RESEARCH ARTICLE

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Liver Cancer Mortality Rates in Peru: Trend Analysis from 2003 to 2017

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Abstract

Background: Liver cancer is one of the leading causes of cancer-related death in Peru, and some reports have indicated an increase in mortality rates among the largest cities. To our knowledge, no study has been carried out at a national level or by geographic area in recent years. Thus, our objective was to examine overall, regional and sex-specific liver cancer mortality rates in Peru between 2003-2017. **Methods:** We retrieved data on liver cancer deaths between 2003 and 2017 from the mortality database of the Peruvian Ministry of Health. Age-standardized mortality rates (ASMR) were estimated per 100,000 person-years using the world standard SEGI population. We analyzed mortality trends using Joinpoint regression Program Version 4.7.0. To examine the spatial distribution of the mortality rates, we used GeoDa software. **Results:** Between 2003 and 2017, 31,473 deaths from liver cancer were reported in Peru. Overall, liver cancer mortality rates have decreased significantly among Peruvian women since 2005 (−3.1% annually) with decreases in the coastal and highland regions ranging from 2.8% to 3.5%. In Arequipa, Cusco, La Libertad, Lima, and Moquegua, rates decreased bewteen 2003 and 2017. Among men in Ancash a significant increase (+12.5 annually) was observed from 2003-2011, followed by a sharpdecline (−10.5 annually) between 2011 and 2017. In contrast, rates in Cajamarca, Junin, and Ucayali decreased between 2003 and 2017. **Conclusions:** Although decreases in liver cancer mortality rates were observed in some regions of Peru, these trends were not statistically significant. In addition, some provinces experienced increases in rates. Effective interventions, such as expanding access to healthcare and controlling the various risk factors for liver cancer, remains a key challenge for the country.

Keywords: Liver cancer- Geographic spatial analysis- Mortality rate- Epidemiology- Peru

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Introduction

Worldwide, liver cancer is the eighth most commonlyoccurring malignant neoplasm, and the fourth leading cause of cancer-related death with more than 866,000 new cases (age-standardized incidence rate of 8.6 per 100,000) and more than 758,000 deaths (age-standardized mortality rate of 7.4 per 100,000) in 2022 [1].

The major risk factors associated with liver cancer are hepatitis B (HBV) and hepatitis C (HCV) virus infections [2, 3], metabolic dysfunction-associated steatotic liver disease (MASLD) [4-6], excess body weight [7, 8], type 2 diabetes mellitus [9], excessive alcohol consumption [10], smoking [11, 12], and aflatoxin B1 (AFB1) exposure [13, 14]. However, these factors vary in their distribution around the world [15].

In recent years, the burden of liver cancer has increased in countries with perceived low risk, likely explained by changes in diet, weight gain, and the increase in prevalence of non-communicable conditions such as diabetes and MASLD. Latin American countries stand out as they still maintain a high mortality rate compared to other regions [16, 17] despite having lower incidence rates. However, Peru is often excluded from the few reports in Latin

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America, limiting our understanding of how the mortality rates in Peru has changed in recent years.

Peru is estimated to have the fourth highest liver cancer mortality rate in South America [1]. Data available from the Population-Based Cancer Registry of Metropolitan Lima [18-20] reported increases in the liver cancer mortality in Lima, the capital of Peru. Between 2004-2005 to 2013-2015, the mortality rate increased from 3.7 to 4.8 per 100,000 in men; and from 3.0 to 3.7 per 100,000 in women [21, 22, 20]. Liver cancer mortality in other regions of Peru has not been extensively explored. Therefore, the purpose of this study was to determine the trends in liver cancer mortality in Peru between 2003-2017, according to geographical area and sex.

Materials and Methods

Source of information

We conducted a descriptive epidemiology study, based on secondary data analysis using the mortality database of the Peruvian Ministry of Health. The Ministry of Health collects mortality data from all health establishments from the National Registry of Identification and Civil Status and the Public Ministry records. Liver cancer deaths were identified using the code C22 as per the International Classification of Diseases (ICD) 10th revision [23]. The information included in the registries is based on reports from health facilities located in the 25 provinces of Peru. The information is available through its online platform: https://www.minsa.gob.pe/portada/transparencia/solicitud/. This database has information on the number of deaths from liver cancer in Peru between 2003 and 2017. The deaths from liver cancer were classified into 5 age groups for all 25 provinces, according to the decedent's place of residence. We corrected for the underreporting rate for each province as previously described [24].

Total population per year was obtained from census data gathered by the National Institute of Statistics and Informatics [25], which is the central governing body of the National Statistical System, responsible for regulating, planning, directing, coordinating and supervising the country's official statistics [25].

Setting

Peru is divided into 25 provinces that are in one of the 3 geographical regions: coast, highlands, and the rainforest. It has a population of 31 million persons who are unevenly distributed among these regions. Although the coast only covers 12% of the territory, it is the most densely populated region with approximately 56% of the total population. The highlands represents approximately 28% of the territory, and is home to 30% of the population; while the rainforest is the largest region of the country, accounting for 60% of the territory but home to only 14% of the population [26].

Statistical analysis

We calculated age-standardized mortality rates (ASMR) per 100,000 person-years using the SEGI world standard population [27]. The Joinpoint Regression Program Version 4.7.0 was used to calculate the estimated annual percent change, the average annual percent change, and their 95 % confidence intervals (95% CI) [28]. We identified statistically significant trend change points (joinpoints) and the rate of change in each trend segment using a Monte Carlo permutation method. A maximum number of three joinpoints was allowed. A segment was considered significant if the slope of the regression line was statistically different from zero ($p<0.05$). The GeoDA software package was used for spatial distribution analysis [29].

Results

A total of 31,343 liver cancer deaths (14,598 in men and 16,745 in women) were reported between 2003 to 2017. Figure 1 and Table 1 shows the age standardized liver cancer mortality rates (ASMRs) per 100,000 during the entire period (2003-2017). The highest ASMRs were in Apurimac (14.0), Huanuco (13.4), and Ayacucho (13.0) for men, and Tacna (16.5), Apurimac (14.0), and Puno (13.3) for women. The lowest ASMRs (<10.0) were observed in therainforest provinces.

Table 2 shows the number of deaths and age-standardized mortality rates per 100,000 person-years in Peru and its regions. For Peruvian men, the ASMR decreased from 7.21 in 2003 to 6.43 in 2017, whereas in

Table 1. Average Age-Standardized Liver Cancer Mortality Rates in Peru, 2003-2017.

Provinces	Men	Women
Amazonas	9.7	9.9
Ancash	6.4	7.0
Apurimac	14.6	14.0
Arequipa	6.5	8.0
Ayacucho	13	11.2
Cajamarca	9.1	9.2
Callao	6.7	5.7
Cusco	10.5	12.5
Huancavelica	10.3	12.3
Huanuco	13.4	12.2
Ica	6.7	8.3
Junin	10	9.3
La Libertad	8.1	9.8
Lambayeque	7.9	8.9
Lima	7.3	6.6
Loreto	8	9.1
Madre de Dios	5.8	9.5
Moquegua	5.7	8.7
Pasco	8.2	11.7
Piura	8.7	9.1
Puno	6.5	13.3
San Martin	10.2	11.2
Tacna	9.7	16.5
Tumbes	6.2	8.0
Ucayali	7.5	7.2

Table 2. Number of Deaths, Age-Standardized Mortality Rates Per 100.000 Person-Years from Liver Cancer in Peru and Regions.

Geographical Areas	Men				Women				M:F Ratio (2003)	M:F Ratio (2017)
	2003		2017		2003		2017			
	Deaths	ASMR	Deaths	ASMR	Deaths	ASMR	Deaths	ASMR		
Country										
Peru	751	7.21	874	6.43	781	6.95	1065	7.1	1	0.9
Regions										
Coast	436	6.53	512	5.63	472	6.36	606	5.84	1	1
Highlands	266	9.27	283	8.46	246	8.01	383	10.46	1.2	0.8
Rainforest	49	5.66	79	6.93	63	8.66	76	7.59	0.7	0.9

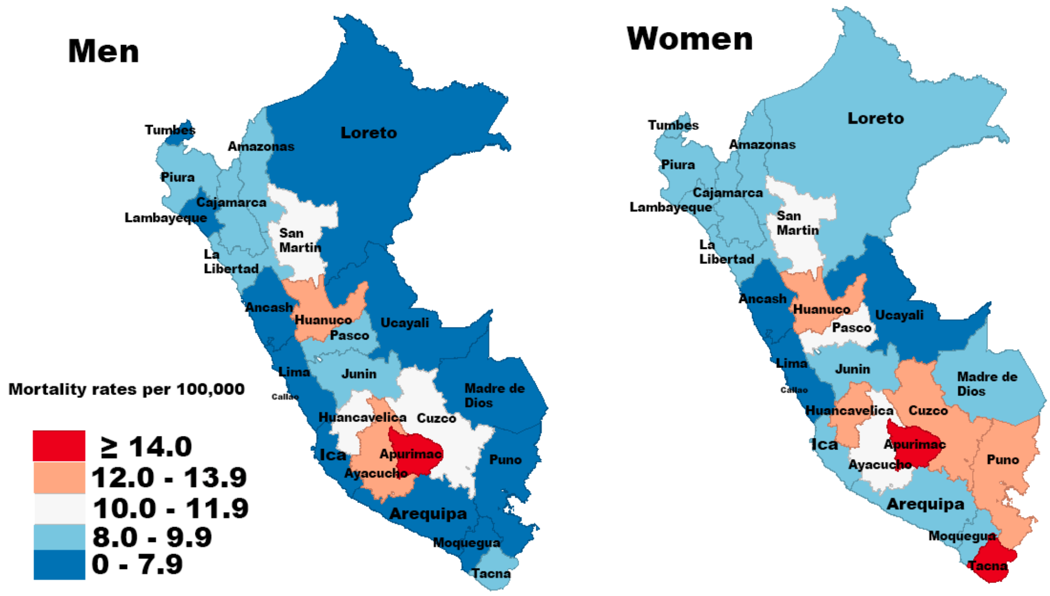

Figure 1. Age-Standardized Mortality Rates for Liver Cancer from Peru, 2003–2017.

Peruvian women, the ASMR increased from 6.95 in 2003 to 7.10 in 2017. Rainforest region reported an increase for men (from 5.66 in 2003 to 6.93 in 2017), whereas the highlands region reported an increase for women (from 8.01 in 2003 to 10.46 in 2017). In 2003, the male-to-female ASMR ratio was ≥1 in Peru, coast, and highlands, while in the rainforest it was <1. In 2017, the male-to-female ASMR ratio was ≥1 in the coast, while was <1 in Peru, highlands and rainforest regions. Table 3 and Figure 2 shows Joinpoint analysis of liver cancer in Peru and its regions between 2003 and 2017. In men, although the ASMRs declined in both Peru and in the individual regions, the declines were not statistically significant.In contrast, , there was a significant decrease among women in Peru overall (−3.1%) and in the coastal region (−3.5%) from 2005 to 2017, and in the highlands region (−2.8%) from 2007 to 2017.

The analysis of liver cancer mortality among men by province found that Ucayali, Apurimac, and Huancavelica had the highest mortality rates in 2003, whereas Apurimac, Ayacucho, and Cusco reported the highest mortality rates in 2017. Of these, Ancash province reported a significant increase of 12.5% per year during 2003-2011, but a significant decrease of 10.5% per year between 2011-

Table 3. Joinpoint Analysis for Liver Cancer from Peru and Its Regions between 2003 and 2017.

Geographical area	Men			Women				
	Years	APC	AAPC	Years	APC	Years	APC	AAPC
Country								
Peru	2003-2017	−1.3 (−2.8,0.2)	−1.3 (−2.8,0.2)	2003-2005	20.2 (−1.0,45.8)	2005-2017	−3.1*(−4.2,−2.0)	−0.1 (−2.6,2.5)
Regions								
Coast	2003-2017	−0.9 (−2.4,0.7)	−0.9 (−2.4,0.7)	2003-2005	17.3 (−6.4,47.1)	2005-2017	−3.5*(−4.8,−2.2)	−0.8 (−3.8,2.2)
Highlands	2003-2017	−1.6 (−3.3,0.1)	−1.6 (−3.3,0.1)	2003-2007	10.2 (−0.9,22.6)	2007-2017	−2.8*(−5.3,−0.2)	−0.8 (−2.4,4.0)
Rainforest	2003-2017	−2.7 (−6.4,1.1)	−2.7 (−6.4,1.1)	2003-2017	−2.0 (−5.4,1.5)			−2.0 (−5.4,1.5)

* p value: <0.05

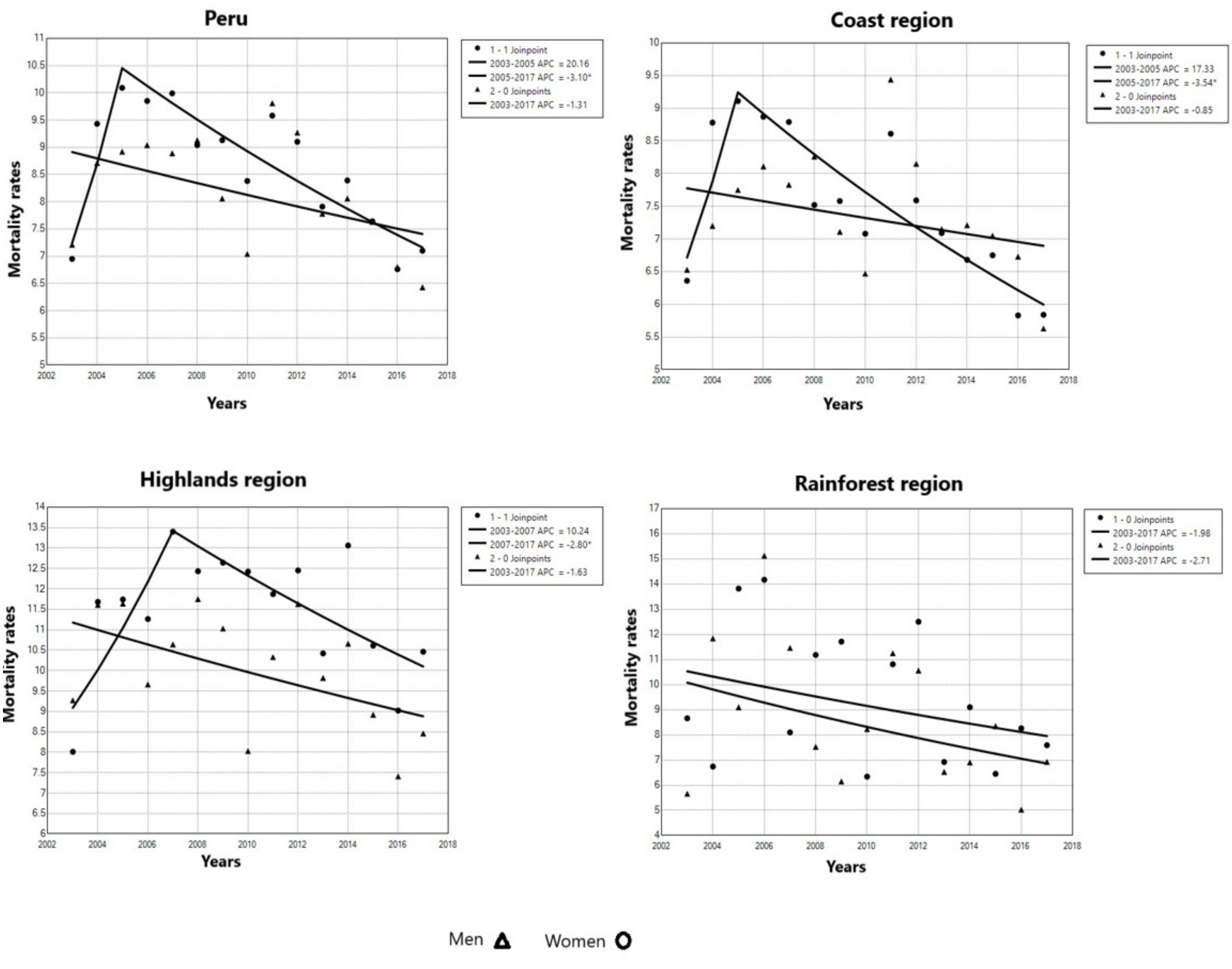

Figure 2. Joinpoint of Liver Cancer Mortality Rates in Peru and Its Regions, 2003-2017.

2017; whereas the provinces such as Cajamarca (−3.0%), Junin (−3.0%), and Ucayali (−12.2%) reported significant decreases between 2003 and 2017 (Supplementary 1 and Supplementary 2). Among women, the provinces of Tacna, Moquegua, and Cusco reported the highest mortality rates in 2003, whereas Madre de Dios, Huanuco, and Tacna reported the highest mortality rates in 2017. The mortality rates declined significantly between 2003 and 2017 in the provinces of Arequipa (−3.8%), Cusco (−3.5%), La Libertad (−2.1%), Lima (−2.5%), and Moquegua (−6.0%), whereas in Junin province, there was an increase of 6% between 2003 and 2012, followed by, a 15.4% afterwardThese changes, however, were not statistically significant (Supplementary 1 and Supplementary 2).

Discussion

This is the first study in Peru to examine liver cancer mortality patterns by region and sex from 2003 to 2017. Mortality rates ranged from 6 to 7 deaths per 100,000. Among women there was a decrease in liver cancer mortality rates, whereas among men, there were stable mortality trends. Unlike the typical male-to-female (M:F) ratio in liver cancer, the M:F ratio in Peru was at or below one between 2003 and 2017.

The liver cancer mortality rates in Peru are comparable to those in Brazil and Chile, but are notably higher than the rates across other Latin American nations [1, 30]. Within the South American context, the primary risk factors for hepatocellular carcinoma (HCC), the most prevalent form of liver cancer, are HCV infection followed by alcoholic cirrhosis [31]. Meanwhile, some Latin American groups have witnessed a rise in HCC cases attributed to MASLD [32]. Remarkably, Peru's mortality rates in this regard rank among the highest in Latin America and the Caribbean. In Peru and among individuals aged 50 years or younger across the South American population, HBV infection is the primary cause of HCC [33, 34]. In contrast to global trends, cohort studies conducted in Peru reveal distinctive clinical profiles of HCC. The condition can notably affectspersons aged less than 45 years, , particularly those in the Andean population, who exhibit a normal and healthy liver. This phenomenon is paralleled by a bimodal age distribution of HCC patients in Peru, leading to two distinct subpopulations characterized by varying clinical attributes [35]. The subgroup consisting of younger ages (≤44 years, with a mean of 25.5 years) tends to present with a higher occurrence of poorly differentiated or undifferentiated high-grade tumors, along with distant metastases, and an elevated prevalence of HBV infection. Conversely, the HCC subgroup aged 44 years, (mean of 65.5 years) displays a greater frequency of multinodular

HCC and an increased rate of HCV infection.[35] This unique clinical spectrum is further compounded by the substantial prevalence of HBV and HCV viruses within the rainforest region, particularly among the indigenous population [36].

Another contributing factor to the elevated liver cancer mortality rates in Peru could be AFB1, a widely recognized hepatocarcinogen [37]. An investigation into food items sold in Lima's markets recently revealed a notable prevalence of AFB1 contamination.,An assessment of 80 liver cancer cases, however, identified the AFB1 signature mutation in codon 249 of the TP53 gene in only one case [31, 38]. However, it's worth noting that the codon 249 mutation is observed in a specific subset of individuals with liver cancer in regions of high AFB1 exposure. Therefore, the possibility of AFB1 acting as a risk factor cannot be dismissed, even in the absence of the TP53 codon 249 mutation [39].

Although Peru reported the highest mortality rates in Latin America, significant declines in rates among women occurred while rates among men remained stable.. Other studies s have reported an increase in mortality rates for Brazilian men, and a decrease for Colombian men. Meanwhile, Colombia and Ecuador have reported decreasing mortality rates for women [17]. Similarly, despite declines of 1.2 between 2018 and 2020, the most recent GLOBOCAN statistics listed Peru as having one of the highest mortality rates in Latin America and the Caribbean [30, 1]. Overall, this study found a liver cancer mortality rate of less than 10 per 100,000 persons, . Nonetheless, Peru's rates are lower than those of countries such as Guatemala and Nicaragua, where the mortality rate is above 10 per 100,000 people. These high rates are likely the result of unhealthy lifestyle factors including drinking, smoking, andunhealthy diets . The prevalence of diabetes and obesity has increased because of these factors, with obesity affecting 62.7% of persons 15 years and older, with women having the highest incidence. Obesity alone has been associated with a 4-fold increase in liver cancer deaths [40].

In Peru, we have observed irregular mortality patterns, characterized by a decline in mortality rates among women residing on the coast and in the highlands, while trends have remained relatively stable in the rainforest region. Notably, despite the rainforest's high endemicity for HBV, a prominent risk factor for liver cancer, there hasn't been a corresponding increase in this region's liver cancer mortality rates. This phenomenon is likely attributed to recent advancements in HBV control efforts [41]. The observed variations in mortality might stem from clinical and biological disparities among hepatocellular carcinoma patients born in the central-southern region. This group tends to be younger, more frequently carriers of HBV, and have lower tumor grades compared to those born in the south-central coastal regions [42]. Interestingly, the reduction in liver cancer mortality may be attributable to the successful implementation of cancer prevention initiatives, such as the Plan Esperanza program and awareness campaigns addressingHBV. . Despite these positive steps, the diversification of responsibilities within the Peruvian National Institutes of Neoplastic Diseases,responsible for safeguarding, promoting, offering comprehensive care, and preventing neoplastic diseases, continues to pose challenges within the broader Peruvian healthcare system.

Limitation of the the current study include the usual caveats of a cancer registry analysis, such as possibility of missing data, lack of specific information on tumor characteristics, limited individual-level information, and variation in death registration completeness and quality. There is always the possibility of underreporting of deaths and the potential for some liver cancer deaths to be misclassified as other causes of death. In addition, the study lacked clinical data on underlying medical conditions and had little information on the prevalence of risk factors.

In conclusion, while mortality rates for women decreased between 2003 and 2017, rates among men were stable. Between 2003 and 2017, the traditional ratio M:F in liver cancer in Peru was equal to or less than one. Effective interventions like expanding access to healthcare and controlling the various risk factors for liver cancer are the main challenges to be overcome in our country.

Author Contribution Statement

Conceived and designed the idea: JSTR. Had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: JSRT, GDK. Contributed to the writing of the manuscript: All authors. Contributed to the statistical analysis: JSRT, GDK. Critical revision of the manuscript: CSA, KAM. Approval of the submitted and final version: All authors.

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Ethics approval and consent to participate

Ethical approval and consent of the participants were not necessary since this study involved the use of a previously published secondary database.

Availability of data and materials

The datasets used and/or analysed during the current study are available in the following link: https://www.minsa.gob.pe/portada/transparencia/solicitud/

Availability of data

This database can be requested via the website: https://www.minsa.gob.pe/portada/transparencia/solicitud/

Any conflict of interest

The authors declare that they have no competing interests.

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