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Mesoamerican nephropathy: Geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica

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ABSTRACT

Objectives: Mesoamerican nephropathy (MeN) is an epidemic of chronic kidney disease (CKD) unrelated to traditional causes, mostly observed in sugarcane workers. We analyzed CKD mortality in Costa Rica to explore when and where the epidemic emerged, sex and age patterns, and relations with altitude, climate and sugarcane production.

Methods: Standardized Mortality Ratios (SMRs) for CKD deaths (1970-2012) among population aged ≥20 were computed for seven provinces and 81 counties over four time periods. Time trends were assessed with age-standardized mortality rates. We qualitatively examined relations between mortality and data on altitude, climate and sugarcane production.

Results: During 1970-2012, age-adjusted mortality rates in the Guanacaste province increased among men from 4.4 to 38.5 per 100.000 versus 3.6 to 8.4 in the rest of Costa Rica, and among women from 2.3 to 10.7 versus 2.6 to 5.0. A significant moderate excess mortality was observed among men in Guanacaste already in the mid-1970s, steeply increasing thereafter; a similar female excess mortality appeared a decade later, remaining stable. Male age-specific rates were high in Guanacaste for age categories ≥30, and since late 1990s also for age 20-29. The male spatiotemporal patterns roughly followed sugarcane expansion in hot, dry lowlands with manual harvesting.

Conclusions: Excess CKD mortality occurs primarily in Guanacaste lowlands and was already present four decades ago. The increasing rates among Guanacaste men in hot, dry lowland counties with sugarcane are consistent with an occupational component. Stable moderate increases among women, and among men in counties without sugarcane, suggest co-existing environmental risk factors.

WHAT THE STUDY ADDS

- Mesoamerican nephropathy (MeN) is a chronic kidney disease epidemic unrelated to traditional causes, most prevalent among relatively young men, in particular sugarcane workers. This study provides the first systematic data for Costa Rica and is the first in Central America to explore the history of MeN as far back as 1970.
- The epidemic is restricted, so far, to the hottest province, Guanacaste. Among men, excess CKD mortality was already noticeable in the mid-1970s and has markedly increased since, with a progressive shift towards younger age groups. Among women, excess CKD mortality emerged later, in the mid-1980s, and has been moderate and stable over time, and without a shift towards younger age groups.
- The spatiotemporal mortality pattern among men follows roughly the sugarcane expansion in hot and dry lowlands and is compatible with an occupational component. The smaller and stable mortality excess among women in Guanacaste, as well as among men in the hot counties of Guanacaste without large-scale sugarcane production, suggest the co-existence of yet unidentified environmental risk factors, possibly interacting with occupational risk factors.

INTRODUCTION

Mesoamerican nephropathy (MeN) is an epidemic of chronic kidney disease of nontraditional origin (CKDnT; also called chronic kidney disease of unknown origin, CKDu) occurring along the Pacific coast of Mesoamerica.[1-6] MeN was first observed in the 1990s among sugarcane workers in Nicaragua, El Salvador and Costa Rica.[7-9] but probably extends also to Guatemala, Honduras and Panama,[10] and Mexico.[2,3] The disease has overwhelmed local health systems[6] and has caused premature death of at least 20,000 men.[4] MeN has been characterized in Nicaragua and El Salvador.[11-13] The disease occurs predominantly among young and middle-aged male agricultural workers, especially sugarcane workers, without conventional risk factors such as hypertension and diabetes.[6] Clinically, the disease resembles a tubulointerstitial disease with low grade proteinuria,[11,12,14] but a biopsy series from El Salvador showed a mixed pattern of tubular atrophy, interstitial fibrosis and extensive glomerulosclerosis.[15,16]

Knowledge about geographical boundaries and the approximate time period in which the epidemic emerged in Mesoamerica is anecdotal. It is thought that CKDnT has been increasing since the late 1990s, when early technical reports started addressing CKDnT in Nicaragua[9] and numbers of patients with end-stage renal disease (ESRD) rapidly increased in hospitals of El Salvador.[17] Although the epidemic concentrates in the lowlands of the Pacific coast extending over at least El Salvador, Nicaragua and Costa Rica, not all communities in these lowlands have a high prevalence.[11] Also, increased CKD prevalence has not been reported at locations at higher altitude, including a sugarcane village at 500 meters above sea level (masl).[12] One study reported high CKD prevalence among men and women in two agricultural communities at 300 masl in El Salvador.[18]

Regarding Costa Rica, clinicians noted more than a decade ago an increased occurrence of CKD in the Guanacaste province,[8] the north Pacific region of the country bordering with Nicaragua. Like in Nicaragua and El Salvador, the disease has been anecdotally linked to sugarcane work.[19] Vital statistics are available in Costa Rica as far back as 1970, which provides an opportunity to explore mortality patterns of CKD decades back in time. This descriptive study analyzed the geographical distribution in conjunction with time trends of mortality from CKD in Costa Rica, with emphasis on the Guanacaste province. We aimed at answering the following questions: a) When and where did the epidemic emerge? b) Do patterns differ among men and women? c) Is there a shift in mortality towards younger age groups over time? d) Does excess CKD mortality seem to be related altitude, climate or sugarcane production?

METHODS

The administrative geographical division of Costa Rica consists of seven provinces (San José, Alajuela, Cartago, Heredia, Guanacaste, Puntarenas and Limón), together with 81 counties, 11 of which are located in Guanacaste. Mortality statistics between 1970 and 2012 were extracted from the Central American Population Center (CCP) of the University of Costa Rica, which hosts the official vital statistics of Costa Rica (http://ccp.ucr.ac.cr/). During this 43-year period, three versions of the international classification of diseases (ICD) were used. We extracted the cases of death for all categories of CKD and unspecified renal failures (no categories of acute kidney failure were included): codes 582, 583, 584 of ICD8 during 1970-1979 (http://www.wolfbane.com/icd/icd8h.htm), codes 582, 583, 585, 586, 587 of ICD9 during 1980-1996 (http://www.wolfbane.com/icd/icd9h.htm), and N18, N19 of ICD10 during 1997-2012 (2nd edition, http://apps.who.int/classifications/apps/icd/icd10online2003/fr-icd.htm) (Table 1). Cases of death were retrieved for the seven provinces and 81 counties, by sex and 10-year age strata.

Population data were obtained from the same CCP source for the censuses conducted in 1973, 1984, 2000 and 2011 (Table 1), also by sex and 10-year age strata for the seven provinces and 81 counties. Extrapolation of the census data to in-between years was based on general population estimates.[20,21] We derived population numbers for the sex-age-county specific strata by multiplying these estimates with the fractions of the corresponding strata in the nearest census.

Table 1. Cases of death of chronic kidney disease in the Guanacaste province and the rest of Costa Rica, by time periods of use of versions 8, 9 and 10 of the International Classification of Disease (ICD), 1970-2012, and person years during the period.

Time periods for ICD versions	**Guanacaste**		**All other provinces**		**Costa Rica**
	Men	**Women**	**Men**	**Women**	**Total**
ICD8 (1970 – 1979)					
582 Chronic nephritis	31	11	190	173	405
583 Nephritis, unqualified	4	3	29	27	63
584 Renal sclerosis, unqualified	1	0	0	2	3
Subtotal ICD8	36	14	219	202	471
ICD9 (1980-1996)					
582 Chronic glomerulonephritis	6	3	40	54	103
583 Nephritis and nephrosis not specified as acute or chronic	3	7	27	22	59
585 Chronic renal failure	196	65	676	500	1437
586 Renal failure, unspecified	11	6	111	101	229
587 Renal sclerosis	0	0	6	4	10
Subtotal ICD9	216	81	860	681	1838
ICD10 (1997 – 2012)					
N18 Chronic kidney disease	623	188	1699	1107	3617
N19 Unspecified kidney failure	16	9	174	170	369
Subtotal ICD10	639	197	1873	1277	3986
Total 1970 – 2012	**891**	**292**	**2952**	**2160**	**6295**
Census population data during study period					
Population 1973 x10^3	91.4	87.3	847.2	845.9	1871.8
Population 1984 x10^3	99.2	96.0	1109.0	1112.6	2416.8
Population 2000 x10^3	133.3	130.9	1769.3	1776.7	3810.2
Population 2011 x10^3	162.0	165.0	1944.1	2030.7	4301.8
Person years 1970-2012 x 10^6	5.17	4.95	63.22	62.13	135.47

We used the Rapid Inquiry Facility (RIF) to assess geographical differences across provinces and counties for four time periods, 1970-1982, 1983-1992, 1993-2002, and 2003-2012. RIF is embedded in a geographical information system (GIS) that requires ArcGIS and connects to an external database of geocoded health and population data, and is especially useful for spatial analyses around sources of presumed environmental hazards, and in small areas.[22,23] With the RIF program we produced maps of indirectly standardized disease risks (i.e. standardized mortality ratios, SMRs) with the Costa Rican population as reference, for men and women separately. This program used empirical Bayes smoothing of the relative risks toward the global mean to account for sampling variability in the observed data but without accounting for spatial autocorrelation to avoid masking of the true risk distribution due to oversmoothing.

Time trends in the seven provinces were computed with age-standardized mortality rates per 100,000 men and women over nine time periods (1970-1972 being a 3-year and all other 5-year periods), as well as rate ratios along with their 95% confidence intervals for Guanacaste versus the rest of the country. In addition, age-adjusted time trends were computed for the counties within Guanacaste, over four time periods due to smaller number of deaths. For the direct age adjustment, the most recent WHO standard population was used.[24] Trends were also computed for 10-year-age-specific mortality rates,[25] comparing Guanacaste with the rest of Costa Rica, for men over the nine periods, and for women over four periods due to smaller numbers of female deaths.

Maps were produced with averages at the county level for elevation, temperature and precipitation together with the location of the six sugarcane production areas of Costa Rica. Altitude data were obtained from Digital Elevation Model (DEM, from El Atlas Digital de Costa Rica 2014) and climate data from the National Meteorological Institute (http://www.imn.ac.cr/). A temperature map was produced by interpolating the average temperature registered by the weather stations in the country between 1998 and 2002. A precipitation map was created by interpolating the average rainfall registered by the meteorological stations during 2008. The map with location of current sugarcane production areas was based on data of the Agro-Industrial Sugarcane League (LAICA for its acronym in Spanish).[26] In addition, production data for the different sugarcane areas were collected from documents in the library of LAICA (http://www.laica.co.cr/biblioteca2/index.do), specifically hectares of cane over time, months of peak harvesting, degree of mechanization, and labor organization for harvesting. Relations between CKD mortality and altitude, climate and characteristics of sugarcane production were assessed qualitatively.

RESULTS

Emergence and geographical spread of the epidemic

During the 43 years between 1970 and 2012, 3843 men and 2452 women died from any kind of chronic or unspecified kidney disease or failure in Costa Rica, 19% (respectively 23% and 12% of total male and female fatalities) in the Guanacaste province with 7.5% of the person years in the follow-up period (see Table 1).

Figure 1 contains maps with smoothed SMRs for the seven provinces and 81 counties of Costa Rica over the four time periods, for men and women 20 years and older. At a province level, excess mortality is only observed in the Guanacaste province for both sexes. Among men, a moderately increased SMR is observed in Guanacaste already in the 1970s, whereas for women a similar increase is observed a decade later. In the most recent decade 2003-2012, mortality among men in Guanacaste is highly increased whereas among women it remains moderately increased as compared to the other provinces of Costa Rica, none of which showed an increased risk at any time.

The geographic patterns by counties show that SMRs of 3 and higher only occurred in the Guanacaste province (see Figure 1). Within Guanacaste, among men the highly increased mortality extended geographically from two counties in the 1970s to six in the most recent decade, specifically the northwestern counties all bordering each other. Also for women in Guanacaste, increased SMRs are observed in an increasing number of counties over time, but the excess is moderate and the geographical pattern is somewhat different from the male pattern. Although a number of counties of other provinces also show increased SMRs, only in one county of the Puntarenas province in the southwest tip of Costa Rica a moderate excess among men is observed consistently since the 1980s. Further, it is noticeable that in the most recent decade a moderately increased mortality extends also to counties of other provinces bordering Guanacaste, in the northeast border towards the Alajuela province for both men and women, and in the southeast border to the Puntarenas province for women. The rates for counties and provinces for the four time periods are shown in Supplemental Table 1.

Analyses restricted to population in working age 30-59 showed similar results (data not shown), but SMRs in Guanacaste were generally higher than in unrestricted analyses.

INSERT FIGURE 1

Time trends of mortality among men and women

Figure 2 shows age-adjusted mortality rates per 100,000 men and women, and rate ratios (RR) for the Guanacaste province versus the rest of Costa Rica, by 5-year periods during 1970-2012, stratified by sex. CKD mortality increased over time markedly more in Guanacaste than in the rest of Costa Rica. In Guanacaste, mortality rates among men increased almost nine-fold over the four decades, from 4.4 to 38.5 per 100.000, and among women more than four-fold, from 2.3 to 10.7 per 100.000, whereas in the rest of Costa Rica (excluding Guanacaste) rates approximately doubled for both sexes, from 3.6 to 8.4 for men and from 2.6 to 5.0 for women.

Statistically significant excess mortality emerged in the Guanacaste Province in the mid-1970s for men (RR 1.7, 95% CI 1.1-2.7, during 1973-1977), and mortality is currently almost five times higher than in the rest of the country (RR 4.6, 95% CI 3.4-5.3 during 2008-2012). Similar significant excess mortality among Guanacaste women appeared a decade later (RR 1.7, 95% CI 1.1-2.7 during 1983-1987) and has remained approximately double the mortality rate of the rest of the country through today (RR 2.1, 95% CI 1.7-2.7 for time period 2008-2012). The mortality rates for each of the six provinces that compose together the rest of Costa Rica were very similar (data not shown) and did not deviate significantly from the combined rate shown in Figure 2.

INSERT FIGURE 2

Within the Guanacaste province, the age-adjusted CKD mortality trends show rather large differences between the counties among men (Supplementary Figure 1). The county with the fastest mortality growth and highest current rate is Cañas (73.7 per 100,000 men during 2003-2012): a 13-fold mortality rate as compared to the 1970s (5.6 per 100,000) and a 7-fold rate compared to Nandayure, the county with the lowest rate in Guanacaste (10.3 per 100,000). Female rates are clearly lower in the northwestern counties as compared to male rates but in the southern counties the sex differences are much smaller. From the 1990s onwards, mortality rates are higher than in the rest of Costa Rica combined, in all counties for males and in nine of the eleven counties for females.

Age-specific mortality trends

Supplementary Figure 2 illustrates 10-year age-specific mortality rates among men and women in Guanacaste and the rest of the country. Except for boys age 19 or younger, excess mortality is observed among men in Guanacaste as compared to the rest of Costa Rica for all age groups, and with increasing trends over time (Section A). Excess CKD deaths in Guanacaste among men occurred already in the 1970s in the age categories between 30 and 69 years, and from the mid-1980s in the age categories of 70 years and older; a much smaller but increasing excess among young men aged 20-29 emerged from the late 1990s. Trends of age-specific mortality rates for women are less clear (Section B). Nonetheless, from the mid-1980s onwards mortality rates are slightly to moderately elevated for age groups between age 20 and 69 among Guanacaste women as compared to women in the rest of the country.

Altitude, climate and sugarcane production

Figure 3 displays maps of elevation, temperature, precipitation and location of sugarcane production areas. Characteristics of the six sugarcane production areas of Costa Rica (so called North Pacific, Central Pacific, North Zone, South Zone, Occidental Central and Oriental Central) are reported in Table 2 and in more detail together with the data sources in Supplementary Table 2. Between 1973 and 2013, the production in the North Pacific almost quadrupled the cane hectarage from 8500 to 32,850 Ha, an expansion over five times larger than in the Central Pacific area and the North and South Zones, whereas the Occidental Central and Oriental Central production areas decreased considerably. The North and Central Pacific production areas are located at the lowest altitude; have the hottest, driest and sunniest climate (see Figure 3 and Supplementary Table 2) and, in addition, the longest harvest time. The North and South Zones are also very hot, but much of the production takes place at somewhat higher altitude with more rainfall and less solar irradiation, and the harvest time is considerably shorter as compared to the Pacific areas. The Occidental Central and Oriental Central sugarcane areas are located at higher altitudes with cooler and rainier climates. The Central Pacific has most mechanized harvesting (90% in 2006) followed by the North Pacific and the North Zone (approximately 35%).

INSERT FIGURE 3

Of the six production areas, only the North Pacific shows a clear excess in CKD mortality over time, which in the most recent time period is extending beyond Guanacaste towards the northeast (men and women) and towards the southeast (women) (see Figure 1). Within the Guanacaste province, five of the six northwestern counties with the highest and most rapidly increasing mortality rates among men are important sugarcane producing counties; in contrast, one of the five most southern counties with considerably lower rates (but still elevated compared to the rest of Costa Rica) has appreciable sugarcane production (Supplementary Figure 1).

Table 2. Production characteristics in the six sugarcane production areas of Costa Rica.

Production area*	Production area (2013)	Ha change since 1973	Peak zafra (# months)	Mechanical harvesting (%, 2006)
North Pacific (1)	32.850	+ 24,350	5	35
Central Pacific (2)	6230	+ 5330	5	90
North Zone (3)	8950	+ 3500	3	35
South Zone (4)	4450	+ 4350	3	5
Occidental Central (5)	4450	- 4650	4	0
Oriental Central (6)	4900	- 8750	4	3

*For data on altitude, temperature, solar irradiation, and precipitation in sugarcane production areas, see Figure 3 and Supplementary Table 2.

Source: library of LAICA (http://www.laica.co.cr/biblioteca2/index.do); for references of specific documents see Supplementary Table 2.

DISCUSSION

The main findings of this study are that excess CKD mortality concentrates in the Guanacaste province and is observable among men from the mid-1970s with an ongoing, steeply increasing trend, whereas among women a stable moderately increased mortality is observed since the mid-1980s. Clear excess mortality among men starts from age 30–39, but over the last 15 years there is a shift of mortality towards younger men aged 20-29. Within Guanacaste, CKD mortality is elevated in particular in the counties with hot and dry lowlands plus extensive sugarcane production.

Comparison with other Mesoamerican countries

Recently the Pan American Health Organization (PAHO) called the world's attention on the epidemic of CKDnT in Mesoamerica by comparing national mortality rates of five Mesoamerican countries with USA and Cuba.[10,27] El Salvador and Nicaragua stand out with national age-adjusted male mortality rates increasing from about 45 per 100,000 men in 2000 to well over 60 in 2009 and considerably lower but increasing mortality rates among women in these same countries, on the order of 15 to 25 per 100,000 women over the decade.[10] In the PAHO statistics, the national Costa Rican rates are below the other Mesoamerican countries and just above USA, around 8-9 and 4-5 for men and women, respectively, during the 2000-2009 decade. These PAHO figures (very similar to our estimates for the entire male and female populations of Costa Rica) mask the epidemic in a small area like Guanacaste, with just over 7% of the country's population. Our results showing excess deaths in young men starting at age 20 are in agreement with the PAHO statistics for Nicaragua and El Salvador.[10]

Recurrent heat stress and dehydration in hot occupations, in particular among sugarcane workers, have been proposed as key etiologic factors of MeN[1,28] based on epidemiologic data,[12,14] occupational hygiene data,[29] and experimental data of repeated dehydration inducing CKD in mice.[30,31] Other potential causes that have been proposed as key or contributing factors include arsenic, cadmium, pesticides, nephrotoxic medications, infectious agents, and genetic susceptibility.[1-5] Although this is a descriptive study, the data merit scrutiny in the light of their compatibility with various hypotheses, which should be further investigated with analytical study designs.

MeN, an occupational disease

Multiple results from this study are in line with what would be expected for an occupationally-related disease: the epidemic appears first in men, increases much more rapidly among men, and shifts toward younger age groups over time among men only. Heavy work on sugarcane fields stands out as a potential high-risk job, for several reasons. Firstly, the disease was anecdotally noted by sugarcane workers themselves in Guanacaste as far back as in the early 1990s[32] as well as by nephrologists somewhat later[8,19]; secondly, sugarcane workers in the Pacific lowlands have been found to be at increased risk for kidney dysfunction in El Salvador[12] and Nicaragua[11,14]; and thirdly sugarcane may have become an increasing source of employment during the follow-up time, with production in Guanacaste increasing from less than 5000 Ha in 1973 to 18,000 Ha in 1991 and about 35.000 Ha in 2012 (see Supplementary Table 2). Crowe et al (2013) found that sugarcane cutters in Guanacaste, Costa Rica, were at risk for heat stress during the majority of their shift.[29] McClean et al. (2012) observed a decline in kidney function over a one harvest season harvest among Nicaraguan sugarcane workers in the job categories with the highest heat exposures.[14]

Our data do not support that work in sugarcane *per se* underlies the epidemic, since only one of the six sugarcane areas coincides with increased mortality risk. In Guanacaste, however, the counties with hot and dry lowlands plus large sugarcane production areas with manual harvesting have very high risk for workers' heat stress, whereas other sugarcane regions have one or more characteristics that could explain lower risk for heat stress (see Supplementary Table 2). We believe that, most likely, the excess of CKD is related to a combination of geographical, climatic, technical and organizational factors during harvesting.

Kidney dysfunction has also been reported in other hot occupations in MeN affected areas of Central America, specifically construction workers, miners and port workers in Nicaragua,[14] and cotton workers[12] and corn and subsistence farmers[18] in El Salvador. We did not explore potential associations with other important crops or hot industries in Guanacaste. However, no other crop has experienced an expansion as large as sugarcane. Rice is a traditional crop with a stable production of about 25,000 Ha since decades; production of melon, mango and orange combined, although increasing since the 1980s, adds to about 15,000 Ha, less than half the sugarcane hectarage (Agricultural Census of 2014, http://www.inec.go.cr/Web/Home/GeneradorPagina.aspx). Of note is also that in the most recent time period the high mortality seems to be spreading to neighboring areas of Guanacaste where no sugarcane production takes place. Therefore, workers in other jobs with heat stress are likely to contribute to the risk for MeN, in Guanacaste and beyond.

Overall, the epidemic in Guanacaste has not reached the level of severity currently observed in El Salvador and Nicaragua.[10,27] The highest mortality rates computed for Guanacaste (38.5 and 10.7 per 100,000 men and women, respectively, for the period 2008-2012) are well below the national rates of El Salvador and Nicaragua in 2009, and in these countries mortality is even higher in MeN affected areas. For example, during 2009-2011 the mortality rates of departments in northwest Nicaragua were more than three times the national rate.[33] No data exist on number of sugarcane workers in the MeN affected areas in the different countries to explain these differences, but based on FAO national production statistics, it can be reasonably assumed that hectares of sugarcane production in the lowlands of El Salvador and Nicaragua, and hence number of workers, have exceeded those in Guanacaste historically (http://faostat.fao.org/site/567/DesktopDefault.aspx?PageID=567#ancor). In addition, an increasing proportion of sugarcane harvesters in Guanacaste are seasonal migrant workers from Nicaragua, most of whom do probably not count in the Costa Rican mortality statistics if they fall ill with CKD.

A possible environmental component

It is intriguing that women in Guanacaste have a higher CKD mortality than women elsewhere in Costa Rica. Because we have no individual data besides age, sex and residence, we do not have information about their occupational history. However, few women in Guanacaste work in agriculture (0.4% and 0.8% of total female population according to census data of 2000 and 2011, respectively) and, with all likelihood, not many of these in heavy sugarcane labor, which is most often performed by men.[34] This may indicate that there exists another factor that affects both sexes. The finding that all counties of Guanacaste had mortality rates above average for the rest of Costa Rica for men and almost all counties for women, including those without sugarcane production, is also consistent with this hypothesis. Thus, possibly another factor, or factors, present in the general environment might interact with occupational risk factors, to produce an epidemic pattern among men.

A possible general environmental risk factor may be quality of drinking water, which is a major community concern. The general public in Guanacaste is especially worried about contamination of their drinking water with arsenic or pesticides. Arsenic has been found in high levels in some of the affected areas.[35] Arsenic has also been proposed as an etiologic factor of a similar CKD epidemic of unknown cause in Sri Lanka,[36] although there is no consensus about it among scientists of this region. A comprehensive review found some evidence for an association with CKD mortality based on ecological studies, but judged the overall evidence of a causal association between arsenic and CKD as insufficient and emphasized the need for studies with improved design.[37] Pesticides are also an intensely debated potential etiology.[6,10,27] McClean (2012) did not find a decline of kidney function among pesticide applicators in sugarcane over the course of one harvest season.[14] Other cross-sectional studies, however, report associations of MeN with pesticide exposure among agricultural workers, albeit based on qualitative measures of exposure.[38-40] Studies on pesticides with high quality exposure assessment are warranted. In addition, exposures to other potential etiologic factors including the frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate muscle and articular pains associated with heavy labor, fertilizers, infectious agents and genetic susceptibility need to be assessed. Such studies should be conducted ideally using an ecosystem health approach.[1]

Limitations and strengths of the study

This study has several limitations. Uncertain quality of mortality statistics, in particular during the 1970s, is one concern. An evaluation of errors in vital statistics in Costa Rica, carried out after the census of 2000, reported an estimated 8% of under-registration of deaths nationally during the year 1970 with an additional 27% of deaths registered without death certificate; however, this unfavorable situation gradually improved to an estimated 0.3% under-registration and less than 1% of deaths registered without certificate during 2000.[41] Deficient quality of mortality statistics could explain in part that there were much fewer cases of CKD-related deaths registered in the early observation periods than today, in Costa Rica in general and maybe especially for Guanacaste, an area of little development during the 1970s. However, there is a clear excess mortality among males in Guanacaste already during the 1970s, but not among females. It seems unlikely that registration in Guanacaste would have had better quality than in other regions of the country, including the capital with the main hospitals, and in addition differentially for men. Therefore, these data support the hypothesis that the epidemic of Mesoamerican nephropathy in Guanacaste started during the 1970s for men or, if there was an under-ascertainment, possibly earlier.

In Costa Rica, the diagnoses of the physicians on all death certificates are centrally recoded into ICD categories by trained personnel at the National Institute of Census and Statistics (INEC). The accuracy of codification at INEC has never been evaluated. However, considering the centralized nature of the codification process, any errors are unlikely to be related differentially to a specific geographical area. It is possible though that greater awareness among clinicians in Guanacaste has improved diagnostic quality differentially, especially in the more recent years, but the pattern of CKD mortality in Guanacaste with large differences for men and women since early in the epidemic precludes that the increase is solely due to improved diagnoses on death certificates.

We included in the analyses, besides categories of chronic kidney disease, also categories of nephritis and nephrosis not specified as acute or chronic and unspecified kidney failure. These undefined nephropathies conform a relatively small fraction (11%) of the total cases, and less in Guanacaste than in the rest of Costa Rica (4.0% vs 11.5% for men, and 8.5% vs 15% for women). Exclusion of these categories would produce somewhat higher risk estimates for the Guanacaste population. Furthermore, all categories include cases that are not CKDnT, but known risk factors such as diabetes, hypertension and smoking have not increased more in Guanacaste than in the rest of Costa Rica.[42] Therefore it seems reasonable to attribute the excess of cases in Guanacaste to the Mesoamerican nephropathy.

With regard to exploring a possible relationship between excess CKD mortality and sugarcane production, the interpretation is limited by our qualitative assessment of rather disperse historical data on technical and organizational issues related to harvesting in the different sugarcane producing areas as well as the absence of labor force data. Nevertheless, the excess of CKD in hot, dry lowland counties with sugarcane production in Guanacaste is consistent with the results of other studies that have reported increased risk for either heat stress or CKD among sugarcane workers.[8,11,12,14,27]

A strength of the study is that it provides the first systematic data for Costa Rica in relation to the Mesoamerican nephropathy, based on mortality statistics of more than four decades with a large number of cases of deaths due to kidney failure, in particular for men. Although this is a descriptive epidemiologic study and no causal conclusions can be drawn, it provides novel insight into the origin of the epidemic and its development over time which may guide further etiologic research.

Conclusions

In conclusion, the patterns of geographical distributions and time trends of CKD mortality in Costa Rica indicate that excess mortality occurs primarily in the Guanacaste province and was already present four decades ago among men. The increasing rates among men in the hot and dry lowlands of Guanacaste with extensive sugarcane production are consistent with an occupational component in the epidemic of Mesoamerican nephropathy, with heat stress and dehydration as possible stressors. The stable moderately increased rates among women, and also among men in counties without sugarcane production, suggest the co-existence of one or more yet unidentified environmental risk factors. Epidemiologic research targeting specific occupational and environmental risk factors and their interactions must follow this descriptive study.

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FIGURE LEGENDS

Figure 1. Smoothed standardized mortality ratios (SMRs) of chronic kidney disease (CKD) in male and female population age 20 and older, by seven provinces and 81 counties of Costa Rica, for four time periods between 1970 and 2012.

Figure 2. Age-adjusted chronic kidney disease (CKD) mortality rates per 100,000 men and women and rate ratios (RR) with 95% confidence intervals (CI) for Guanacaste versus the rest of Costa Rica, by 5-year periods, 1970 – 2012.

Figure 3. a) Sugarcane production areas of Costa Rica: 1. North Pacific, 2. Central Pacific, 3. North Zone, 4. South Zone, 5. Occidental Central, 6. Oriental Central; b) Elevation; c) Mean temperature (1998-2002); d) Mean precipitation (2008).

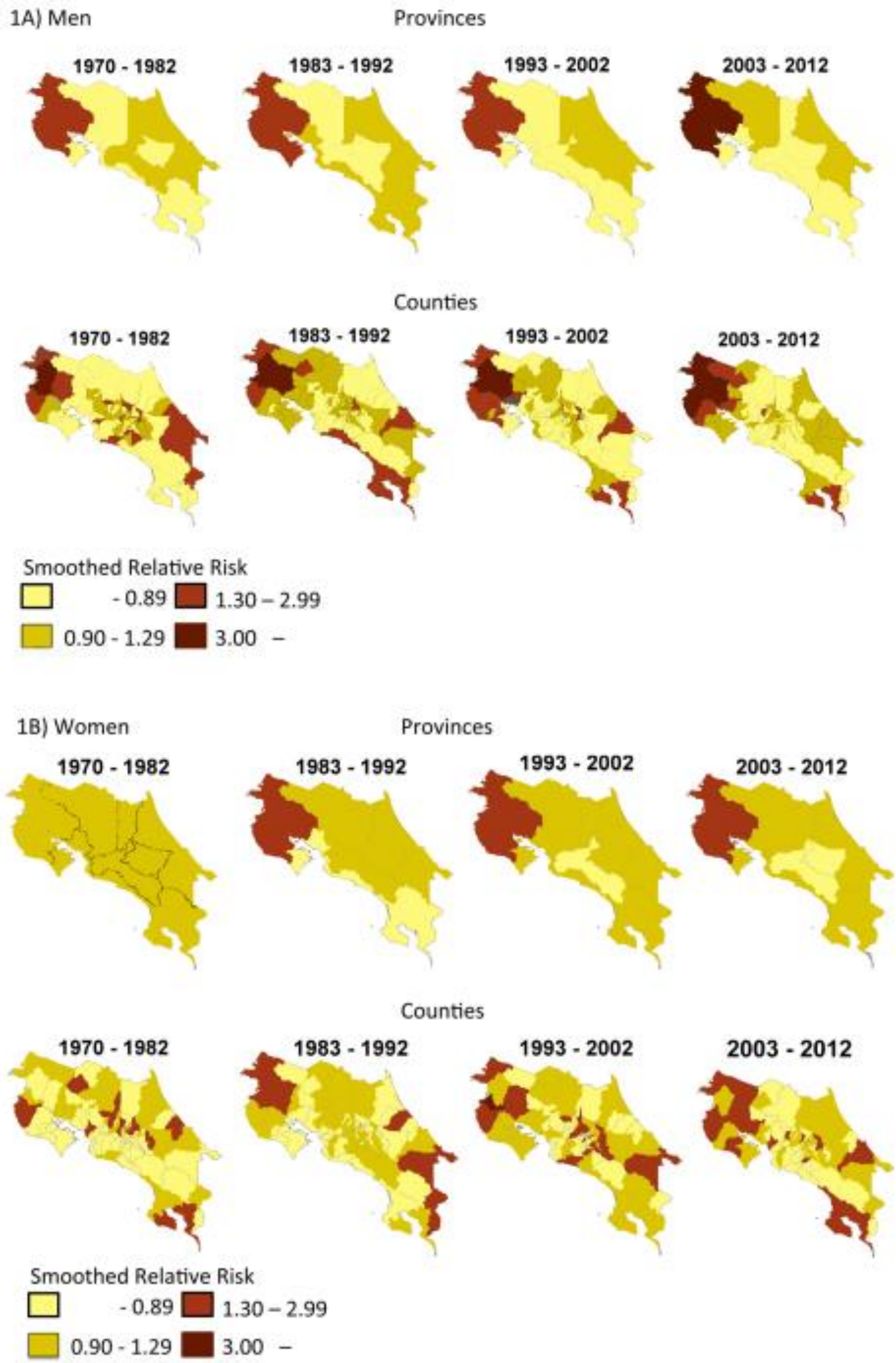
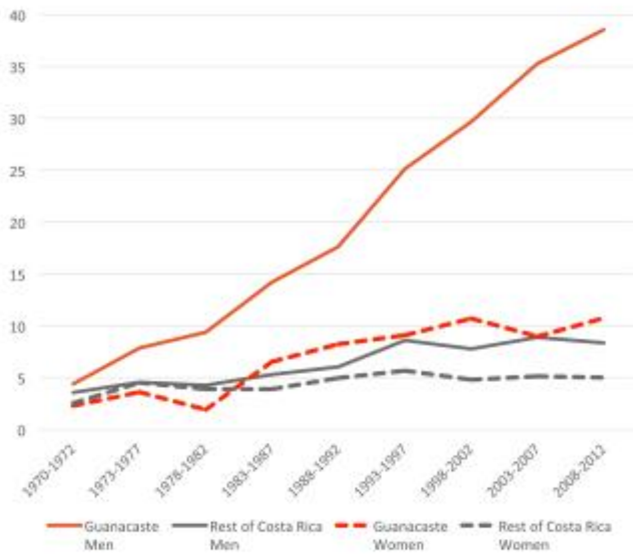

1A) Men
Provinces
1970 - 1982
1983 - 1992
1993 - 2002
2003 - 2012
Counties
1970 - 1982
1983 - 1992
1993 - 2002
2003 - 2012
Smoothed Relative Risk
- 0.89
1.30 – 2.99
0.90 - 1.29
3.00 –
1B) Women
Provinces
1970 - 1982
1983 - 1992
1993 - 2002
2003 - 2012
Counties
1970 - 1982
1983 - 1992
1993 - 2002
2003 - 2012
Smoothed Relative Risk
- 0.89
1.30 – 2.99
0.90 - 1.29
3.00 –

Figure 1



	Men			Women		
Time period	RR	95% CI		RR	95% CI	
1970-1972	**1.23**	0.58	2.59	**0.91**	0.28	2.92
1973-1977	**1.72**	1.08	2.74	**0.80**	0.42	1.53
1978-1982	**2.19**	1.45	3.32	**0.49**	0.22	1.11
1983-1987	**2.68**	1.95	3.70	**1.68**	1.06	2.69
1988-1992	**2.92**	2.22	3.84	**1.66**	1.13	2.44
1993-1997	**2.93**	2.36	3.62	**1.60**	1.15	2.21
1998-2002	**3.83**	3.21	4.56	**2.23**	1.69	2.95
2003-2007	**3.97**	3.38	4.66	**1.75**	1.31	2.33
2008-2012	**4.60**	3.98	5.31	**2.13**	1.66	2.74

Figure 2

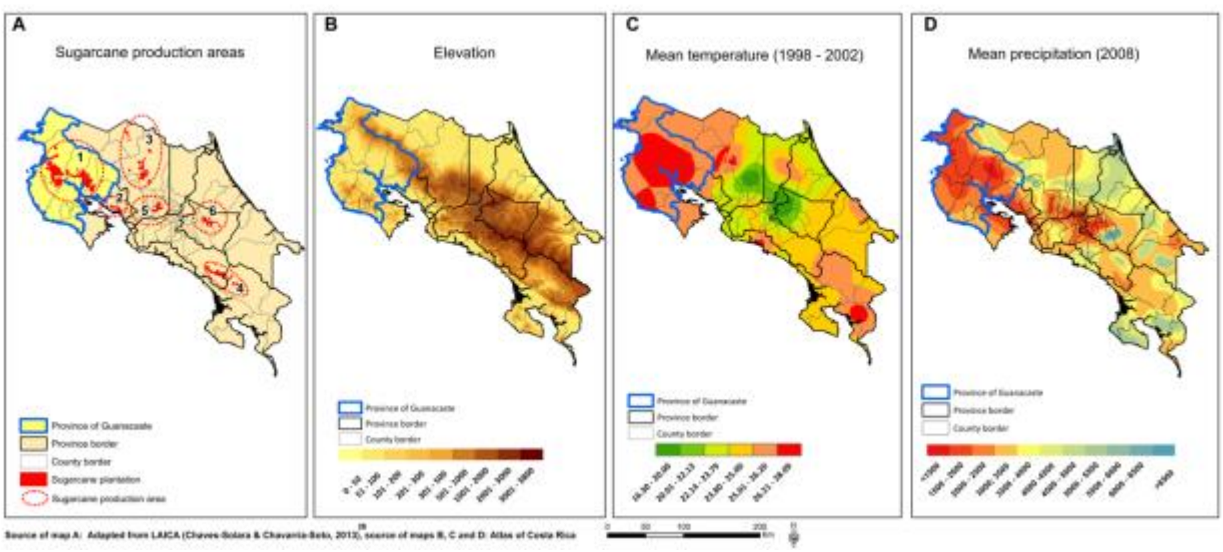
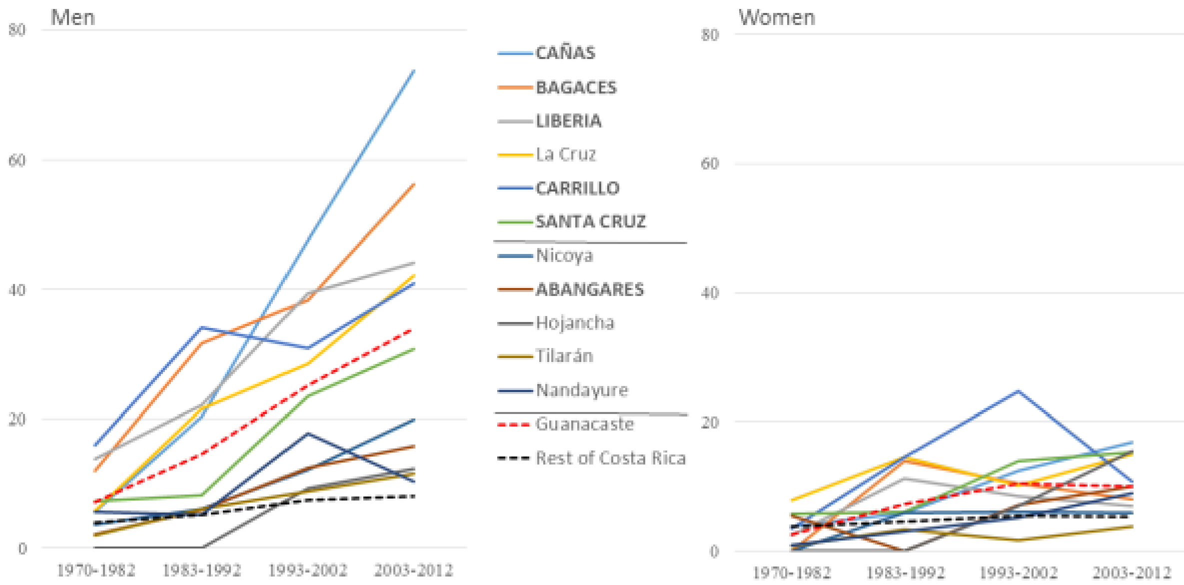
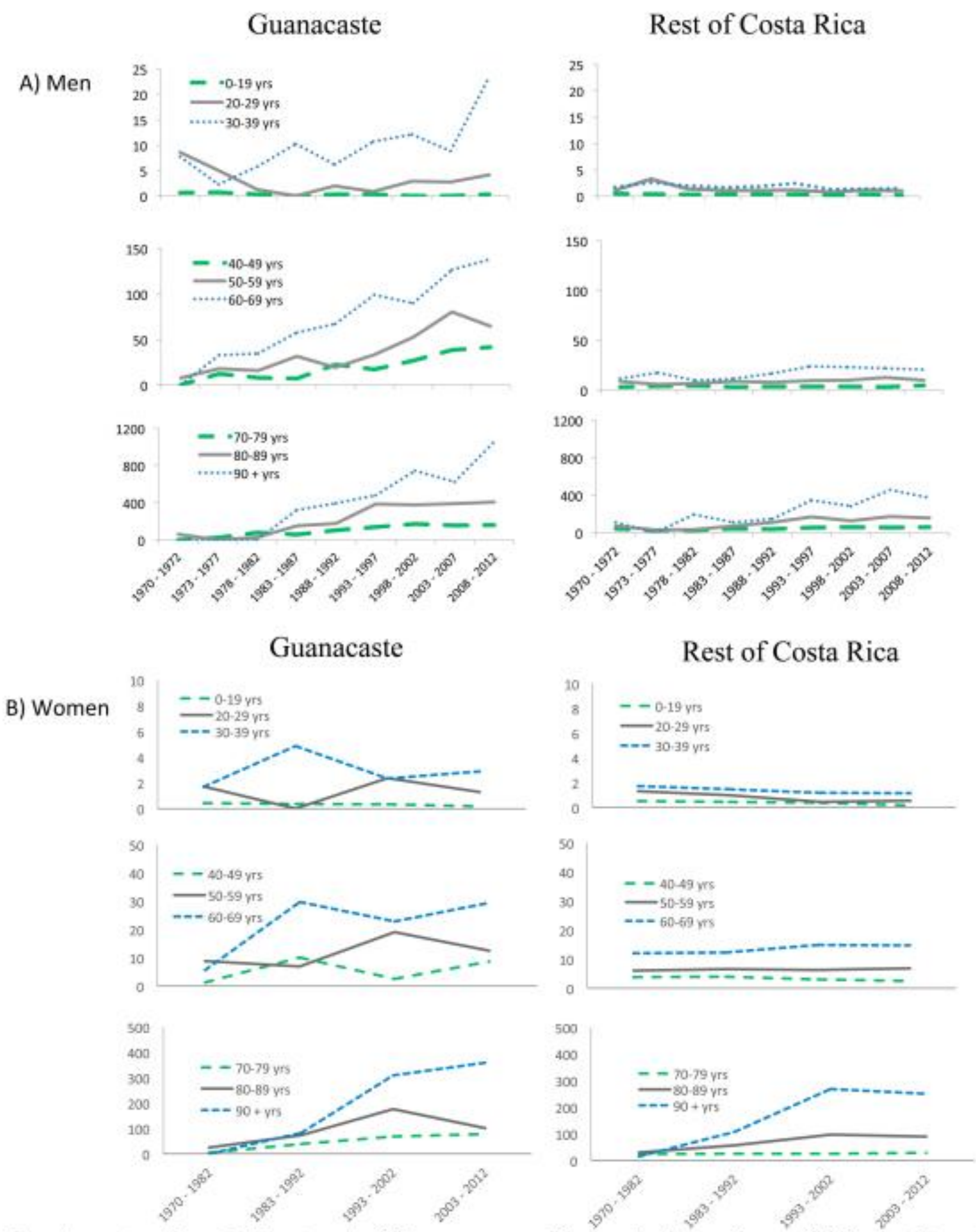


Figure 3



Supplementary Figure 1. Age-adjusted mortality trends per 100,000 men and women in Guanacaste, by counties, 1970-2012. Counties with substantial sugarcane production are in capital letters. The first six counties are located in the northwest, the last five counties towards the south.

Supplement



Supplementary Figure 2: Time trends of 10-year age-specific chronic kidney disease (CKD) mortality rates in the Guanacaste province and the rest of Costa Rica during 1970-2012: A) men (nine periods) and B) women (four periods). Note the differences in scale for the graphs with age groups 0-39, age 40-69, and age 70 and older.

Supplementary Table 1. Unadjusted national, provincial and county CKD mortality rates with 95% confidence intervals (CI) for men and women by four time periods: 1970-1982, 1983-1992, 1993-2002, 2003-2012. Counties with empty spaces did not report CKD deaths during that period.

Males		**1970 - 1982**			**1983 - 1992**			**1993 - 2002**			**2003 - 2012**		
			95% CI			**95% CI**			**95% CI**			**95% CI**	
Province	**County**	**Rate**	**Low**	**High**	**Rate**	**Low**	**High**	**Rate**	**Low**	**High**	**Rate**	**Low**	**High**
Alajuela	Alajuela	4.85	2.77	7.87	4.01	2.79	5.58	5.72	3.44	8.93	14.8	12.4	17.8
	Alfaro Ruíz	9.81	1.19	35.4	2.51	0.06	14.0				5.20	0.63	18.8
	Atenas	4.11	0.38	15.2	1.85	0.19	6.77	5.51	0.65	19.9	8.43	3.78	16.1
	Grecia	3.98	1.08	10.2	2.41	0.88	5.25	3.10	0.64	9.06	10.8	7.01	16.0
	Guatuso				19.6	6.64	43.6	5.22	0.13	29.1	19.5	8.92	37.1
	Los Chiles				3.26	0.39	11.8	3.92	0.10	21.8	15.9	7.22	30.2
	Naranjo	2.99	0.35	10.8	4.78	1.92	9.87	5.53	1.14	16.2	18.4	12.0	27.0
	Orotina	7.32	1.32	21.8	1.16	0.03	6.44				14.3	6.49	27.1
	Palmares	3.79	0.46	13.7	2.06	0.25	7.44	2.15	0.05	12.0	5.21	2.03	10.9
	Poás							5.58	0.67	20.2	16.3	8.92	27.4
	San Carlos	3.41	1.25	7.42	3.98	2.32	6.38	4.08	1.64	8.42	10.7	7.80	14.4
	San Mateo							10.5	0.27	58.6	10.5	1.68	32.0
	San Ramón	4.30	1.34	10.1	1.92	0.62	4.49	0.99	0.02	5.51	8.85	5.66	13.2
	Upala	2.24	0.06	12.5	4.04	1.31	9.44	1.99	0.05	11.1	22.6	14.9	32.9
	Valverde Vega	7.72	0.93	27.9	6.16	1.68	15.8	4.31	0.11	24.0	15.7	6.74	31.19
All Alajuela		4.64	3.47	6.08	5.97	4.77	7.37	9.14	7.92	10.6	12.8	11.5	14.2
Cartago	Alvarado	4.41	0.11	24.6							9.80	2.67	25.1
	Cartago	4.21	1.93	8.00	3.03	1.65	5.09	6.16	3.19	10.8	11.6	8.61	15.3
	El Guarco	2.11	0.05	11.7	4.72	1.53	11.0	4.22	0.50	15.3	7.82	3.14	16.1

Supplementary Table 2. Production and climatic characteristics during months of peak harvest in the six sugarcane production areas of Costa Rica

Production area (PA) (see Figure 3) Height (masl)	**Production[1] area 1973 1984 2010 2013 (Ha change)**	**Months of peak zafra[2]**	**Average minimum / maximum temperatures (°C) Monthly rainfall (mm)[3]**	**Average maximum sunlight per day (hrs) / solar radiation (MJ/m^2)[4]**	**% of hectares mechanically harvested (2006)[5]**	**Organization of harvest[1]**
North Pacific (PA-1) (20-140, majority below 50)	8500 18,400 29,900 32,850 (+24,350 Ha)	5 (Dec-April)	21.4 / 34.3 9	10.2 / 23	35	• 3 large mills owning majority of harvested land • ~2530 producers in 2011
Central Pacific (PA-2) (<20-450) Puntarenas Central (<20)	900 4100 4000 6000 (+5100)	5 (Dec-April)	24.4 / 30.6 13	9.1 / 20	90	• 1 mill owning about 80% of harvested land (2005) • ~80 producers in 2011
Esparza (450)	n.a. 800 n.a. 230 (-570 Ha)		20.2 / 33.1 31	n.a./ n.a.[6]		
North Zone (PA-3) (40-650) San Carlos (650)	5450 4200 6050 7400 (+1950)	3 (Feb-April)	17.3 / 26.0 114	6.9 / 16	30	• Several mills, with one larger mill expanding land ownership in Los Chiles • ~715 producers in 2011
Los Chiles (40)	0 0 1150 1550 (+1550 Ha)		21.0 / 32.4 34	n.a. / n.a.	Highly mechanized[7]	