesticides to reconstruct historical exposure, addressing a potential latency period. Medicare-provided ZIP Codes allowed us to link SEER-Medicare and PUR data in a GIS. GIS is a powerful method allowing for the overlay of multiple spatial data sources based on a common geographic frame of reference. Specifically, we were able to overlay PLSS sections, the geographic level of reporting of PURs, with Medicare-provided ZIP Codes to estimate pesticide exposure for each study subject.

When examining the entire sample of SEER-Medicare cases and controls, ZIP Code-level pesticide exposure was not associated with HCC after adjustment. However, among rural <20,000 population residents, moderate compared to low ZIP Code-level organochlorine pesticide exposure was significantly associated with an increased risk of HCC after adjustment. Although there was a positive association between high compared to low exposure and HCC, the association was not statistically significant. Potential explanations for the absence of a significant result in the high exposure category include a small sample size and the use of a RUCC rurality metric to select individuals with an opportunity for pesticide exposure. Agricultural pesticide applications predominantly occur in rural, less densely populated geographic areas (Ward et al., 2000). Stratifying the analysis according to rural/urban residence was an attempt to examine the effect of pesticide exposure on HCC according to differential levels of opportunity for pesticide exposure. This was especially important to consider as the majority of cases (94.6%) and controls (93.8%) resided urban areas. However, rurality occurs on a continuum, where a geographic area defined as rural according to a given metric may be sparsely populated, but is associated with few agricultural lands and thus minimal agricultural pesticide exposure (Warren and Smalley, 2014). Rural areas in California may include deserts (Mojave), National Forests (Shasta-Trinity), and mountain ranges (Sierra Nevada) that may be sparsely inhabited by humans but do not provide favorable conditions for agriculture (National Park Service, 2015).

In an effort to identify individuals at risk for pesticide exposure with greater specificity, we used a geospatial method incorporating NLCD agricultural land cover information in California over time. The NLCD method was validated using California Department of Water Resources (CDWR) land use surveys (LUS's) in 2001 and 2006 (years with concurrent LUS's) (California Department of Water Resources, 2015). Using n=20 ZIP Codes within the Alpine, Lake, Madera, and Mono County LUS survey extents in 2001 and n=89 ZIP Codes within the Alameda, Del Norte, Kern, and Tulare County LUS survey extents in 2006, the proportion of agricultural land cover within each ZIP Code was highly correlated when calculated using the NLCD and LUS gold standard in 2001 (Spearman correlation 0.92, $p<0.0001$) and in 2006 (Spearman correlation 0.75, $p<0.0001$). Using a ≥50% agricultural land cover cutoff relevant to our study, substantial agreement was observed in 2001 (kappa 0.64, $p=0.0021$) and excellent agreement in 2006 (kappa 0.95, $p<0.0001$). After restricting analyses to California residents of agriculturally intensive areas, previous ZIP Code-level exposure to organochlorine pesticides was significantly associated with an increased risk of HCC after adjustment. Applied organochlorines in California between 1974 and 2008 included endosulfan, toxaphene, and dicofol. When considering exposure as greater than or equal to the 75th percentile among controls, ZIP Code-level organochlorines were significantly associated with an increased risk of HCC when taking into account exposure lags of 10 and 20 years. This potentially reflects temporal trends in organochlorine usage, which has dramatically declined since the 1970s. Thus, exposure occurring in the time period of at least 20 years before diagnosis between 2000 and 2009 may be more relevant in elevating HCC risk, as opposed to considering exposure from all years before diagnosis. There was evidence of an interaction between sex and ZIP Code-level pesticide exposure, where the effect of organochlorines on HCC was more pronounced among males (not significant among females). This interaction has been previously

explored, where higher serum DDT was associated with an increased risk of HCC among males and a decreased risk among females, although neither were statistically significant (Persson et al., 2012). An antagonistic interaction between pesticides and sex is plausible given DDT's estrogenic activity (Jaga, 2000), where males are characterized by lower endogenous estrogen levels and may be more affected by exogenous estrogenic compounds (Persson et al., 2012). This interaction may also be a manifestation of sex-linked biological differences in how chemicals are absorbed and metabolized (Arbuckle, 2006), estrogen as protective against HCC due to its anti-inflammatory effects (Shi et al., 2014), and related to the specific pesticide source of exposure (agricultural exposure) addressed in this study. As farming is more common among males compared to females (U.S. Census Bureau, 2013), this occupational exposure may differentially affect males vs. females. A lack of association among females may also be affected by a small subanalysis sample size.

We did not exclude individuals who were originally entitled to Medicare due to disability and/or ESRD. Although these individuals are not considered representative of Medicare beneficiaries in terms of their clinical and demographic characteristics (Davila et al., 2005; Warren et al., 2002), the majority of both cases (89.2%) and controls (91.8%) in our study were entitled to Medicare due to attaining the age of 65 years. Furthermore, individuals with a disability, such as chronic liver disease and conditions related alcoholism, represent those with risk factors who would likely develop HCC (Social Security Administration, 2014). Sensitivity analyses excluding those entitled not due to age demonstrated stronger positive, significant associations between organochlorines and HCC among agricultural residents. This potentially demonstrates how this subgroup of Medicare beneficiaries, due to their health, may have been confined to their homes, minimizing agricultural pesticide exposure, or living in relatively less rural areas to facilitate their healthcare access (e.g., dialysis centers for ESRD).

Strengths include being the first epidemiologic study using GIS to study pesticides and HCC by implementing a novel data linkage between SEER-Medicare cancer outcomes and health conditions data and PUR pesticide applications using Medicare-provided ZIP Codes. ZIP Codes have been previously used to study pesticides and cancer mortality in California (Clary and Ritz, 2003). While all previous U.S. studies examining pesticides and HCC have relied on self-reported exposure, we utilized all agricultural use pesticide applications of specific chemicals reported to the California state government by farmers and commercial pest control operators. Our population-based study was able to sample from all HCC cases reported to California cancer registries between 2000 and 2009 as part of the SEER program who were aged 65 years and older enrolled in Medicare. Controls were sampled from the same population that gave rise to the cases, using a 5% random sample of Medicare beneficiaries residing in SEER areas. Great care was taken to include HCC cases with the greatest specificity, including diagnostically confirmed first cancer cases, minimizing inclusion of metastatic liver cancer. Using claims from Medicare, a federal health insurance program servicing 97% of the ≥65-year-old population (Engels et al., 2011), important HCC risk factors were included in the statistical analysis to address potential confounding. We carried back the earliest available Medicare-provided ZIP Code to 1974 and were able to craft a comprehensive and historical pesticide exposure metric for all cases and controls. This addresses the documented 20-year latency period of some HCC risk factors

(Ananthakrishnan et al., 2006). Our study results are consistent with previous literature linking organochlorines with HCC. Although PURs began reporting pesticide use in 1974 and DDT was banned in 1972, statistically significant positive associations were observed in our study between HCC and organochlorines, the pesticide chemical class to which DDT belongs. Pesticides within a given chemical class have similar chemical structures and biological mechanisms of action (Alavanja et al., 2004), therefore, other organochlorines may pose similar risks for liver-related outcomes. Furthermore, dicofol, an organochlorine pesticide applied in the U.S. during the study time period, is synthesized from and contains DDT as an impurity (California Department of Pesticide Regulation, 2008). Although the U.S. Environmental Protection Agency temporarily suspended dicofol use in 1986 until it could be produced with less than 0.1% DDT impurity, dicofol use in California represents another potential source through which humans were exposed to DDT following its ban in 1972.

Several limitations provide opportunities for future research. Our study was not able to take into account other sources of pesticide exposure such as individual-level occupation, diet, and residential pesticide use. However, the source of exposure addressed in this study, residential proximity, has been used as a surrogate for pesticide exposure occurring through a variety of routes, including dermal contact in crop fields (Gunier et al., 2001). Pesticides that do not belong to the organochlorine, organophosphate, and carbamate chemical classes may be associated with HCC. Individuals diagnosed with cancers other than liver were not included in control sampling. As 16.9% (n=108,684) of cancers other than liver diagnosed among those 65 years and older, of known race, and reported to a California registry between 2000 and 2009 were prostate (National Cancer Institute, 2014b), and pesticides have been linked to increasing prostate cancer risk (Ritchie et al., 2003), the study results may have been artificially inflated. Usage of Medicare claims is associated with inherent limitations as only conditions diagnosed and recorded by a healthcare provider are captured. Claims lack sensitivity with some conditions, including HCV, which are underdiagnosed in the elderly population (Engels et al., 2011). However, in this sample, 10.6% of all sampled controls were tested for HBV and/or HCV at least one year before selection according to Healthcare Common Procedure Coding System codes (e.g., 87340, testing for HBsAg). Alcoholic liver disease was used as a proxy for alcohol consumption, which likely underestimated consumption in our study population and only captured relatively heavier alcohol consumption. The generalizability of our findings is somewhat limited given the median age of HCC diagnosis in the U.S. is 63 years (National Cancer Institute, 2014c) and sampled cases were at least 66 years old. We excluded individuals enrolled in Part C due to their lack of Medicare claims. Between 2000 and 2009, approximately 31.0 to 37.9% of Medicare beneficiaries in California enrolled in Part C (The Kaiser Family Foundation, 2007). Approximately 98.9% of cases excluded from our study due to HMOs resided in an urban area. When considering all California Medicare beneficiaries enrolled in Part C sometime between 2000 and 2009, between 64.9 and 94.4% resided in an urban area (The Kaiser Family Foundation, 2007). Assuming the association between urban residence and Part C enrollment is nondifferential between cases and controls, excluding Part C enrollees may have biased results towards the null. Regarding the subanalysis, although NLCD land cover data outside of California could have been used to identify residents of agricultural

areas, a small proportion of cases (n=81; 2.7%) and controls (n=433; 3.0%) had ZIP Codes outside of California (i.e., mode ZIP Code was outside of California).

The major limitation of our study is exposure misclassification. By carrying back the earliest available Medicare-provided ZIP Code, we assumed individuals were residentially stable as early as their 30s and into midlife. This assumption may be conceivable given 89.6% of cases and 90.7% of controls had one to two ZIP Codes (using available Medicare-provided ZIP Codes from 1991 until year before diagnosis/selection). Furthermore, only 2% (n=72) of cases and 2% (n=313) of controls moved from rural to urban areas or vice versa, potentially demonstrating that the exposure assigned to these individuals using their carried-back ZIP Code is representative of what they would have experienced anyway by virtue of typically residing in only urban, or only rural, areas during their lifetime. Medicare-provided ZIP Codes represent the last available billing ZIP Code in that year, which may not reflect residence or intra-annual residential mobility. Pesticide exposure occurring in California ZIP Codes not found in the TIGER/Line® ZIP Code file or outside of California was not captured in the exposure calculation. However, the majority of ZIP Codes among cases (88.9%) and controls (88.3%) were in California and in the TIGER/Line® ZIP Code file and cases and controls were frequency-matched on duration of California residence (i.e., opportunity for pesticide exposure). Although we used the midpoint of each year to match controls to cases as performed in previous studies, an alternative is usage of the specific month and year of diagnosis. However, the impact of controls subsequently becoming cases after the midpoint of a year in which they were matched to a case was minimal as a very small proportion of controls subsequently became cases (n=21; 0.14% of controls) and n=13 of these controls became cases after the midpoint of a given year.

ZIP Codes are coarse spatial resolution variables, ranging from 0.01 to 5,254 km^2 in California. ZIP Codes are frequently modified and represent linear features created for the purposes of mail delivery (Grubesic and Matisziw, 2006). ZIP Codes in rural geographic areas, typically associated with relatively lower population densities compared to urban areas, are larger in size compared to urban ZIP Codes (Grubesic, 2008). California has become more urbanized over time (LaDochy et al., 2007), which would have manifested in many ZIP Code boundary changes, including previously rural ZIP Codes becoming smaller in area and urban ZIP Code boundary modifications. As the distribution of rural/urban residence is comparable between cases and controls and a very small and comparable proportion of cases and controls were tied to rural/urban migration, exposure misclassification due to spatiotemporal changes in ZIP Code boundaries would likely be nondifferential between cases and controls.

ZIP Code-level pesticide exposure metrics are ecologic, taking into account pesticide exposure occurring within an entire ZIP Code. As a result, exposure could have been over- or underestimated for any given study subject. Exposure misclassification would also manifest from the modifiable areal unit problem (MAUP), or observing different results according to how data are aggregated (O'Sullivan and Unwin, 2010). In this study, we aggregated PLSS section pesticide use to the ZIP Code level. ZIP Codes vary in size and shape across California, and different results would likely be observed if examining pesticide exposure at different scales (PLSS section vs. ZIP Code) and using different zones

(different partitioning of California at a ZIP Code-level scale). Spatial analyses exploring the potential impact of the MAUP demonstrated likely nondifferential exposure misclassification, where yearly PLSS section pesticide use densities across California exhibited statistically significant positive spatial autocorrelation, minimal variation of PLSS section use densities was observed within ZIP Codes, and case vs. control residence across California was overall randomly distributed. Clusters of high case and control residence were identified in several metropolitan areas, but PLSS section pesticide use densities within ZIP Codes in these areas were homogenous. The effect of exposure misclassification may differ if aggregating to other areal units such as census tracts. A more meaningful GIS pesticide exposure metric would use finer spatial resolution data, such as geocoded residential locations, match PUR data to CDWR LUS's, and examine specific pesticides to estimate agricultural pesticide use occurring within a 500 m (radius) buffer (distance associated with pesticide drift and previously used in epidemiologic studies) (Rull and Ritz, 2003).

5. Conclusions

Among California residents of agriculturally intensive areas in the SEER-Medicare population, previous ZIP Code-level organochlorine pesticide exposure was significantly associated with an increased risk of developing HCC after adjusting for liver disease and diabetes. Among males, organochlorines were significantly associated with an increased risk of HCC but not associated among females. This is the first epidemiologic study using GIS to study pesticide exposure and HCC. Our study highlights another potential risk factor for HCC in the U.S. population that should be further examined. We used Medicare-provided ZIP Codes to estimate pesticide exposure, which is a coarse spatial resolution variable subject to changes over time. Future research should explore the use of finer spatial resolution data, such as geocoded residences, in addition to collecting information regarding other sources of pesticide exposure to further elucidate the association between pesticides and HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- SEER-Medicare and Pesticide Use Report data were linked using ZIP Codes in a GIS.
- This epidemiologic case-control study focused on California, United States.
- Remote sensing land cover data identified populations at risk for pesticide exposure.
- ZIP Code-level organochlorine pesticide exposure significantly elevated HCC risk.
- ZIP Code organochlorines increased risk among males (no association among females).

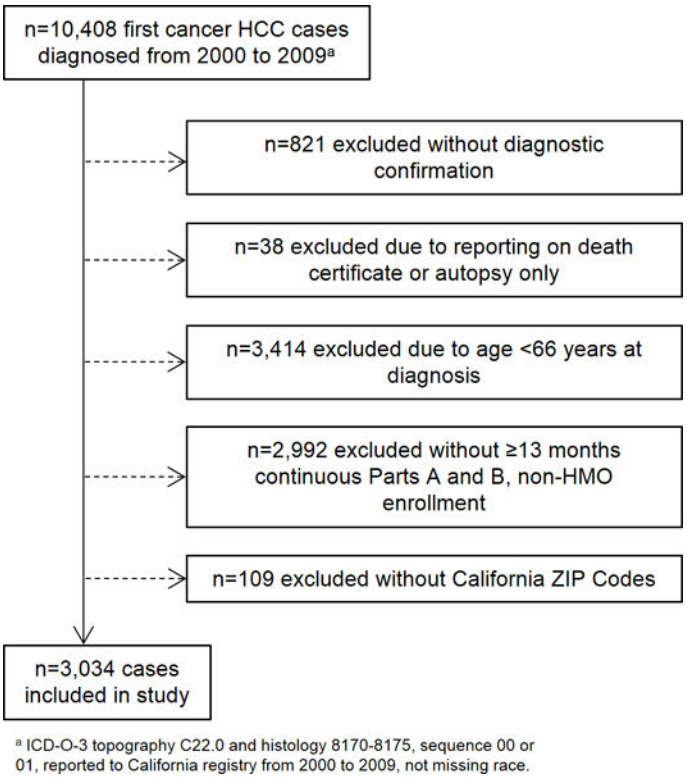

Fig. 1.

Eligibility criteria applied to first cancer hepatocellular carcinoma cases in California diagnosed from 2000 to 2009 using SEER-Medicare.

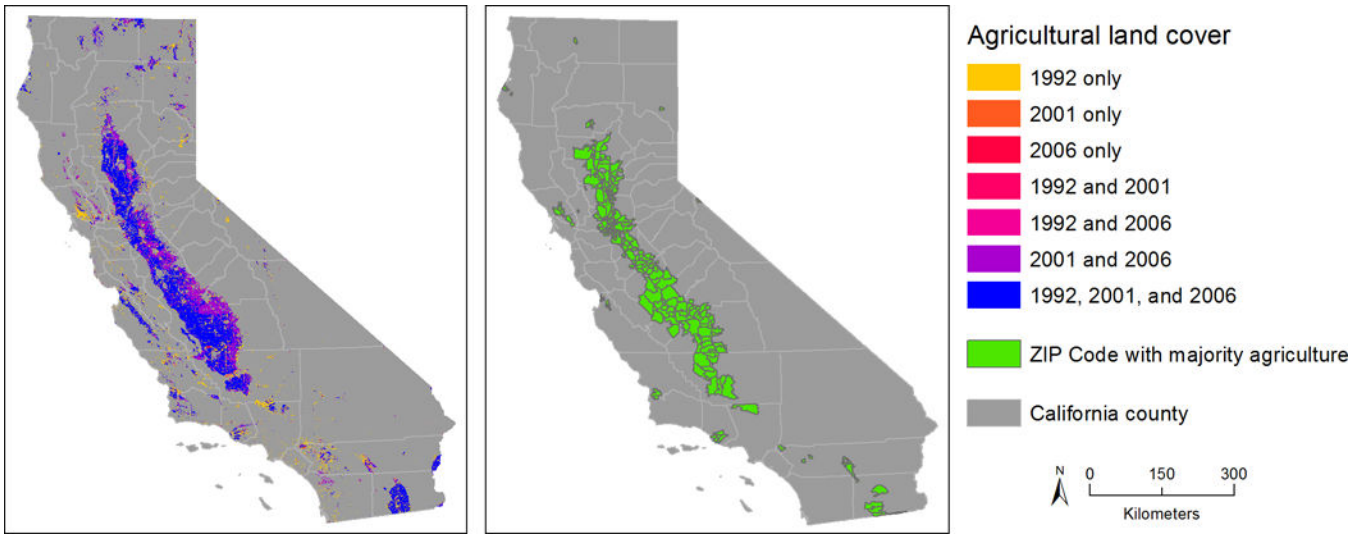

Fig. 2. National Land Cover Database (NLCD) agricultural land cover in California in 1992, 2001, and 2006

ZIP Codes with a majority area intersecting agricultural land cover in any year (right) were used to select SEER-Medicare cases and controls with an opportunity for pesticide exposure examined in the subgroup analysis (California residents of agriculturally intensive areas).

Table 1

Included vs. excluded hepatocellular carcinoma cases from SEER-Medicare in California, 2000–2009.

Characteristic	Included cases[a] (n=3,034) n (%)	Excluded cases[a,b] (n=7,374) n (%)	p-value[c]
Age in years: mean (SD)	75.1 (6.3)	66.1 (11.0)	**<0.0001**
Year			0.5364
2000–2002	749 (24.7)	1,758 (23.8)	
2003–2005	885 (29.2)	2,132 (28.9)	
2006–2009	1,400 (46.1)	3,484 (47.3)	
Sex			**<0.0001**
Male	1,915 (63.1)	5,407 (73.3)	
Female	1,119 (36.9)	1,967 (26.7)	
Race			**<0.0001**
White	1,548 (51.0)	4,178 (56.7)	
Black	152 (5.0)	529 (7.2)	
Other	265 (8.7)	789 (10.7)	
Asian	793 (26.1)	1,185 (16.1)	
Hispanic	256 (8.4)	642 (8.7)	
Native American	20 (0.7)	51 (0.7)	
California residence			**<0.0001**
1–5 years	838 (27.6)	4,164 (56.5)	
6–10 years	1,077 (35.5)	1,611 (21.9)	
≥11 years	1,119 (36.9)	1,599 (21.7)	
State buy-in (low socioeconomic status)	1,586 (52.3)	2,149 (29.1)	**<0.0001**
Rural/urban residence[d]			**<0.0001**
Urban	2,796 (94.6)	5,991 (96.5)	
Rural ≥20,000 pop	86 (2.9)	104 (1.7)	
Rural <20,000 pop	75 (2.5)	113 (1.8)	

Abbreviations: pop, population; SD, standard deviation.

[a] The source population of SEER-Medicare cases included all individuals diagnosed with hepatocellular carcinoma (ICD-O-3 C22.0 and 8170-8175) as a first cancer between 2000 and 2009 reported to a California registry, not of unknown race, and in the Medicare Enrollment Database (requirement to be included in SEER-Medicare data linkage).

[b] Cases were excluded from the study due to lack of diagnostic confirmation, being reported on death certificate or autopsy only, <66 years old at diagnosis, not having ≥13 months of continuous Parts A and B, non-HMO enrollment before diagnosis, or no available California Medicare ZIP Codes by diagnosis.

[c] Two-sided p-values from two-sample t-tests for continuous variables and from chi-square tests for categorical variables are presented. Statistically significant results ($p<0.05$) are bold.

[d] Some cases are missing rural/urban residence due to the absence of their ZIP Code in the TIGER/Line® ZIP Code file used to intersect with counties. Some excluded cases are missing rural/urban residence due to lacking California ZIP Codes.

Table 2

Population characteristics of hepatocellular carcinoma cases and frequency-matched controls from SEER-Medicare in California, 2000–2009.

	Entire sample			California residents of agriculturally intensive areas		
Characteristic	**Cases[a] (n=3,034) n (%)**	**Controls[a] (n=14,991) n (%)**	**p-value[b]**	**Cases (n=227) n (%)**	**Controls (n=1,437) n (%)**	**p-value[b]**
Age in years: mean (SD)	75.1 (6.3)	75.1 (6.3)		74.9 (6.0)	74.4 (6.0)	
Year						
2000–2002	749 (24.7)	3,707 (24.7)		54 (23.8)	378 (26.3)	
2003-2005	885 (29.2)	4,353 (29.0)		77 (33.9)	421 (29.3)	
2006-2009	1,400 (46.1)	6,931 (46.2)		96 (42.3)	638 (44.4)	
Sex						
Male	1,915 (63.1)	9,469 (63.2)		131 (57.7)	941 (65.5)	
Female	1,119 (36.9)	5,522 (36.8)		96 (42.3)	496 (34.5)	
Race[c]						
White	1,548 (51.0)	7,739 (51.6)		137 (60.4)	826 (57.5)	
Black	152 (5.0)	743 (5.0)		<11	63 (4.4)	
Other	265 (8.7)	1,266 (8.5)		25 (11.0)	109 (7.6)	
Asian	793 (26.1)	3,924 (26.2)		18 (7.9)	156 (10.9)	
Hispanic	256 (8.4)	1,252 (8.4)		37 (16.3)	271 (18.9)	
Native American	20 (0.7)	67 (0.5)		<11	12 (0.8)	
California residence						
1-5 years	838 (27.6)	4,145 (27.7)		53 (23.4)	372 (25.9)	
6-10 years	1,077 (35.5)	5,307 (35.4)		77 (33.9)	491 (34.2)	
≥11 years	1,119 (36.9)	5,539 (36.9)		97 (42.7)	574 (39.9)	
Duration of Medicare coverage (years)[d]			0.9652			0.4558
1.1-4.1	755 (24.9)	3,736 (24.9)		48 (21.2)	355 (24.7)	
4.2-6.1	2,279 (75.1)	11,255 (75.1)		179 (78.9)	1,082 (75.3)	
HCV	672 (22.2)	71 (0.5)	**<0.0001**	–	–	
HBV	177 (5.8)	20 (0.1)	**<0.0001**	–	–	
Unspecified hepatitis	379 (12.5)	75 (0.5)	**<0.0001**	–	–	
Alcoholic liver disease	212 (7.0)	44 (0.3)	**<0.0001**	–	–	

Characteristic	Entire sample			California residents of agriculturally intensive areas		
	Cases[a] (n=3,034) n (%)	Controls[a] (n=14,991) n (%)	p-value[b]	Cases (n=227) n (%)	Controls (n=1,437) n (%)	p-value[b]
Non-specific cirrhosis	516 (17.0)	41 (0.3)	**<0.0001**	–	–	
Liver disease[e]			**<0.0001**			
None	1,861 (61.3)	14,783 (98.6)		–	–	
Hepatitis only	592 (19.5)	133 (0.9)		–	–	
Cirrhosis	581 (19.2)	75 (0.5)		–	–	
Liver disease (subgroup analysis)[f]				77 (33.9)	20 (1.4)	**0.0129**
Diabetes	1,300 (42.9)	2,054 (13.7)	**<0.0001**	102 (44.9)	199 (13.9)	**<0.0001**
Obesity	125 (4.1)	365 (2.4)	**<0.0001**	13 (5.7)	47 (3.3)	0.9426
Rare genetic disorders[c]	43 (1.4)	17 (0.1)	**<0.0001**	<11	<11	**<0.0001**
HIV[c]	<11	<11	**0.0072**	<11	<11	**<0.0001**
Smoking	262 (8.6)	795 (5.3)	**<0.0001**	15 (6.6)	86 (6.0)	0.8126
State buy-in (low socioeconomic status)	1,586 (52.3)	6,070 (40.5)	**<0.0001**	108 (47.6)	564 (39.3)	**0.0001**
ZIP Code percentage employed in agriculture: median (IQR)	0.2 (0.1, 0.7)	0.2 (0.1, 1.0)	**0.0002**	5.0 (2.5, 7.4)	4.5 (2.1, 7.4)	0.4146
Rural/urban residence[c]			**0.0453**			0.0614
Urban	2,796 (94.6)	13,674 (93.8)		201 (88.6)	1,268 (88.2)	
Rural ≥20,000 pop	86 (2.9)	415 (2.9)		<26	139 (9.7)	
Rural <20,000 pop	75 (2.5)	482 (3.3)		<26	30 (2.1)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; pop, population; SD, standard deviation.

[a] Twenty-one controls subsequently became cases; 11,613 controls served once, 1,347 served twice, 195 served three times, 21 served four times, and 3 served five times.

[b] No statistical tests are presented for matching factors age, year, sex, race, and California residence. For all other variables, two-sided p-values from univariable conditional logistic regression models (robust variance estimation) conditioning on the matching factors are presented. Statistically significant results (p<0.05) are bold.

[c] In accordance with the SEER-Medicare data use agreement, cell sizes <11 are suppressed.

[d] Years of non-continuous enrollment in Parts A and B, non-HMO coverage within 6 years of diagnosis/selection. Coverage was categorized using the 25th percentile among cases (4.1 years).

[e] Liver disease was used in statistical modeling, representing none (no hepatitis, alcoholic liver disease, and non-specific cirrhosis), hepatitis only (hepatitis without alcoholic liver disease and cirrhosis), and cirrhosis (alcoholic liver disease or non-specific cirrhosis with or without hepatitis).

[f] Liver disease used in statistical modeling among agricultural residents was defined as yes/no hepatitis, alcoholic liver disease, or non-specific cirrhosis.

Table 3

Odds ratios and 95% confidence intervals for pesticide exposure and hepatocellular carcinoma using Pesticide Use Reports and SEER-Medicare in California, 2000–2009.

Pesticide exposure category (kg/km^2)[a]	Cases (n=3,034) n (%)	Controls (n=14,991) n (%)	Unadjusted OR (95% CI)[b]	p-value[b]	Adjusted OR (95% CI)[b]	p-value[b]
Entire sample						
All classes[c,d]				0.0559		0.6769
Low: ≤0.07	1,054 (34.7)	4,947 (33.0)	–		–	
Mod: 0.07–1.85	1,007 (33.2)	4,948 (33.0)	0.96 (0.87, 1.05)	0.3407	1.00 (0.87, 1.16)	0.9611
High: ≥1.85	973 (32.1)	5,096 (34.0)	0.89 (0.81, 0.98)	**0.0194**	0.95 (0.82, 1.09)	0.4421
Organophosphates				**0.0348**		0.6146
Low: ≤0.04	1,060 (34.9)	4,948 (33.0)	–		–	
Mod: 0.04–1.02	998 (33.0)	4,949 (33.0)	0.94 (0.86, 1.03)	0.2046	0.99 (0.86, 1.14)	0.8640
High: ≥1.02	976 (32.2)	5,094 (34.0)	0.89 (0.81, 0.98)	**0.0181**	0.95 (0.83, 1.10)	0.4836
Organochlorines				**0.0481**		0.3288
Low: ≤0.001	1,057 (34.8)	4,947 (33.0)	–		–	
Mod: 0.001–0.16	977 (32.2)	4,947 (33.0)	0.93 (0.84, 1.02)	0.1038	0.92 (0.79, 1.06)	0.2325
High: ≥0.16	1,000 (33.0)	5,097 (34.0)	0.92 (0.83, 1.01)	0.0712	0.96 (0.84, 1.11)	0.6123
Carbamates				0.1777		0.5582
Low: ≤0.01	1,039 (34.3)	4,949 (33.0)	–		–	
Mod: 0.01–0.44	1,018 (33.6)	4,946 (33.0)	0.98 (0.89, 1.08)	0.6919	0.99 (0.86, 1.13)	0.8382
High: ≥0.44	977 (32.2)	5,096 (34.0)	0.91 (0.83, 1.00)	0.0543	0.94 (0.82, 1.09)	0.4161
Urban						
All classes				0.0509		0.7453
Low: ≤0.08	975 (34.9)	4,512 (33.0)	–		–	
Mod: 0.08–1.74	930 (33.3)	4,511 (33.0)	0.96 (0.87, 1.06)	0.3832	1.01 (0.87, 1.17)	0.8863
High: ≥1.74	891 (31.9)	4,651 (34.0)	0.88 (0.80, 0.97)	0.0129	0.95 (0.82, 1.10)	0.4832
Organophosphates				**0.0189**		0.6051
Low: ≤0.04	985 (35.2)	4,512 (33.0)	–		–	
Mod: 0.04-0.97	916 (32.8)	4,512 (33.0)	0.93 (0.85, 1.03)	0.1562	0.99 (0.86, 1.15)	0.9047
High: ≥0.97	895 (32.0)	4,650 (34.0)	0.88 (0.79, 0.97)	**0.0089**	0.94 (0.81, 1.09)	0.4366
Organochlorines				**0.0301**		0.2098

Pesticide exposure category (kg/km^2)[a]	Cases (n=3,034) n (%)	Controls (n=14,991) n (%)	Unadjusted OR (95% CI)[b]	p-value[b]	Adjusted OR (95% CI)[b]	p-value[b]
Low: ≤0.001	980 (35.1)	4,512 (33.0)	–		–	
Mod: 0.001-0.16	888 (31.8)	4,512 (33.0)	0.91 (0.82, 1.00)	0.0521	0.89 (0.76, 1.03)	0.1161
High: ≥0.16	928 (33.2)	4,650 (34.0)	0.91 (0.83, 1.01)	0.0686	0.96 (0.82, 1.11)	0.5360
Carbamates				0.2272		0.6046
Low: ≤0.01	953 (34.1)	4,512 (33.0)	–		–	
Mod: 0.01–0.43	938 (33.6)	4,513 (33.0)	0.99 (0.89, 1.09)	0.7802	0.99 (0.85, 1.14)	0.8194
High: ≥0.43	905 (32.4)	4,649 (34.0)	0.91 (0.83, 1.01)	0.0718	0.95 (0.82, 1.10)	0.4977
Rural ≥20,000 pop						
All classes				**0.0353**		0.3617
Low: ≤0.04	29 (33.7)	136 (32.8)	–		–	
Mod: 0.04–66.99	32 (37.2)	136 (32.8)	2.48 (1.00, 6.17)	0.0500	5.17 (0.17, 158.78)	0.3470
High: ≥66.99	25 (29.1)	14 (34.5)	2.81 (0.91, 8.66)	0.0721	3.36 (0.15, 73.77)	0.4426
Organophosphates				0.0516		0.3693
Low: ≤0.01	28 (32.6)	135 (32.5)	–		–	
Mod: 0.01–44.25	34 (39.5)	138 (33.3)	2.48 (1.01, 6.07)	**0.0473**	5.17 (0.18, 149.23)	0.3382
High: ≥44.25	24 (27.9)	142 (34.2)	2.47 (0.74, 8.23)	0.1404	3.36 (0.13, 87.90)	0.4675
Organochlorines				**0.0351**		0.2730
Low: ≤0.003	24 (27.9)	135 (32.5)	–		–	
Mod: 0.003-8.65	38 (44.2)	139 (33.5)	2.48 (0.92, 6.69)	0.0727	2.17 (0.49, 9.62)	0.3087
High: ≥8.65	24 (27.9)	141 (34.0)	3.04 (1.01, 9.16)	**0.0477**	2.32 (0.38, 14.21)	0.3636
Carbamates				0.0528		0.3515
Low: ≤0.004	29 (33.7)	137 (33.0)	–		–	
Mod: 0.004–15.02	31 (36.1)	135 (32.5)	2.28 (0.92, 5.67)	0.0768	5.17 (0.18, 148.29)	0.3373
High: ≥15.02	26 (30.2)	143 (34.5)	2.68 (0.85, 8.47)	0.0933	3.36 (0.16, 71.31)	0.4376
Rural <20,000 pop						
All classes				0.3849		0.3132
Low: ≤0.02	21 (28.0)	160 (33.2)	–		–	
Mod: 0.02–0.95	26 (34.7)	158 (32.8)	1.35 (0.65, 2.76)	0.4200	1.76 (0.55, 5.61)	0.3381
High: ≥0.95	28 (37.3)	164 (34.0)	1.27 (0.61, 2.64)	0.5168	2.24 (0.33, 15.25)	0.4094
Organophosphates				0.3844		0.3111
Low: ≤0.02	22 (29.3)	160 (33.2)	–		–	

Pesticide exposure category (kg/km^2)[a]	Cases (n=3,034) n (%)	Controls (n=14,991) n (%)	Unadjusted OR (95% CI)[b]	p-value[b]	Adjusted OR (95% CI)[b]	p-value[b]
Mod: 0.02–0.65	26 (34.7)	159 (33.0)	1.39 (0.69, 2.81)	0.3558	1.89 (0.63, 5.68)	0.2588
High: ≥0.65	27 (36.0)	163 (33.8)	1.23 (0.59, 2.54)	0.5813	2.02 (0.33, 12.37)	0.4456
Organochlorines				0.1193		**0.0428**
Low: ≤0.0002	19 (25.3)	159 (33.0)	–		–	
Mod: 0.0002–0.09	32 (42.7)	160 (33.2)	2.12 (0.96, 4.71)	0.0636	3.91 (1.39, 10.99)	**0.0099**
High: ≥0.09	24 (32.0)	163 (33.8)	1.40 (0.65, 2.99)	0.3864	2.10 (0.61, 7.22)	0.2387
Carbamates				0.5146		0.3183
Low: ≤0.01	22 (29.3)	160 (33.2)	–		–	
Mod: 0.01-0.24	23 (30.7)	159 (33.0)	1.26 (0.61, 2.61)	0.5266	1.74 (0.60, 5.08)	0.3102
High: ≥0.24	30 (40.0)	163 (33.8)	1.17 (0.59, 2.33)	0.6493	1.94 (0.36, 10.38)	0.4400

Abbreviations: CI, confidence interval; mod, moderate; OR, odds ratio; pop, population.

[a] esticide use densities were categorized using tertiles among controls.

[b] ORs, 95% CIs, and two-sided p-values were estimated using univariable conditional logistic regression models (robust variance estimation) conditioning on the matching factors for unadjusted models and using multivariable conditional logistic regression (robust variance estimation) adjusting for liver disease, diabetes, rare genetic disorders, and state buy-in and conditioning on the matching factors for adjusted models. Statistically significant results ($p<0.05$) are bold.

[c] Refers to all combined chemical classes: organophosphates, organochlorines, and carbamates.

[d] The following are adjusted ORs for the other predictors in the multivariable conditional logistic regression model: hepatitis only vs. no liver disease (OR 35.95, 95% CI 23.94, 53.99), cirrhosis vs. no liver disease (OR 62.51, 95% CI 27.40, 142.58), diabetes (OR 4.44, 95% CI 3.81, 5.16), rare genetic disorders (OR 6.22, 95% CI 1.57, 24.67), state buy-in (OR 1.39, 95% CI 1.20, 1.61).

Table 4

California residents of agriculturally intensive areas: unadjusted odds ratios and 95% confidence intervals for pesticide exposure and hepatocellular carcinoma using Pesticide Use Reports and SEER-Medicare in California, 2000–2009.

Pesticide exposure category (kg/km^2)[a]	Cases (n=227) n (%)	Controls (n=1,437) n (%)	Unadjusted OR (95% CI)[b]	p-value[b]
All classes				0.3656
Low: ≤59.38	71 (31.3)	474 (33.0)	–	
Mod: 59.38–104.76	73 (32.2)	474 (33.0)	0.98 (0.65, 1.48)	0.9152
High: ≥104.76	83 (36.6)	489 (34.0)	1.43 (0.95, 2.14)	0.0859
Organophosphates				0.1447
Low: ≤29.59	72 (31.7)	475 (33.1)	–	
Mod: 29.59-57.43	72 (31.7)	475 (33.1)	1.11 (0.74, 1.66)	0.6231
High: ≥57.43	83 (36.6)	487 (33.9)	1.53 (1.02, 2.29)	**0.0392**
Organochlorines				**0.0033**
Low: ≤3.68	61 (26.9)	474 (33.0)	–	
Mod: 3.68-10.38	75 (33.0)	475 (33.1)	1.47 (0.95, 2.56)	0.0833
High: ≥10.38	91 (40.1)	488 (34.0)	2.21 (1.42, 3.45)	**0.0005**
Carbamates				**0.0494**
Low: ≤15.05	67 (29.5)	474 (33.0)	–	
Mod: 15.05-32.98	71 (31.3)	475 (33.1)	1.29 (0.84, 1.96)	0.2442
High: ≥32.98	89 (39.2)	488 (34.0)	1.63 (1.08, 2.47)	**0.0204**

Abbreviations: CI, confidence interval; mod, moderate; OR, odds ratio.

[a] Pesticide use densities were categorized using tertiles among controls.

[b] ORs, 95% CIs, and two-sided p-values were estimated using univariable conditional logistic regression models (robust variance estimation) conditioning on the matching factors. Statistically significant results ($p<0.05$) are bold.

Table 5

California residents of agriculturally intensive areas: adjusted odds ratios and 95% confidence intervals for organochlorine pesticide exposure and hepatocellular carcinoma using Pesticide Use Reports and SEER-Medicare in California, 2000–2009.

Lag[a]	Organochlorine exposure category (kg/km^2)	Adjusted OR (95% CI)[b]	p-value[b]	Males: adjusted OR (95% CI)[b]	p-value[b]	Females: adjusted OR (95% CI)[b]	p-value[b]
Tertiles							
None			0.5956		0.2390		0.7203
	Low: ≤3.68	–		–		–	
	Mod: 3.68-10.38	0.89 (0.43, 1.84)	0.7511	1.03 (0.50, 2.13)	0.9364	0.57 (0.03, 11.68)	0.7134
	High: ≥10.38	1.55 (0.87, 2.78)	0.1395	2.04 (1.08, 3.87)	**0.0289**	0.79 (0.16, 3.94)	0.7736
10			0.2080		0.0585		0.8186
	Low: ≤4.80	–		–		–	
	Mod: 4.80–12.57	1.21 (0.55, 2.64)	0.6409	1.38 (0.62, 3.08)	0.4369	0.79 (0.04, 15.79)	0.8783
	High: ≥12.57	1.91 (1.01, 3.62)	**0.0463**	2.69 (1.37, 5.29)	**0.0041**	0.74 (0.12, 4.48)	0.7440
15			0.3096		0.1815		0.8741
	Low: ≤5.38	–		–		–	
	Mod: 5.38–12.67	1.10 (0.51, 2.39)	0.8093	1.06 (0.48, 2.33)	0.8872	1.37 (0.16, 12.08)	0.7776
	High: ≥12.67	1.75 (0.94, 3.29)	0.0800	2.30 (1.18, 4.47)	**0.0140**	0.96 (0.21, 4.29)	0.9519
20			0.2393		0.2943		0.5428
	Low: ≤5.70	–		–		–	
	Mod: 5.70–14.32	1.10 (0.54, 2.24)	0.7990	0.89 (0.42, 1.88)	0.7532	1.80 (0.30, 10.72)	0.5183
	High: ≥14.32	1.87 (1.00, 3.53)	0.0514	2.19 (1.13, 4.25)	**0.0205**	1.44 (0.29, 7.15)	0.6550
75th pctl[c]							
None[d]	≥14.53	1.87 (1.17, 2.99)	**0.0085**	2.76 (1.58, 4.82)	**0.0004**	0.83 (0.35, 1.93)	0.6600
10	≥16.85	1.82 (1.12, 2.96)	**0.0159**	2.58 (1.46, 4.58)	**0.0012**	0.86 (0.36, 2.06)	0.7353
15	≥18.08	1.68 (1.00, 2.82)	0.0518	2.34 (1.29, 4.25)	**0.0052**	0.83 (0.30, 2.26)	0.7092
20	≥19.30	1.71 (1.05, 2.80)	**0.0313**	2.32 (1.35, 4.02)	**0.0025**	0.81 (0.27, 2.46)	0.7109

Abbreviations: CI, confidence interval; mod, moderate; OR, odds ratio; pctl, percentile.

[a] An exposure lag of 10, 15, or 20 years considered pesticide exposure occurring outside of that particular window before diagnosis/selection. There were 227 cases and 1,437 controls with no lag, 214 cases and 1,366 controls with a 10-year lag, 214 cases and 1,336 controls with a 15-year lag, and 214 cases and 1,330 controls with a 20-year lag. Some cases and controls were missing lagged pesticide exposure due to their earliest available ZIP Code being missing or not in the TIGER/Line® ZIP Code file.

[b] ORs, 95% CIs, and two-sided p-values were estimated using multivariable conditional logistic regression (robust variance estimation) adjusting for liver disease and diabetes and conditioning on the matching factors. Statistically significant results ($p<0.05$) are bold.

[c] Subjects were exposed if the ZIP Code organochlorine pesticide use density was ≥75th pctl among agricultural controls.

[d] The following are adjusted ORs for the other predictors in the multivariable conditional logistic regression model: liver disease (OR 49.23, 95% CI 2.91, 833.83), diabetes (OR 5.92, 95% CI 3.37, 10.41). The following are adjusted ORs in the male-stratified model: liver disease (OR 24.77, 95% CI 3.11, 197.44), diabetes (OR 4.90, 95% CI 2.67, 9.02).