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ORIGINAL ARTICLE

Cancer mortality and oil production in the Amazon Region of Ecuador, 1990–2005

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Abstract
Objectives To compare cancer mortality rates in Amazon cantons (counties) with and without long-term oil exploration and extraction activities.
Methods Mortality (1990 through 2005) and population census (1990 and 2001) data for cantons in the provinces of the northern Amazon Region (Napo, Orellana, Sucumbios, and Pastaza), as well as the province with the capital city of Quito (Pichincha province) were obtained from the National Statistical Office of Ecuador, Instituto Nacional del Estadistica y Censos (INEC). Age- and sex-adjusted mortality rate ratios (RR) and 95% confidence intervals (CI) were estimated to evaluate total and cause-specific mortality in the study regions.
Results Among Amazon cantons with long-term oil extraction, activities there was no evidence of increased rates of death from all causes (RR = 0.98; 95% CI = 0.95–1.01) or from overall cancer (RR = 0.82; 95% CI = 0.73–0.92), and relative risk estimates were also lower for most individual site-specific cancer deaths. Mortality rates in the Amazon provinces overall were significantly lower than those observed in Pichincha for all causes (RR = 0.82; 95% CI = 0.81–0.83), overall cancer (RR = 0.46; 95% CI = 0.43–0.49), and for all site-specific cancers.
Conclusions In regions with incomplete cancer registration, mortality data are one of the few sources of information for epidemiologic assessments. However, epidemiologic assessments in this region of Ecuador are limited by underreporting, exposure and disease misclassification, and study design limitations. Recognizing these limitations, our analyses of national mortality data of the Amazon Region in Ecuador does not provide evidence for an excess cancer risk in regions of the Amazon with long-term oil production. These findings were not consistent or supportive of earlier studies in this region that suggested increased cancer risks.

Keywords Epidemiology · Petroleum · Neoplasms · Mortality · South America

Introduction

The impact of agricultural and industrial development on the health of the people in developing regions of Latin America and other developing countries, both the direct effects of environmental agents and the indirect effects of concomitant migration, crowding, and poverty, have been difficult to accurately and objectively measure. Poor socioeconomic conditions, inadequate water and sanitation quality, limited educational achievement, and lack of adequate public health infrastructure are common in such regions, and their detrimental effects on health are difficult to distinguish and frequently confound public health investigations of the impact of industrialization and development.

Oil is the one of most important exports in the Ecuadorian economy; however, the process of oil exploration and extraction and its impacts on the environment and its potentially adverse effects on health are the subject of considerable controversy. During oil exploration and

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drilling, low levels of chemical and metal contaminants may be present in the drilling muds and the formation waters that are produced and drained into separation ponds. In addition, when petroleum and natural gases are burned, nitrous, sulphuric, and carbon oxides, heavy metals, and hydrocarbon particulates can be released into the air (International Agency for Research on Cancer 1980). Crude oil is a mixture of paraffinic, naphthenic, and aromatic hydrocarbons, including benzene, and small amounts of sulfur, nitrogen, oxygen, and metal-containing compounds (Hawley 1981). Potential exposure to hydrocarbons from petroleum industry activities include inhalation of vapors and dermal contact of crude oil, intermediate products (during refining), and end products (in marketing or distribution) (International Agency for Research on Cancer 1989).

Studies that have specifically examined the potential health effects due to community exposure to oil exploration and production are few and limited in design and exposure assessment. In a series of recent publications, it was suggested that environmental contamination related to oil production was associated with increased cancer rates in communities that were in close proximity to oil production activities in the Amazon Region of Ecuador (Hurtig and San Sebastian 2002, 2004; San Sebastian and Hurtig 2004, 2002; San Sebastian et al. 2001). Problems with data quality, exposure and case ascertainment, interpretation of results, and study reproducibility, however, limit the reliability and accuracy of these results. These limitations have left the question of how oil production activities may have affected community health largely unanswered (Siemiatycki 2002; Arana and Arellano 2007).

Studying the impact of environmental exposures on cancer in the Amazon Region of Ecuador is a difficult task. The hospitals in this region have no histopathological services and no access to radiotherapy or chemotherapy treatment. Ecuador has no mandatory cancer registries in the Amazon Region, and available statistics on cancer incidence for the region are most likely incomplete and biased in their ascertainment by geography, socioeconomic status, and access to medical care. Official mortality data registered from death certificates are important resources in epidemiologic studies because they record cause of death and characteristics of the deceased in a standardized format. While the prevalence of diagnostic errors, incompleteness, coding and processing errors, and underregistration of death certificates has been widely studied (Cordeiro 1999; D'Amico et al. 1999; Lahti and Penttila 2001; Lu et al. 2001; Moriyama 1989; Percy et al. 1981; Smith Sehdev and Hutchins 2001), mortality data compiled by the national census bureau currently represent the most widespread coverage of health outcomes data available in Ecuador. Further, although cancer mortality rates will underestimate incidence, particularly for diseases with high survival rates, mortality patterns generally mirror cancer incidence, and thus mortality data can still provide reasonably accurate estimates of relative risk. To our knowledge, no published studies have examined national mortality data to investigate cancer risk and oil extraction activities in the Amazon Region of Ecuador or in other regions of Latin America.

Most of the epidemiologic studies that address the issue of carcinogenicity of petroleum chemicals have utilized cohort mortality study designs and included petroleum workers who were exposed as early as the 1930–1950s. In their extensive review of epidemiologic studies of over 350,000 petroleum workers, Wong and Raabe observed no increases in mortality from most cancers, including digestive, lung, bladder, kidney, and brain cancer (Wong and Raabe 2000). There was a slight elevation in mortality from skin cancer observed among petroleum workers as a whole, and elevations in prostate cancer in specific worker groups, although analyses by duration of employment, as a surrogate for potential exposure, revealed no exposure–response effects (Wong and Raabe 2000). Results from other occupational studies have produced similarly null findings (Divine and Barron 1987; Gottlieb 1980; Gottlieb et al. 1979; Mills et al. 1984; Sewell et al. 1986; Siemiatycki et al. 1987; Wong and Raabe 1995). One nested case-control study of study of lympho-hematopoietic cancers selected from a cohort of Australian petroleum workers observed excesses of leukemia among workers with low levels of estimated benzene exposure (Glass et al. 2003), although these results were based on small numbers of leukemia cases and similar risks were not reported in recent cohort analyses of these same workers (Gun et al. 2006). Prior to above-mentioned meta-analysis and the Australian study, the International Agency for Research on Cancer (IARC) concluded that "crude oil was not classifiable as to its carcinogenicity in humans (Group 3)" based on available epidemiologic and animal data (International Agency for Research on Cancer 1989).

To assess whether there was evidence that communities in close proximity to oil production activities had higher rates of mortality, particularly cancer mortality, relative to those that are not in close proximity, we calculated all cause and cause-specific mortality rates in selected cantons in the northern Amazon Region (Sucumbios, Napo, Orellana, and Pastaza provinces). We also compared the overall and cause-specific causes of death in the Amazon provinces, relative to Pichincha province (Ecuador's most populated province and the province where the capitol city Quito is located).

Materials and methods

Instituto Nacional de Estadistica y Censos (INEC)

The Instituto Nacional de Estadistica y Censos (INEC) provided all data for this analysis. INEC is the Ecuadorian institution that collects, analyzes, and reports statistical information on health, economic, socio-demographic, population, and other topics (http://www.inec.gov.ec). Mortality and census data from all cantons in the northern Amazon Region (Napo, Orellana, Pastaza, and Sucumbios) and Pichincha province were included. Mortality and population data at the parroquia (parish) level were not available for these analyses.

Mortality data and cause of death classification

Mortality data for the years 1990–2005 were reported at the canton level, stratified by sex and age group (5-year age group intervals, beginning at age 5). Deaths occurring under 1 year of age and from ages 1 to 4 were categorized separately. The coded underlying cause-of-death classifications were supplied by INEC and were based on the International Classification of Diseases, tenth revision (ICD-10). For reporting purposes, INEC combined colon and rectal cancers. They also combined the different forms of leukemia. Cancers of the uterine cervix (cervical cancer), uterine corpus (endometrial cancer), and uterus, NOS (not otherwise specified) were combined in our analyses; although etiologically heterogeneous, their misclassification in death certificate data makes their individual assessment unreliable and pooling them is a common practice in assessments of mortality rates of uterine cancers (Percy et al. 1981; Bocciolone et al. 1993; Bosetti et al. 2005). This analysis included 20 major categories of cancer death and 13 major categories of other causes of death (Table 1).

Population data

Data on the population of Ecuador were available from national decennial census surveys conducted in 1990 and 2001. All data were reported at the canton level, summarized by gender and age group (5-year age groups, starting with under 1 year, 1–4 years, etc.). Because our study period spanned 1990–2005, census data for individual years 1991–2000 and for 2002–2005 were imputed for each canton from the decennial surveys assuming a constant age- and sex-specific linear change (Ries et al. 2006).

Combining cantons that were divided by political divisions

As of 2001, Ecuador was divided into 22 provinces, which are subdivided into approximately 218 cantons. The number of cantons over time has been dynamic; for instance, between 1990–1994, 24 new cantons were created, primarily by splitting off from existing ones (Ecuador and 1970). To include data from the cantons that were created during the study period, we combined the census and mortality data for newly created and parent cantons to recreate the original classification of cantons in 1990 (Table 2). The Amazon Region experienced strong population growth during the study period, with growth rates of over 75% (range, 28.7–113.5%) in the cantons near oil production facilities and growth rates around 45% (range, 16.2–55.7%) in the unexposed regions over an eleven-year period (Table 3).

Classifications used in comparisons of cantons exposed and unexposed to long-term oil production activities

Exposed populations included all residents of cantons in the northern Amazon Region (Napo, Sucumbios, Orellana, Pastaza) with a higher density of oil production activities from 1970 to 1990. We compared cantons designated as having long-term oil production in the previous incidence studies by San Sebastian and colleagues (Hurtig and San Sebastian 2004, 2002) with maps showing recent oil well locations and drilling dates obtained from IHS Energy (http://energy.ihs.com) overlaid onto canton outlines downloaded from the SIISE (Sistema Integrado de Indicadores Sosiales del Ecuador) database. Based on visual inspection of these maps, we confirmed the long-term presence of oil wells in these cantons, and we included three additional cantons (Cascales, Cuyabeno, and Putumayo) as oil-producing cantons in addition to the four cantons already selected in the San Sebastian studies (Lago Agrio, Shushufindi, Orellana, and La Joya de Los Sachas). All other cantons (those with few or no oil wells) in the four northern Amazon Region were considered unexposed (Table 3, Fig. 1). The decision to include cantons with lower oil well density as unexposed in our analysis was made based on the relative likelihood of individual exposure and the duration of petroleum extraction activities. To ensure that misclassification of exposure status did not significantly affect estimates, a sensitivity analysis was performed using an unexposed group that included only cantons in the two southern Amazon provinces (Zamora Chinchipe and Morona Santiago). These southern Amazon cantons had no history of oil exploration or drilling. Being geographically different from the northern Amazon Region, however, they may be less similar with respect to unmeasured demographic, socioeconomic, health care delivery, and cancer reporting metrics than cantons in the northern Amazon, which represent the region from which the exposed population arose.

Table 1 ICD-10 codes and corresponding cause of death classifications (World Health Organization 1994)

Code	Cause of death
Cancer	
C01-C80	Total cancer (excluding those of lymphoid, hematopoietic, or related tissue)
C00-C14	Lip, oral cavity, and pharynx
C15	Esophagus
C16	Stomach
C18-C21	Colon, rectum, anus
C22	Liver
C25	Pancreas
C32	Larynx
C33-C34	Trachea, bronchus, and lung
C43	Melanoma (skin)
C50	Breast
C53	Cervix
C54-C55	Uterus
C56	Ovaries
C61	Prostate
C67	Bladder
C70-C72	Meninges, brain, spinal, and other central nervous system (CNS)
C82-C85	Non-Hodgkin's lymphoma (NHL)
C90	Multiple myeloma and malignant plasma cell neoplasms
C91-C95	Leukemia (lymphoid, myeloid, monocytic, other)
Other	
A00-B99	Infectious and parasitic disease (includes intestinal infectious diseases, tuberculosis, bacterial diseases, and viral infections)
J00-J98	Diseases of the respiratory system
E00-E88	Endocrine, nutritional, and metabolic diseases (includes diabetes mellitus and other disorders of glucose regulation and pancreatic internal secretion, malnutrition, obesity, disorders of the thyroid gland, metabolic disorders)
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (includes anemia (nutritional, hemolytic, and aplastic), coagulation defects
G00-G98	Diseases of the nervous system (includes inflammatory diseases, systemic atrophies, demyelinating diseases, nerve disorders, cerebral palsy)
I00-I99	Diseases of the circulatory system (includes rheumatic fever, hypertension, ischemic heart disease, pulmonary heart disease, cerebrovascular disease)
K00-K92	Diseases of the digestive system (includes diseases of oral cavity, esophagus, appendix, intestines, peritoneum, liver, gallbladder, biliary tract, and pancreas)
N00-N98	Diseases of the genitourinary system (includes renal failure, inflammatory disease of the female pelvic organs, disease of male genital organs)
P00-P96	Certain conditions originating in the perinatal period (affecting the fetus and newborn by complications and conditions during pregnancy, labor, and delivery)
Q00-Q99	Congenital malformation, deformations, and chromosomal abnormalities
R00-R99	Symptoms, signs, and abnormal clinical and laboratory findings
V01-V89	External causes of morbidity and mortality (includes accidents, suicides, assault, operations of war, and complications of medical and surgical care)
O00-O99	Pregnancy, childbirth, and the puerperium

Using data from IHS Energy for the 20 cantons in the northeastern Amazon Region that included the number of oil wells, the drill date (spud date), and the type of well, we also classified cantons according to their relative density of oil wells over time. Since well operation dates were not available, we estimated the working duration of each oil well as the number of years between spud date (date drilling began) through 2005 (the last year of death data

Table 2 Newly created cantons, year of separation, and recombined groupings for analysis

Province	Canton	Year created	Historically split from canton(s)	Analytically re-combined with canton(s)
Napo	Carlos Julio Arosemena Tola	1998	Tena	Tena
Orellana	Loreto	1993	Archidona, Quijos	Archidona, Quijos
Pastaza	Santa Clara	1992	Pastaza	Arajuno, Pastaza
	Arajuno	1998	Pastaza	Pastaza, Santa Clara
Morona Santiago	Huamboya	1992	Palora, Morona	Morona, Palora, Pablo VI, Taisha, Tiwintza
	San Juan Bosco	1993	Limon Indanza	Limon Indanza
	Logrono	1998	Sucua	Sucua
	Pablo VI	2002	Huamboya	Morona, Huamboya, Palora, Taisha, Tiwintza
	Taisha	1998	Morona	Morona, Huamboya, Palora, Pablo VI, Tiwintza
	Tiwintza	2002	Santiago, Morona	Morona, Huamboya, Palora, Pablo VI, Taisha
Zamora Chinchipe	El Pangui	1991	Yanzatza	Yanzatza
	Centinela del Condor	1996	Zamora	Zamora, Paquisha
	Palanda	1998	Chinchipe	Chinchipe
	Paquisha	2002	Centinela del Condor	Zamora, Centinela del Condor
Pichincha	San Miguel de los Bancos	1991	Quito	Quito, Pedro Vicente Maldonado, Puerto Quito
	Pedro Vicente Maldonado	1992	San Miguel de los Bancos	Quito, San Miguel de los Bancos, Puerto Quito
Sucumbios	Cascales	1991	Gonzalo Pizarro	N/A. Began counting mortality events beginning in 1991
	Cuyabeno	1998	Lago Agrio	Lago Agrio

Table 3 Total population of "exposed" and "unexposed" cantons in 1990 and 2001 censuses

	1990	2001	% growth	% growth/year
Exposed cantons of the Northern Amazon Region	105,906	187,568	77.1	7.0
Lago Agrio and Cuyabeno	41,254	73,431	78.0	7.1
Shushufindi	18,977	32,184	69.6	6.3
La Joya del Los Sachas	16,193	26,363	62.8	5.7
Orellana	19,674	42,010	113.5	10.3
Cascales	5,014	7,409	47.8	4.3
Putumayo	4,794	6,171	28.7	2.6
Unexposed cantons of the Northern Amazon Region	116,244	168,838	45.2	4.1
Sucumbios	2,441	2,836	16.2	1.5
Gonzalo Pizarro	4,472	6,964	55.7	5.1
Aguarico	3,150	4,658	47.9	4.4
Loreto, Archidona, and Quijos	24,178	37,518	55.2	5.0
Tena, Carlos Julio Arosemena Tola	35,747	48,950	36.9	3.4
El Chaco	4,445	6,133	38.0	3.5
Mera	5,947	8,088	36.0	3.3
Arajuno, Pastaza, and Santa Clara	35,864	53,691	49.7	4.5

follow-up). Wells that were considered "developmental" or "exploratory" were included. An "oil exploration activity" density value (the number of well-years of operation per 100 square kilometer for each canton) was calculated as follows:

Well-years/100 km^2 = (# of wells in canton × duration from spud date through 2005)/(area of canton in square kilometers × 100).

The results showed natural breakpoints for oil well density across cantons based on their distribution of well-

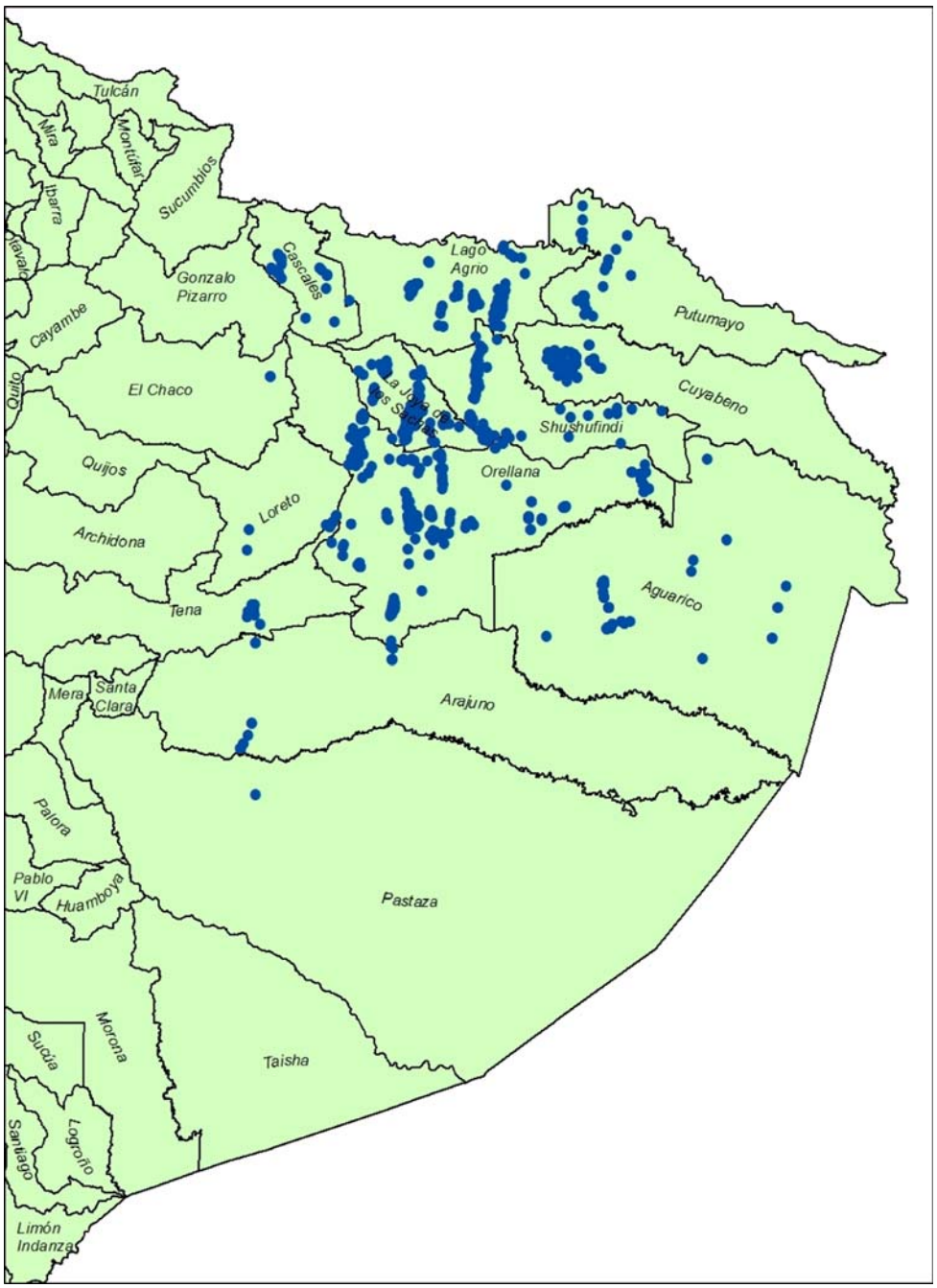

Fig. 1 Oil well locations in Amazon Region, 1990

years/100 km^2 (Table 4). Three categories emerged: "high" density, "moderate" density, and "low or none".

Classifications used in comparisons of amazon versus Pichincha province

In the comparison of causes of death and mortality rates in the Amazon Region with those in Pichincha province, deaths in all cantons in Napo, Sucumbios, Orellana, and Pastaza provinces were compared with deaths in all cantons in Pichincha province, from 1990–2005. The Amazon Region included cantons Lago Agrio, Cuyabeno, Shushufindi, La Joya de Los Sachas, Orellana, Cascales, Putumayo, Gonzalo Pizarro, Sucumbios, Aguarico, Loreto, Archidona, Quijos, Tena, Carlos Julio Arosemena Tola, El Chaco, Mera, Arajuno, Pastaza, and Santa Clara and Pichincha province included cantons Quito, San Miguel del Los Bancos, Pedro Vicente Maldonado, Puerto Quito, Cayambe, Mejia, Pedro Moncayo, Ruminahui, and Santo Domingo.

Table 4 Exposure classification of cantons, based on distribution of oil well density

Category	Canton	Oil-well years per 100 square kilometers
"Low or None" = 0–<1 well-year per 100 km^2	Archidona	0.9
	El Chaco	0.0
	Mera	0.0
	Gonzalo Pizarro	0.0
	Sucumbios	0.0
"Moderate" = 1–100 well-years per 100 km^2	Tena	10.5
	Aguarico	33.0
	Pastaza	9.4
	Putumayo	38.0
"High" = 100 + well-years per 100 km^2	Orellana	145.3
	La Joya de los Sachas	360.5
	Cascales	116.9
	Lago Agrio	102.2
	Shushufindi	190.1

Calculation of person-years at risk

Several assumptions were made in the calculation of the number of person-years at risk for this study: each canton was assumed to be in existence for the entire calendar year; each person living in a given canton was assumed to contribute a full-year to the total for that year; and the number of deaths occurring each year was assumed to be a minimal fraction of the total population. Therefore, the population count for each year is equal to the number of person-years at risk for that year, and the total number of person-years accrued is the sum of the total population for each of the 16 years of study.

Statistical methods

Mortality rates directly standardized to the combined age- and sex-distribution of Pichincha, Napo, Sucumbios, Orellana, and Pastaza provinces were calculated for total mortality, total cancer deaths, cancer-specific deaths (uterine, prostate, stomach, cervical, liver and gallbladder, lung and bronchus, central nervous system, bladder, non-melanoma skin, breast, non-Hodgkin's lymphoma, colorectal, and leukemia), and selected other causes of death (infectious disease, circulatory disease, respiratory disease, and external causes) for each analytic group (e.g., oil-producing versus other Amazon Regions, Amazon versus Pichincha).

Adjusted mortality rate ratios (RRs) were calculated by dividing the directly standardized mortality rate in the exposed region (numerator) by the directly standardized mortality rate in the unexposed region (denominator). An approximate two-sided $100\% \times (1-\alpha)$ confidence interval (CI) for *ln(RR)* was calculated by, $\ln(\mathrm{RR}) \pm Z_{1-\alpha/2}\sqrt{\frac{1}{a_1}+\frac{1}{a_2}}$, where a_1 and a_2 are the number of observed deaths from the exposed and comparison groups. The two-sided confidence interval for RR is obtained by taking the antilog of the values calculated from the above expression (Rosner 2000).

Results

Evaluation of oil-producing areas within amazon region

From 1990–2005, there were 2,569,685 person-years (50.2% male) and 7,713 total deaths (males, $n = 4{,}901$; females, $n = 2{,}812$) in oil-producing regions and 2,428,113 person-years (49.9% male) and 7,622 total deaths (males, $n = 4{,}520$; females, $n = 3{,}102$) in other Amazon comparison regions (Table 5). Adjusted death rates between oil-producing and other Amazon Regions were similar, or lower, for oil-producing cantons when measuring deaths due to all causes (RR = 0.98; 95% CI = 0.95–1.01), all cancer deaths (RR = 0.82; 95% CI = 0.73–0.92), circulatory disease (RR = 0.75; 95% CI = 0.67–0.83), infectious diseases (RR = 0.83; 95% CI = 0.75–0.91), and respiratory disease (RR = 0.73; 95% CI = 0.64–0.82). Death rates from external causes (RR = 1.46; 95% CI = 1.35–1.59) were significantly higher in oil-producing cantons. Death rates were lower in oil-producing cantons for cancers of the larynx, lung, esophagus, stomach, colon and rectum, other digestive organs, breast, uterus, prostate, bladder, pancreas, and central nervous system, leukemia, and NHL, although these reductions were not statistically significant. For two cancer outcomes, the results were significantly lower: other digestive cancers (RR = 0.70; 95% CI = 0.53–0.94) and central nervous system (CNS) cancers: (RR = 0.40; 95% CI = 0.17–0.95). There were non-statistically significant increases in deaths from oral cancers (RR = 1.28; 95% CI = 0.36–4.54), liver cancer (RR = 1.52; 95% CI = 0.95–2.43), and multiple myeloma (RR = 2.51; 95% CI = 0.23–27.64) in the oil-producing regions. For both melanoma and multiple myeloma cancers, the relative risk estimates were based on two reported cases in the oil-producing region, a number too small for meaningful interpretation. Among females only, relative risk estimates were similar to aggregate results with the exception of liver cancers, which were not elevated (RR = 0.73; 95% CI = 0.36–1.49), and CNS cancers, which were now slightly elevated (RR = 1.33; 95% CI = 0.42–4.21). Among males, relative rates of cancer were generally higher than aggregate (both male and female combined) results. Mortality from liver cancer was

Table 5 Age- and sex-adjusted mortality rate ratios comparing exposed and unexposed cantons in the Northern Amazon Region, 1990–2005

Cause	Total[a,b]				Males[a,c]				Females[a,d]			
	# Deaths				# Deaths				# Deaths			
	Exposed	Unexposed	Rate Ratio (RR)	95% CI	Exposed	Unexposed	Rate Ratio (RR)	95% CI	Exposed	Unexposed	Rate Ratio (RR)	95% CI
Total	7,713	7,622	0.98	0.95–1.01	4,901	4,520	1.03	0.99–1.07	2,812	3,102	0.89	0.85–0.94
Any cancer	484	605	0.82	0.73–0.92	269	298	0.91	0.78–1.08	215	307	0.70	0.59–0.83
Laryngeal	3	4	0.95	0.21–4.25	3	2	1.67	0.28–10.00	0	2	0	
Lung/bronchus	28	40	0.75	0.47–1.22	23	23	1.01	0.57–1.80	5	17	0.30	0.11–0.82
Oral	6	4	1.28	0.36–4.54	3	2	1.22	0.20–7.33	3	2	1.36	0.23–8.15
Esophageal	9	14	0.63	0.27–1.45	7	11	0.61	0.24–1.58	2	3	0.70	0.12–4.21
Stomach	101	112	0.96	0.74–1.26	72	62	1.20	0.85–1.68	29	50	0.59	0.38–0.94
Colorectal	12	15	0.83	0.39–1.77	6	6	1.03	0.33–3.19	6	9	0.66	0.24–1.86
Other digestive	81	115	0.70	0.53–0.94	38	53	0.71	0.47–1.08	43	62	0.70	0.47–1.03
Breast									9	15	0.58	0.26–1.33
Uterine									51	63	0.80	0.55–1.15
Ovarian									7	12	0.54	0.21–1.37
Prostate					27	46	0.65	0.40–1.04				
Urinary bladder	4	6	0.53	0.15–1.89	3	6	0.42	0.10–1.67	1	0		
Liver	41	30	1.52	0.95–2.43	28	12	2.43	1.24–4.78	13	18	0.73	0.36–1.49
Pancreatic	10	21	0.53	0.25–1.14	7	9	0.81	0.30–2.18	3	12	0.27	0.08–0.94
Leukemia	46	53	0.82	0.56–1.22	27	33	0.77	0.46–1.28	19	20	0.93	0.50–1.74
Non-Hodgkin's lymphoma	12	15	0.75	0.35–1.60	9	12	0.69	0.29–1.65	3	3	1.05	0.21–5.22
Multiple myeloma	2	1	2.51	0.23–27.64	1	0			1	1	0.93	0.06–14.89
Central nervous system	8	16	0.40	0.17–0.95	1	11	0.08	0.01–0.60	7	5	1.33	0.42–4.21
Melanoma	2	1	2.32	0.21–25.57	1	0			1	1	0.95	0.06–15.25
Uncertain behavior	25	22	1.18	0.67–2.09	13	10	1.40	0.61–3.19	12	12	0.98	0.44–2.17
Circulatory disease	566	735	0.75	0.67–0.83	344	418	0.79	0.69–0.92	222	317	0.67	0.57–0.80
External causes	1,608	1,006	1.46	1.35–1.59	1,305	777	1.52	1.39–1.66	303	229	1.24	1.05–1.48
Infectious diseases	714	838	0.83	0.75–0.91	399	479	0.80	0.70–0.92	315	359	0.86	0.74–1.00
Respiratory disease	443	605	0.73	0.64–0.82	259	335	0.75	0.64–0.88	184	270	0.69	0.57–0.83

[a] Person-years = estimated population size * number of years of follow-up

[b] Exposed regions (total) = 2,569,685 person-years; unexposed regions = 2,428,113 person-years

[c] Exposed regions (males) = 1,288,999 person-years; unexposed regions = 1,211,361 person-years

[d] Exposed regions (females) = 1,280,686 person-years; unexposed = 1,216,752 person-years

significantly elevated among men (RR = 2.42; 95% CI = 1.24–4.78). Among children ages 0–14, the ratio of adjusted leukemia mortality rates were below 1.0 in oil-producing areas, relative to other Amazon Regions (RR = 0.91; 95% CI = 0.49–1.69), with variation across specific age groups: children ages 0–4 (RR = 1.34; 95% CI = 0.47–3.87), children aged 5–9 (RR = 0.75; 95% CI = 0.26–2.17), and children aged 10–14 (RR = 0.72; 95% CI = 0.23–2.26) (Table 6).

In analyses comparing oil-producing cantons to cantons in the two southern Amazon provinces, similar trends were observed. For the oil-producing regions, relative risk estimates were slightly above 1.0 for uterine, oral, liver, and lung cancer, multiple myeloma, and non-Hodgkin's lymphoma. Relative risks were below 1.0 for mortality from breast, CNS, colorectal, laryngeal, melanoma, ovarian, pancreatic, and stomach cancers. However, with the exception of stomach cancer (RR = 0.74; 95% CI = 0.56–0.97), all risk estimates fell short of being statistically significant (data not shown).

To assess whether there was evidence of dose-response based on the density of oil wells in each canton, we also conducted analyses comparing rates of death in cantons with "moderate" or "high" oil well density, relative to those with "little or none". No statistically significant elevations in cancer rates were observed in cantons with high density of oil wells, relative to those with little or none, with the exception of an elevation in deaths from external causes (RR = 1.14; 95% CI = 1.03–1.27). Statistically significant elevations were observed for total cancer deaths, deaths from "other digestive cancers", and deaths from circulatory disease in cantons with medium oil well density relative to none (data not shown). All relative risk estimates in this ecologic exposure–response analysis were based on very small numbers of death.

Table 6 Sex-adjusted mortality rate ratios for childhood leukemia by age group, comparing exposed and unexposed cantons in the Northern Amazon Region, 1990–2005

Age group	# Deaths		Rate ratio (RR)	95% CI
	Exposed	Unexposed		
0–4 years[a,b]	8	6	1.34	0.47–3.87
5–9 years[a,c]	6	8	0.75	0.26–2.17
10–14 years[a,d]	5	7	0.72	0.23–2.26
0–14 years[a,e]	19	21	0.91	0.49–1.69

[a] Person-years = Estimated population size × number of years of follow-up

[b] Exposed regions (0–4 years) = 363,117; unexposed regions (0–4 years) = 364,233

[c] Exposed regions (5–9 years) = 351,448; unexposed regions (5–9 years) = 353,275

[d] Exposed regions (10–14 years) = 309,935; unexposed regions (10–14 years) = 311,214

[e] Exposed regions (0–14 years) = 1,024,500; unexposed regions (0–14 years) = 1,028,722

Comparisons of Amazon Region and Pichincha

From 1990–2005, there were 4,997,798 person-years of observation (50% male) in the four northern Amazon provinces (Napo, Sucumbios, Orellana, and Pastaza) and 15,335 deaths (males, $n = 9{,}421$; females, $n = 5{,}914$). In Pichincha province, there were 34,939,506 total person-years (49.3% male) and 151,703 deaths (males, $n = 83{,}510$; females, $n = 68{,}193$). Cancers accounted for 7.1% of the total deaths in the Amazon and was the fourth most common major cause of death, after external causes (17.1%), infectious diseases (10.1%), and circulatory disease (8.5%). In Pichincha province, cancer was the cause of 15.5% of all deaths, making it the second most common of the major causes of death (after circulatory disease [21.1%]). The largest proportions of deaths in both the Amazon (41.5%) and Pichincha (29.6%) were attributed to diseases of the endocrine, nervous, digestive, and genitourinary systems, blood diseases, pregnancy/childbirth, congenital conditions, and other abnormal clinical symptoms not assigned elsewhere (Table 7).

Age- and sex-adjusted mortality rate ratios comparing the Amazon and Pichincha province show that the rates of death from all causes (RR = 0.82, 95% CI = 0.81–0.83), any cancer (RR = 0.46, 95% CI = 0.43–0.49), circulatory disease (RR = 0.41, 95% CI = 0.38–0.43), and respiratory disease (RR = 0.56, 95% CI = 0.52–0.59) were lower in the Amazon, relative to Pichincha, while deaths attributed to infectious diseases (RR = 1.24, 95% CI = 1.17–1.31) and unknown causes (RR = 1.19, 95% CI = 1.12–1.26) were higher in the Amazon Region (Table 7). Death rates from external causes such as accidents, suicides, and medical complications were similar between the two areas (RR = 1.02, 95% CI = 0.98–1.06). Mortality rates for specific cancers were consistently lower in the Amazon Region compared to Pichincha, with relative risks of death from cancer in the Amazon ranging from 0.09 (melanoma) to 0.73 (laryngeal cancer). With the exception of relative risks for laryngeal and oral cancer (RR = 0.61, 95% CI = 0.32–1.15), all rate ratios indicating lower mortality rates in the Amazon relative to Pichincha were statistically significant. Analyses stratified by sex yielded similar estimates.

Discussion

In the current analysis, mortality in cantons with long-term oil extraction activities were similar, or lower, compared to

Table 7 Age- and sex-adjusted mortality rate ratios comparing Amazon provinces with Pichincha province, 1990–2005

Cause	Total[a,b]				Males[a,c]				Females[a,d]			
	# Deaths				# Deaths				# Deaths			
	Amazon	Pichincha	Rate ratio (RR)	95% CI	Amazon	Pichincha	Rate ratio (RR)	95% CI	Amazon	Pichincha	Rate ratio (RR)	95% CI
Total	15,335	151,703	0.82	0.81–0.83	9,421	83,510	0.89	0.88–0.91	5,914	68,193	0.71	0.69–0.73
Any cancer	1089	23,454	0.46	0.43–0.49	567	10,864	0.51	0.46–0.55	522	12,590	0.41	0.37–0.45
Laryngeal	7	98	0.73	0.34–1.58	5	78	0.67	0.27–1.66	2	20	1.05	0.25–4.50
Lung/bronchus	68	1,434	0.49	0.39–0.63	46	870	0.54	0.40–0.72	22	564	0.41	0.27–0.63
Oral	10	175	0.61	0.32–1.15	5	92	0.58	0.24–1.43	5	83	0.64	0.26–1.59
Esophageal	23	386	0.64	0.42–0.97	18	302	0.64	0.40–1.03	5	84	0.62	0.25–1.54
Stomach	213	4,228	0.53	0.46–0.61	134	2,277	0.60	0.50–0.71	79	1,951	0.42	0.34–0.53
Colorectal	27	1,095	0.25	0.17–0.37	12	455	0.26	0.15–0.47	15	640	0.25	0.15–0.41
Other digestive	196	4,167	0.46	0.40–0.53	91	1,795	0.48	0.39–0.59	105	2,372	0.44	0.36–0.54
Breast									24	1,150	0.20	0.13–0.30
Uterine									114	1,991	0.57	0.47–0.68
Ovarian									19	411	0.45	0.28–0.71
Prostate					73	1,712	0.45	0.35–0.57				
Urinary bladder	10	277	0.40	0.21–0.75	9	178	0.53	0.27–1.03	1	99	0.10	0.01–0.72
Liver	71	1,192	0.62	0.49–0.78	40	533	0.74	0.54–1.02	31	659	0.48	0.34–0.69
Pancreatic	31	784	0.41	0.29–0.59	16	365	0.44	0.27–0.73	15	419	0.37	0.22–0.62
Leukemia	99	1,492	0.53	0.43–0.65	60	771	0.60	0.46–0.78	39	721	0.43	0.31–0.60
Non-Hodgkin's lymphoma	27	663	0.40	0.27–0.58	21	330	0.57	0.37–0.89	6	333	0.17	0.07–0.38
Multiple myeloma	3	250	0.12	0.04–0.36	1	131	0.08	0.01–0.57	2	119	0.17	0.04–0.69
Central nervous system	24	669	0.31	0.21–0.47	12	363	0.29	0.16–0.51	12	306	0.35	0.19–0.62
Melanoma	3	322	0.09	0.03–0.27	1	140	0.07	0.01–0.50	2	182	0.11	0.03–0.43
Uncertain behavior	47	949	0.45	0.34–0.60	23	463	0.44	0.29–0.67	24	486	0.46	0.30–0.69
Circulatory disease	1,301	31,977	0.41	0.38–0.43	762	15,630	0.47	0.44–0.51	539	16,347	0.32	0.30–0.35
External causes	2,614	19,794	1.02	0.98–1.06	2,082	15,220	1.06	1.01–1.11	532	4,574	0.87	0.80–0.96
Infectious diseases	1,552	8,854	1.24	1.17–1.31	878	4,912	1.27	1.18–1.36	674	3,942	1.20	1.11–1.30
Respiratory disease	1,048	13,911	0.56	0.52–0.59	594	7,637	0.57	0.53–0.62	454	6,274	0.53	0.48–0.59

[a] Person-years = Estimated population size × number of years of follow-up

[b] Amazon provinces (total) = 4,997,798 person-years; Pichincha province = 34,939,506 person-years

[c] Amazon provinces (males) = 2,500,360 person-years; Pichincha province = 17,239,342 person-years

[d] Amazon provinces (females) = 2,497,438 person-years; Pichincha province = 17,700,163 person-years

those without such activities for overall mortality, overall cancer, circulatory disease, infectious disease, and respiratory diseases, and for many site-specific cancers, with relative risk estimates generally near 1.00 (RR range = 0.40–1.52). In analyses using regional oil well density as a surrogate for exposure, there were no statistically significant elevations in cancer rates in cantons with a high density of oil wells, relative to those with a low or zero density. The rates of total cancer deaths and deaths from "other digestive diseases" were higher in cantons of medium oil well density relative to those with few or no oil wells. However, considered in the context of the lack of elevations in the high well density regions, overall these data are not indicative of a potential exposure response relationship. Comparing mortality in the Amazon and Pichincha province, mortality rates from all causes, cancer, circulatory disease, and respiratory disease were lower in the Amazon than in Pichincha province, while death rates from infectious diseases were higher.

The only statistically significant elevation in cancer in oil-producing cantons was an observed elevation in liver cancer deaths among males. However, this observation is more likely attributable to chance, possibly due to multiple comparisons, than to a direct relationship with liver cancer mortality. Liver cancer has not been previously associated with exposures to crude oil, oil refining, or benzene in previous epidemiologic studies (Wong and Raabe 2000). Liver cancer occurrence is relatively high in developing countries with rapid population growth (Bosch et al. 2005; McGlynn and London 2005), probably attributable to the association of liver cancer with infectious agents (e.g., hepatitis virus B or C), and it is the most common cause of cancer death in several Latin American countries (Bosetti et al. 2005). Another possible explanation for the observed increase is misdiagnosis of underlying cause of death on death certificates. Liver is a common site for metastases from many cancers (Abeloff 2004), and in regions where histopathologic services are not available to determine the original tissue type of the cancer, deaths from other cancer sites may be mistakenly recorded as liver cancer. Based on this information, we concluded that it was unlikely that the observed elevation is related to potential exposure to oil extracting activities.

Perhaps of more interest is the lower rates observed for many cancer outcomes in petroleum activity cantons, relative to those without petroleum related activity. One potential explanation is that underreporting may have biased estimates. Assuming there is no a priori reason to believe that vital statistics reporting is dependent upon exposure status (e.g., whether a death goes unreported is independent of the presence of oil activities in that canton), one would expect that this selection bias to be non-differential and therefore bias would be towards the null (in this situation that would imply that true cancer rates in exposed regions are even more reduced than what is observed). On the other hand, one might assume that communities in oil-producing cantons have better reporting due to better access to health clinics, social services, etc., as a consequence of oil extraction activity in the community, or that unexposed communities have higher proportions of indigenous people or less access to health services (both of which could lead to underreporting of vital statistical data (San Sebastian and Hurtig 2004). In these cases we would have expected to see elevations (rather than reductions) in mortality rate ratios among oil-producing cantons, since underreporting would likely be higher in the unexposed communities. Underreporting in the oil-producing cantons could lead to underestimation of mortality rate ratios; however, this scenario seems unlikely.

Another potential explanation is that cantons where petroleum activities have occurred have higher proportions of immigrants, and these people may be healthier than those in other cantons (non-immigrants). This observation of better health status among migrants has been frequently documented in other populations (Baron-Epel and Kaplan 2001; Bentham 1988; Gissler et al. 2003; Kelaher and Jessop 2002). Population growth over the study period was more rapid in oil-producing cantons (see Table 3). Ecuadorian government policy encouraged people to move to this area by providing access to land, which has led to increased agricultural activity as well as some petroleum industry work activity (although this industry accounts for only a small percentage of the population). Given the influx of migrants, their potentially better health status may explain the lower observed mortality rate ratios in the oil-producing regions of the Oriente.

The results of this mortality study contradict those observed in a series of ecologic studies by Hurtig and San Sebastian (Hurtig and San Sebastian 2004, 2002; San Sebastian and Hurtig 2004). In the Hurtig and San Sebastian studies, statistically significant elevations in rates of all cancers combined and of cancers of the stomach, rectum, skin melanoma, kidney, and soft tissue were reported among males, and elevated cancer rates of the cervix and lymph nodes were reported among females in counties in close proximity to oil wells in the provinces of Sucumbios, Orellana, Napo, and Pastaza (Hurtig and San Sebastian 2002). In a similarly designed ecologic study, excess leukemia was reported (RR = 2.56; 95% CI = 1.35–4.86) among children ages 0–14 years who lived in cantons classified as in close proximity to oil wells (Hurtig and San Sebastian 2004). In another study that compared indigenous and non-indigenous peoples who live in the four Amazon provinces, indigenous men and women were at significantly lower risk of a number of cancers, including stomach, skin, prostate, lymph nodes, leukemia, breast, and

cervix, relative to non-indigenous people from the same regions, although indigenous males had higher rates of testicular cancer (San Sebastian and Hurtig 2004).

Several methodological differences may explain the discrepancies between the current mortality analysis and the previous cancer incidence studies. The different classifications of exposed and unexposed populations and different methods for estimating the annual population of the counties selected are two important differences. In this mortality analysis, cantons in the Ecuadorian Amazon were classified into those with exposure to long-term oil extraction activities using data from various agencies (see Sect. "Methods") to determine well locations, drilling dates, and geographic areas, which resulted in classifying seven "exposed" cantons and thirteen "unexposed" cantons. In the cancer incidence studies by San Sebastian and colleagues, exposed cases were those who reported residence at diagnosis in four cantons where oil activities had been ongoing for at least 20 years, while unexposed cases were those who resided in eleven cantons or parroquias without these activities, although not all potentially unexposed regions were included. Even when we analyze just these four cantons we did not confirm the excess as reported by San Sebastian et al. and Hurtig et al. Several methodological aspects of studies conducted by San Sebastian and colleagues are unclear: (1) what sources of data were used to classify exposure, (2) whether study areas were selected at the canton or parroquia level, and (3) why all non-exposed cantons in the northern Amazon Region were not included as part of the comparison group. Consequently, we were unable to replicate the exposure classifications used by San Sebastian and colleagues. For both the current mortality study and the San Sebastian cancer incidence studies, population at risk estimates were made using national census data from INEC. In developing countries where development and industrialization can bring about large influxes of immigration and rapid changes in population size, enumeration of the population at risk is challenging. The San Sebastian incidence studies relied on the 1990 data to estimate population at the midpoint of their study period (1992) and assumed this average population size across the duration of the study period. This method likely underestimated the population of the exposed regions, which experienced more rapid population growth than unexposed regions (see Table 3). This underestimation of the population at risk in exposed regions would artificially inflate cancer rates in these areas and may explain their observation of elevated cancer risks (Tong 2000). To demonstrate the effect that this underestimation can have on risk estimates, consider the study of cancer in the town of San Carlos, by San Sebastian and colleagues. When using a conservative estimate of population size, elevations in cancer rates were observed (San Sebastian et al. 2001). However, in a re-analysis by Arano and Arellano using census data to enumerate the population size, excess cancers were no longer observed (Arana and Arellano 2007). In the current mortality study, data from both the 1990 and 2001 censuses were used to quantify growth rates at the canton level, and canton population during intercensal years was imputed as a function of these canton-, age-, and sex-specific growth rates. We believe this methodology more accurately reflects the actual population of the area over the study period, reducing population underestimation due to differential migration rates between cantons and producing more accurate estimates of excess cancer risk.

Also significant are the differences in data types, sources, and ascertainment between the incidence and mortality studies. San Sebastian and colleagues evaluated cancer incidence, generally considered to be a better measure of the risk of developing disease than mortality (Rothman and Greenland 1998). While cancer mortality patterns are often similar to cancer incidence patterns, particularly for diseases with low survival rates, for cancers with higher survival rates, mortality studies will underestimate true disease incidence. However, relative risk estimates from mortality data can still provide unbiased relative risk estimates. In the Amazon Region of Ecuador, one would expect mortality trends to parallel reported cancer incidence since there is no basis to assume that proximity to oil production facilities would differentially impact cancer survival.

The Amazon Region has no mandatory cancer registries, and cancer cases identified in the previous incidence studies were those diagnosed in the Quito health care system and reported to the National Tumor Registry (NTR) and reported residence in the Amazon (Hurtig and San Sebastian 2004, 2002; San Sebastian and Hurtig 2004). Because provincial hospitals and health centers in the Amazon are not fully equipped for cancer diagnosis or treatment, suspected cases in the Amazon are referred to the capitol city of Quito. However, the distance between Quito and the Amazon can be as much as a 12-h bus ride from more remote areas, and such travel may pose a significant prohibitive factor for many. Thus cancer cases identified in the NTR may be very different from those that remain unreported. These differences may be reflected by tumor type, stage/severity of disease, and host and exposure characteristics, such as age, socioeconomic status, geographical subregion, etc. For example, if cancer cases in oil-producing areas are more likely to travel to Quito for treatment than cases residing in non-oil producing areas due to access to better roads and/or transportation, cancer rates in oil-exposed regions would appear to be inflated relative to non-oil areas. Because there is no way of knowing how this method of case ascertainment may have

affected the selection of cases included in the study, it is difficult to predict or statistically adjust for the degree and direction of any selection bias (Armstrong et al. 1992).

Mortality data abstracted from death certificates provide an important source of information to measure the burden of disease in a population, and official mortality registers are often used in epidemiologic research. However, the limitations of studies using death certificate data are well known (Cordeiro 1999; D'Amico et al. 1999; Lahti and Penttila 2001; Lu et al. 2001; Moriyama 1989; Percy et al. 1981; Smith Sehdev and Hutchins 2001). The quality of recorded cause of death classification is limited by the diagnostic abilities of the medical facility and/or physician. In developing countries, especially in areas where access to medical care and training of providers may be limited or diagnosing physicians may not be in attendance, death certificates may be incomplete or incorrectly filled out, particularly with respect to identifying direct and underlying causes of death. The proxy indicator of the quality of mortality data is the proportion of deaths that are medically certified and what proportion of certified deaths are assigned to "symptoms, signs, and ill-defined conditions" or "SSI" (R00-R99); differences in these two measures between areas are useful in detecting differentials in access to medical care (Silvi 2003). From 1990–2005, 31.8% of all deaths in the northern Amazon were without medical certification and 26.7% were assigned to "SSI", with no significant differences in the proportions between oil-exposed and unexposed cantons. The validity of death certificate data is also affected by the under-registration of deaths. In many developing countries, the coverage of the civil registration system is incomplete and varies according to geographic areas, age group, and other parameters. In general, registration coverage is poorer in rural areas, in areas with poor living conditions, and for deaths occurring at younger ages (i.e., infant deaths) (Silvi 2003).

Both the current mortality analysis and the previous incidence studies were ecologic studies, in which cancer rates were compared between groups of people, whose exposure status was assigned based on residence in a particular community and which may not reflect true individual exposure. The primary limitation of ecologic analyses to draw causal inferences is the risk of ecologic bias, or the failure of ecologic estimates to reflect true biologic effects at the individual level (Rothman and Greenland 1998; Morgenstern 1998). Ecologic biases stem from the aggregations of data, which reduces information and prevents the identification of associations of interest in the underlying individual-level model (Wakefield 2008). These biases can arise when unmeasured risk factors are distributed differently across groups being compared or when aggregate risks do not reflect individual risks (Rothman and Greenland 1998). For example, the areas being compared in ecologic studies may differ in background rates of disease that are not captured with aggregate data. If the proportion of individuals with higher rate of disease were higher in one area than the other, an ecologic association would be observed that is unrelated to the exposure of interest but caused by that extraneous confounding factor. Confounding in ecologic studies is difficult to characterize, because it is comprised of both within and between area variation in risk factors (Wakefield 2008). Although standardizing by common confounders, such as age and sex, between populations is possible if death rates are known within these strata, data on other confounders that may bias associations (e.g., diet, smoking, family history of disease) are largely unknown in ecologic studies. Ecologic studies also do not account for residential migration, and if a person resided/was exposed in a different location from where their disease status was recorded (in this case, cancer incidence or death), an association may be spuriously created or masked. The aggregate data used for exposure assessment in ecologic studies do not capture duration, frequency, or intensity of exposure, information that is frequently used to establish causality in epidemiologic studies. In this study, our proxy exposure classification (oil well density) may not represent actual oil production and is even more indirect at estimating individual exposure. Ecologic studies can be informative when exposures occur at a group level, and they are particularly useful when evaluating the impacts of community-level interventions and as an initial evaluation of potential health effects of environmental factors (Morgenstern 1998). However, given the limitations of ecologic studies and their risk of bias, causal associations cannot be inferred from these types of studies alone, and results must be interpreted with caution.

In developing countries such as Ecuador, the likelihood of high levels of underreporting of incidence and mortality events limits the ability of epidemiologic studies to assess the impact of exposures on health outcomes. Nevertheless, mortality data compiled from death certificates provide the most complete coverage and most likely the least systematically biased source of health outcomes data currently available in Ecuador. The national mortality data collected and summarized by INEC does not currently support a relationship of oil extraction activities and adverse health outcomes in potentially exposed communities. The Amazon populations face a variety of public health challenges, and improvements in study design, disease registration, data coding and collection procedures will help to improve epidemiologic research in this region.

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