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## Geographic variation of gallbladder cancer mortality and risk factors in Chile: a population-based ecologic study

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### Abstract

Chile's gallbladder cancer rates are among the highest in the world, being the first cancer killer among Chilean women. To provide insights into the etiology of gallbladder cancer, we conducted an ecologic study examining the geographical variation of gallbladder cancer and several putative risk factors. The relative risk of dying from gallbladder cancer (relative to the national average mortality rate) between 1985 and 2003 was estimated for each of the 333 Chilean counties, using a hierarchical Poisson regression model, adjusting for age, sex, and geographical location. The risk of gallbladder cancer mortality was analyzed in relation to region (costal, inland, northern, and southern), poverty, Amerindian (Mapuche) population, typhoid fever, and access to cholecystectomy, using logistic regression analysis. There were 27,183 gallbladder cancer deaths, age-sex-adjusted county mortality rates ranging from 8.2 to 12.4 per 100,000 inhabitants, being higher in inland and southern regions; compare to the north-coastal, the northern-inland region had a 10-fold risk odds ratio (OR) (95% of confidence interval (95% CI): 2.4–42.2) and the southern-inland region had a 26-fold risk (OR 95% CI: 6.0–114.2). Independent risk factors for gallbladder cancer were: ethnicity (Mapuche) OR:3.9 (95% CI 1.8–8.7), typhoid fever OR:2.9 (95% CI 1.2–6.9), poverty OR:5.1 (95% CI 1.6–15.9), low access to cholecystectomy OR:3.9 (95% CI 1.5–10.1), low access to hospital care OR:14.2 (95% CI 4.2–48.7) and high urbanization OR:8.0 (95% CI 3.4–18.7). Our results suggest that gallbladder cancer in Chile may be related to both genetic factors and poor living conditions. Future analytic studies are needed to further clarify the role of these factors in gallbladder cancer etiology.

### Keywords

gallbladder cancer; gallstones; Mapuche; typhoid; genetics

### INTRODUCTION

Chile's gallbladder cancer incidence and mortality rates are among the highest in the world, with a mortality rate of 15.6 per 100,000 person-years in women and 7.0 per 100,000 person-years in men<sup>1</sup>. Gallbladder cancer is the first cause of cancer death among Chilean women, above breast, lung and cervical cancers (Figure 1). In Chile, the highest mortality rates are seen in Southern regions, especially in areas with high poverty, a large Amerindian (Mapuche)

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population, and insufficient access to health services, including access to surgery for gallbladder diseases (cholecystectomy)<sup>1,2</sup>.

Apart from age, female gender, and a history of gallstones, the etiology of gallbladder cancer remains unclear. Reasons for the very high rates of gallbladder cancer in Chile are not known but both lifestyle and genetic factors have been suggested<sup>3-6</sup>. American Indians in the U.S. also have very high rates of gallstones and gallbladder cancer, like the Amerindians in Chile (Mapuche), suggesting a role of genetic susceptibility for both populations<sup>4,5,7</sup>. Chronic carriage of typhoid has been suggested as a risk factor for gallbladder cancer in India<sup>6</sup>, where the incidence of typhoid fever is high. Typhoid fever was endemic in Chile between 1960 and 1982, thus it is possible that typhoid may be contributing to the high risk of gallbladder cancer in Chile<sup>8</sup>.

To better understand the reasons for the high incidence and mortality of gallbladder cancer in Chile, we conducted a population-based ecologic study examining the relative risks of gallbladder cancer mortality between 1985 and 2002 for each of the 333 counties in Chile, as well as the relationships between several putative risk factors and the geographic variation of gallbladder cancer mortality.

## METHODS

### Study Population and Data Sources

Several national data sources were used for this analysis. Specifically, gallbladder cancer mortality rates for each of the 333 Chilean counties between 1985 and 2002 were calculated, using data from the Ministry of Health of Chile<sup>9</sup>. Chilean population estimates (approximately 15 million in total) by age, sex, race (self-declared), and county were obtained from the 2002 Census<sup>10</sup>. Data on the poverty index (the percent of the population in the county whose income does not cover minimum goods and services) was obtained from the 2003 survey Caracterización Socioeconómica Nacional (CASEN)<sup>11</sup>, and incidence rates of typhoid fever between 1999 and 2004 were based on data from Epidemiological Surveillance Statistics<sup>12</sup>.

### Geographical Variations in Gallbladder Cancer Mortality

Since gallbladder cancer is a rare disease and many counties have small populations, we used a Poisson regression model to calculate spatially smoothed gallbladder cancer mortality risks for each county relative to the national average, adjusting for the population size and age-sex composition. We used a hierarchical Poisson regression model, which combines unstructured variability and spatial dependence (structured variability)<sup>13</sup>. This spatial variability was estimated by an *a priori* Intrinsic Conditional Autoregressive Distribution (Bayesian analysis)<sup>14</sup>. The model can be represented by:

$$\begin{aligned} O_i &\sim \text{Poisson}(\mu_i) \\ \log \mu_i &= \log E_i + \alpha_0 + b_i + h_i \end{aligned}$$

In this model,  $\alpha_0$  is the intercept that represents the logarithm of the national gallbladder cancer rate (baseline) throughout Chile;  $b_i$  is the random area-specific effect in the logarithm of relative risk explained by the neighbors of the  $i$ th county and  $h_i$  is the random area-specific unexplained residual. We conducted Bayesian analysis of these models with parameters obtained using Markov-Monte Carlo techniques employed in the program WinBUGS<sup>15</sup>. Convergences were evaluated based on standard criteria using the program BOA<sup>16</sup>. Comparison and selection of models were based on the *Deviance Information Criterion*<sup>17</sup>. Based on the results of this model, counties were dichotomized into high ( $RR > 1$ ) and low ( $RR \leq 1$ ) gallbladder cancer mortality

risk, using a ROC curve. Temporal trends for gallbladder cancer mortality between 1985 and 2002 were also calculated, using a Poisson regression model.

### Risk Factors for Gallbladder Cancer Mortality

Multivariate logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for gallbladder mortality in relation to geographic location, percent living in poverty, urbanization (as stated by the National Institute of Statistics), typhoid incidence rate (1999–2004), percent of Amerindians (Mapuche) in the population, access to hospital care for gallbladder cancer patients (estimated as the ratio of the number of gallbladder diseases hospitalizations over the number of deaths from gallbladder cancer) and cholecystectomy (estimated from major surgery in patients with gallbladder disease).

Gallbladder cancer mortality risk was evaluated comparing counties with a gallbladder cancer mortality relative risk (RR) greater than 1 with those with RR less than or equal to 1 (risk is relative to the national rate). Geographic location was assessed using four regions (north-coast, north-inland, south-coast, and south-inland). A county was considered coastal if it touched the coastline, while an inland county has no coastal borders. ROC curve analysis was used to dichotomize the proportion of the Mapuche population ( $\geq$  or  $<$  3.7%), and typhoid fever incidence ( $\geq$  or  $<$  7.2 per 100,000 population). Poverty level was categorized as: low (Poverty Index CASEN  $<$  20%), medium (Poverty Index CASEN between 20 and 40%), and high (Poverty Index CASEN  $>$  40%) and urbanization as low ( $<$  40%), medium (between 40–75%), and high ( $>$  75%). The ratio of gallbladder diseases hospitalizations over the number of deaths from gallbladder cancer was categorized as: high ( $>$  60), medium (30–60), and low (less than 30). Access to cholecystectomy was categorized as: high ( $>$  80%), medium (between 50 and 80%) and low ( $<$  50%).

## RESULTS

Geographic variation in gallbladder cancer mortality by county between 1985 and 2002, relative to average national mortality rates, adjusting for county-specific population size, and age and sex distributions, is shown in Figure 2. As shown, the highest gallbladder cancer mortality rates occurred in the southern part of the country, in particular the south-inland region.

Selected characteristics of the 333 Chilean counties by geographical location are shown in Table I. The Chilean population tended to cluster in the north-inland region, while the Mapuche population was higher in the south, representing 6.5% of the population. Southern regions, both inland and coastal, also had high levels of poverty, were more rural, had a high incidence of typhoid fever, and lower rates of gallbladder surgery; cholecistectomy ratio was highest in the north-inland counties and lowest in the south-inland counties (81% and 59% of gallbladder disease hospitalizations received surgery respectively). Gallbladder cancer mortality ranged from 8.22 to 12.44 per 100,000 inhabitants, with the south-inland region having the highest rates. Average relative risk for GBC mortality was lowest in the North-Coastal counties and higher in the South-Inland counties. The North inland and coastal counties have negative trend of the relative risk for GBC mortality, i.e. slightly decreases risk trend over the period. Both South coastal and inland counties have an upward trend.

Based on the geographical analysis, counties with  $RR > 1$  for gallbladder cancer mortality were classified as high risk, while those with  $RR < 1$  were classified as low risk. A multivariable logistic regression analysis of the gallbladder cancer risk is presented in Table II. Eleven percent of the counties in the north-coastal areas were classified as high-risk, while 67% of the south-inland counties were high-risk. Compared to the north-coast region, north-inland areas had a 10-fold (95% CI 2.4–42.2) risk of gallbladder cancer, and south-inland regions had a 26-fold risk (95% CI 6.0–114.2) of gallbladder cancer mortality (Table II). A large Mapuche population, high rates of typhoid fever, high poverty levels and high urbanization were risk

factors for gallbladder cancer mortality, while high access to hospital care and high access to cholecystectomy were protective factors.

## DISCUSSION

In this population-based ecological study of 333 counties in Chile, we show that there is a large geographic variation in gallbladder cancer risk not explained by chance, or age-sex distribution of the population. The highest mortality occurred in the southern regions, in particular the south-inland region. Our results also show that a high proportion of Mapuche Amerindians in the population, typhoid fever and poverty are important risk factors in the southern regions of Chile. It is not surprising that counties with large Mapuche population had higher risk for gallbladder cancer in Chile, since they have Amerindian origin and American Indians have one of the highest rates of gallstones and gallbladder cancer in the world<sup>5,6,18–20</sup>. The concomitant high rates of gallbladder cancer in Mapuches and American Indians suggest a possible role of genetic susceptibility. Similar to American Indians, Mapuches have high rates of obesity, diabetes, metabolic syndrome, and cholesterol gallstones<sup>7,20–23</sup> all of which are risk factors for gallbladder cancer and are conditions with a genetic basis. Several observations have suggested that gallbladder cancer has a strong genetic component. For example, family history of gallstones has been shown to increase the risk of gallbladder cancer<sup>24</sup> and certain genetic variants in estrogen metabolism (particularly among obese and diabetic individuals)<sup>25</sup>, inflammation, and lipid metabolism<sup>26–28</sup> have been linked to an increased risk of gallstones and gallbladder cancer. Molecular studies of gallbladder cancer have also reported mutations of proto-oncogenes like K-ras and beta-catenin, alterations in some tumor suppressor genes, such as p53 and APC, and instability of microsatellites<sup>29–31</sup>. It is possible that the much higher risk of gallbladder cancer in the inland regions is related to a higher homogeneity of the Mapuche population due to a higher degree of inbreeding<sup>32</sup>. Although the percent of Mapuche in the population is similar that in inland and coastal southern counties (6.5% each), proximity to the sea has permitted for a higher genetic interchange<sup>32</sup>.

It is possible that the higher rates of typhoid contribute to the excess risk of gallbladder cancer. The observation that typhoid fever is a significant risk factor for gallbladder cancer in Chile is consistent with previous reports suggesting a link between chronic typhoid carriage and gallbladder cancer in typhoid-endemic area, such as India<sup>19,33,34</sup>. Chile has been a highly endemic area for typhoid fever since 1950, with an annual incidence rate of about 60 per 100,000 person-years until 1976<sup>8</sup>. Between 1976 and 1985, an epidemic of typhoid surged in most urban areas of Chile due to the deteriorating living conditions, and the incidence increased to 121 per 100,000 person-years. However, in 1985, the incidence of typhoid started to decrease, and this trend continued until 1991, when typhoid incidence rate reached the current level of 3.3 per 100,000 person-years<sup>8</sup> (Figure 3). The precipitous drop in typhoid incidence between 1985 and 1992 was the result of intensive intervention measures taken to avoid the expansion of the cholera epidemic that had been affecting Peru since 1991<sup>8</sup>. Typhoid fever is caused by *Salmonella typhi* (*S. typhi*). Two to five percent of all individuals who develop clinical or subclinical infection with *S. typhi* become chronic carriers<sup>35</sup>. The propensity to become a chronic carrier after acute infection increases with age and is greater in women<sup>36</sup>. Previous studies in Chile have shown that chronic *S. typhi* carriers had a higher frequency of the erythrocyte ABH non-secretor phenotype than non-carriers, suggesting that the carrier state may be influenced by genetic predisposition and that the ABH carbohydrates secreted in the bile may interfere with *S. typhi* colonization in the bile tract, resulting in increased gallstone formation and increased probability of becoming chronic carriers (OR=15)<sup>35,36</sup>. It is noteworthy that Chile has one of the highest rates of gallstones and typhoid fever in the world. In Chile, during the hyperendemic period of typhoid (1976–1985), more than 90,000 people were exposed to *S. typhi*<sup>36</sup>. In 1980 the estimated carrier rate was 694 per 100,000 population, with unusually high rates estimated for middle-age-women (aged 30–39, 5586 per 100,000 and

aged 40–49, 4575 per 100,000)<sup>36</sup>. Women in these age groups also have usually high rates of gallstones, ranging from 43% to 60%<sup>36</sup>. The combination of high rates of chronic typhoid carriage and gallstones is likely to result in an increase in incidence of gallbladder cancer in the future. Gallbladder cancer mortality in Chile has risen steadily and we could expect to see a future surge of incidence as a result of the typhoid epidemic between 1976–1985 typhoid endemic. However, since the latency period between typhoid and gallbladder cancer is long, most chronic carriers are still young, and not enough years have elapsed, it is still unclear when the 1976–1985 typhoid epidemic would impact the incidence of gallbladder cancer in Chile. Nevertheless, if cholecistectomy rates increase, particularly in high risk counties, the effect of the chronic *S typhi* carriers in gallbladder cancer incidence could be averted.

Poverty is an important risk factor for gallbladder cancer. Many factors, including typhoid infection, diet, and access to medical procedures, are related to poverty. In developing countries, cholecystectomy is associated with decreasing rates of gallbladder cancer incidence and mortality<sup>37</sup>. In Chile, although economic conditions have improved over time, we have not yet seen a large decrease in gallbladder cancer risk, due largely to the fact that most gallstone patients from high- risk areas do not have access to cholecystectomy procedures<sup>1,38,39</sup>. A study on the American Indians in New Mexico (a high risk populations for gallbladder cancer) showed that their incidence of gallbladder cancer has declined faster than other ethnic groups, presumably because of their better access to cholecystectomy<sup>40</sup>.

Reasons for the positive association between urbanization and gallbladder cancer are unknown but may be related to westernized lifestyles, better diagnosis or better reporting of gallbladder cancer. Surveys in Chile showed that people in rural areas had less risk factor for gallstone; in particular they had lower levels of cholesterol, triglycerides, and low-density lipoprotein cholesterol, than people in urban areas<sup>41</sup>. In addition, the prevalence of diabetes and obesity is higher in urban areas<sup>21</sup>. Together, these findings support the observation that more urbanized populations should have higher gallbladder cancer rates.

Certain nutritional factors may be related to the much higher rates of gallbladder cancer in the southern regions, but we do not have the data to evaluate their role. In an earlier study in Chile, consumption of red chili pepper, beef, and pork was linked to an increased risk of gallbladder cancer<sup>42</sup>. These types of foods are frequently eaten in the southern regions<sup>42,43</sup>. Inland counties have less access to seafood and vegetables, which have been associated with a reduced risk of gallbladder cancer<sup>42,44</sup>.

In summary, our ecologic study showed that there is a large geographic variation in gallbladder cancer mortality in Chile, with a much higher rate in the south-inland region. Future studies in Chile are needed to confirm the role of typhoid fever and genetic susceptibility to gallbladder cancer in Amerindians.

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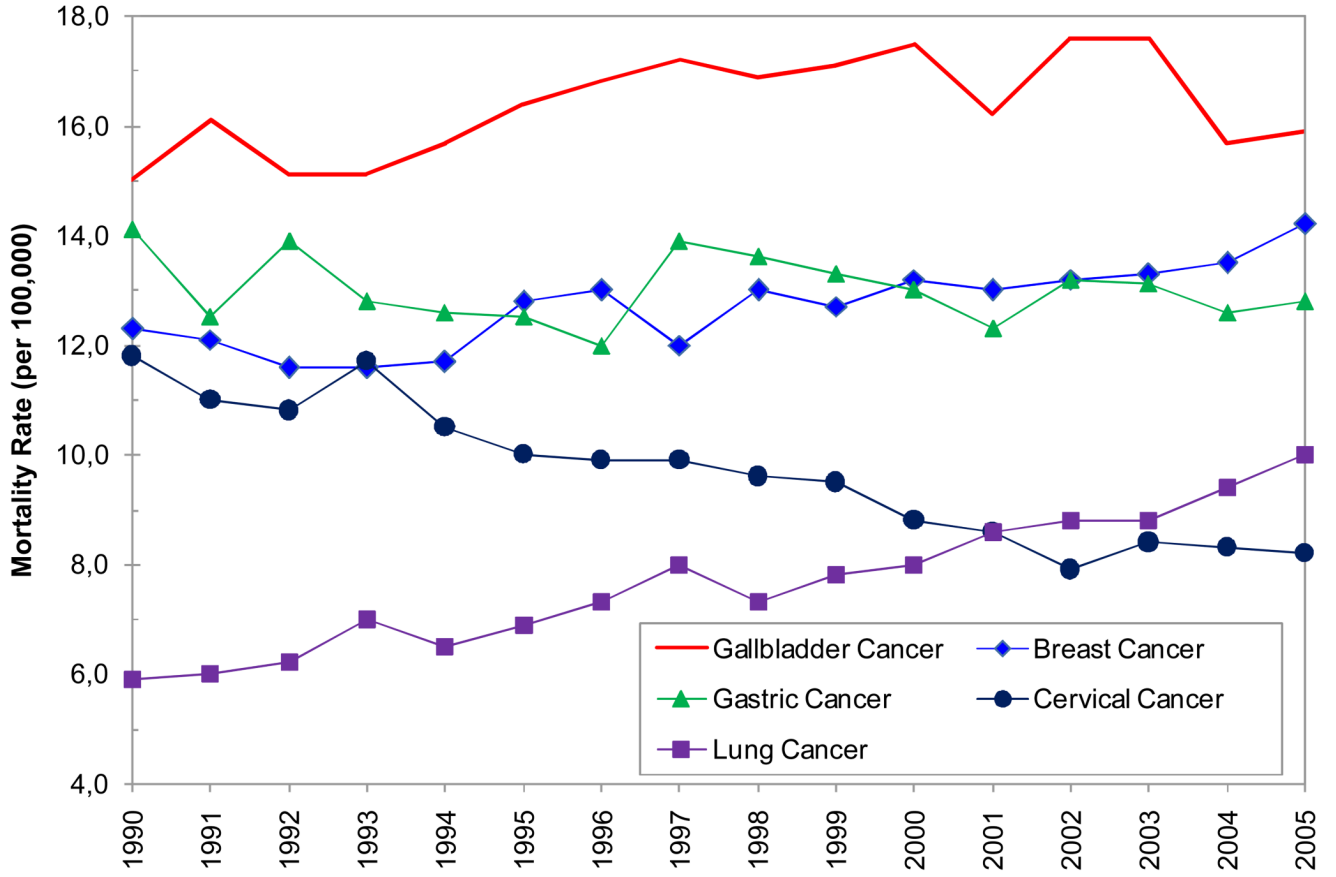
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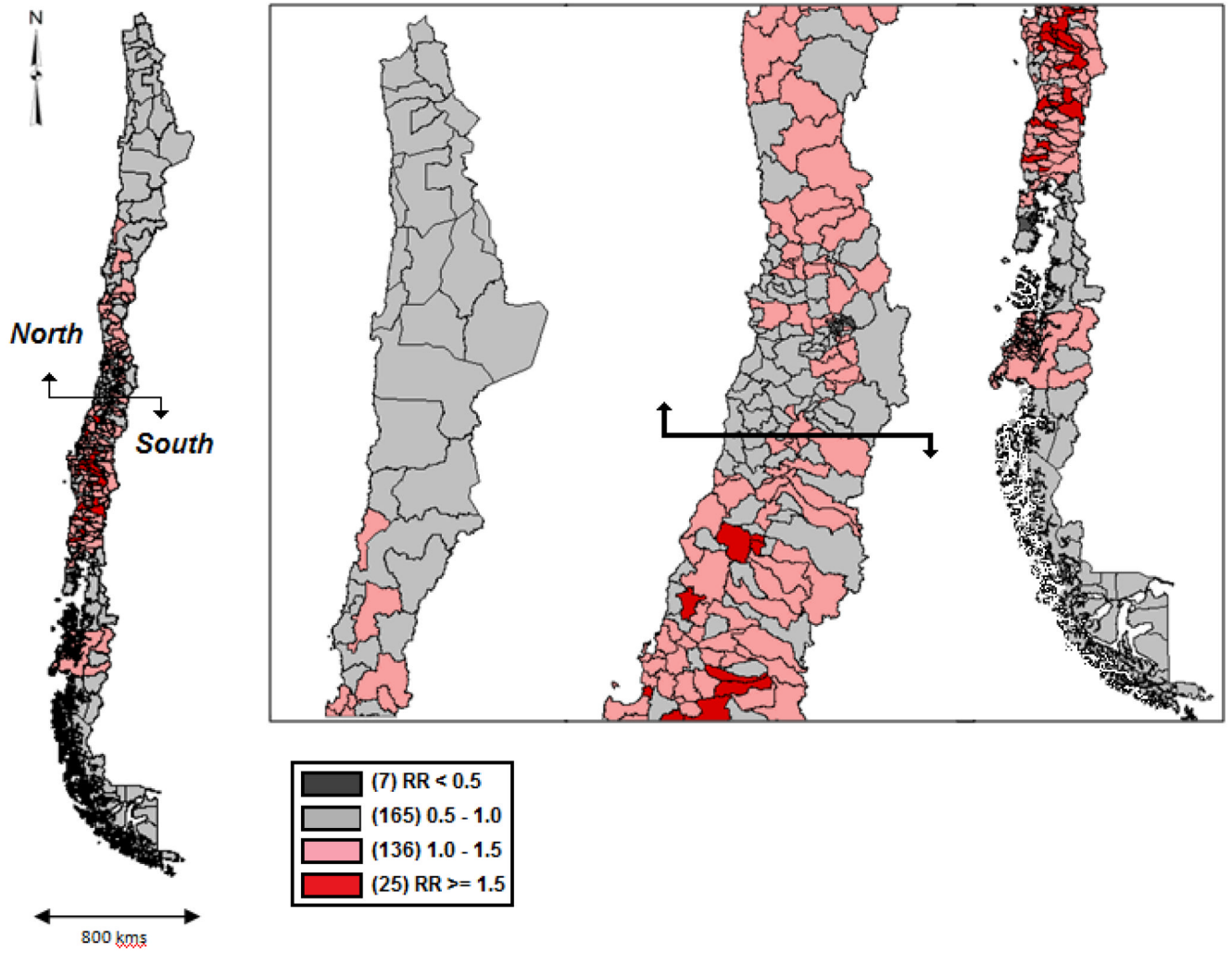
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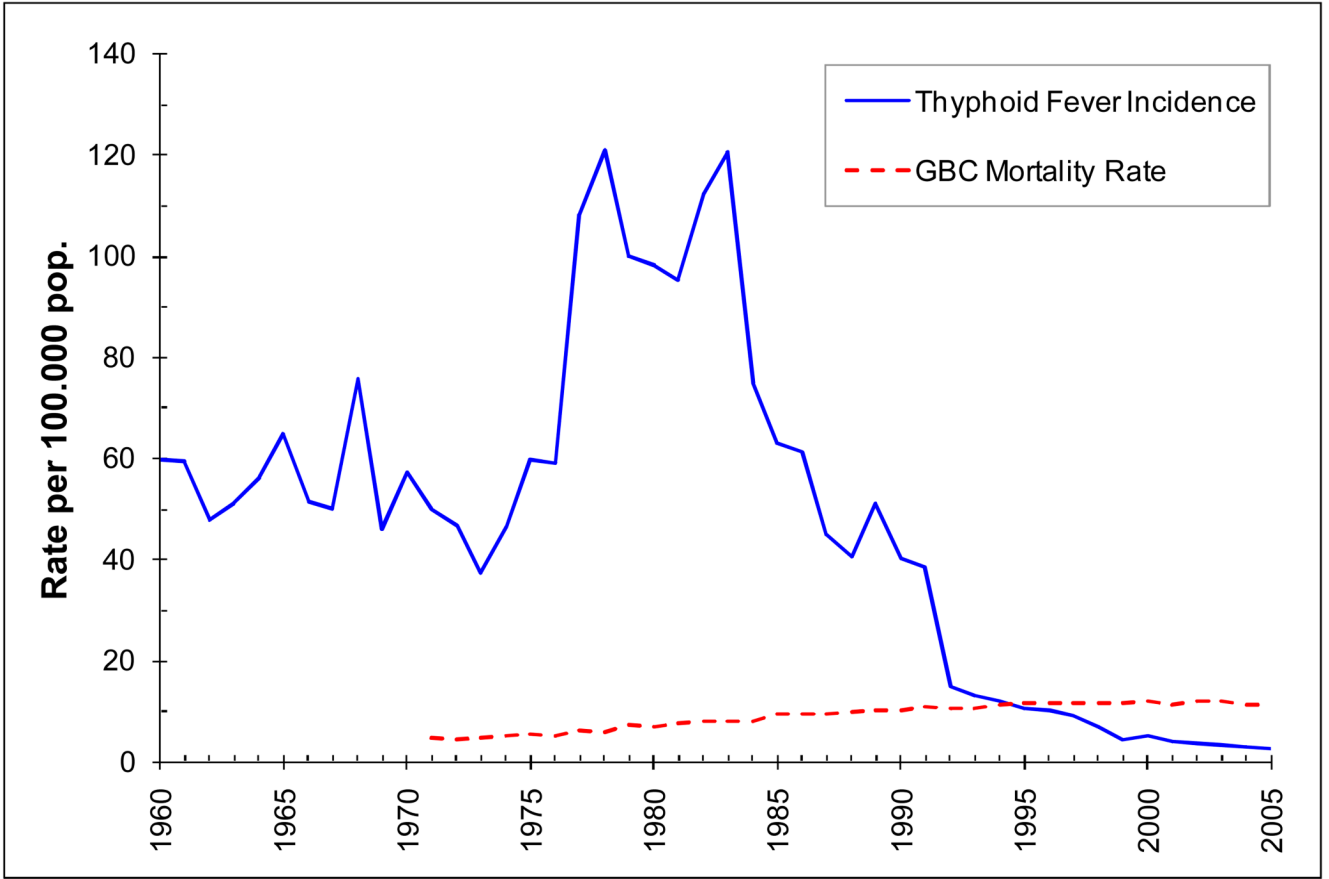
**FIGURE 1.** First five causes of cancer deaths among Chilean women. All of Chile, 1990–2005. Crude Mortality Rate per 100,000 women  
Elaborated by the author from Chilean Ministry of Health Mortality database<sup>9</sup>







**FIGURE 2.** Geographic variation of Relative risk (RR) of gallbladder cancer in Chile (1985–2002) by county with reference to the national average, adjusted for county population size, age-sex distribution and spatially smoothed



**FIGURE 3.** Temporal trend of typhoid fever incidence rate and of gallbladder cancer (GBC) mortality rate in Chile between 1960–2005  
Elaborated by the author from Chilean Ministry of Health Mortality database<sup>9</sup>

TABLE I

Selected Characteristics of the 333 Counties by Geographic Regions, Chile

	North-Coast	North-Inland	South-Coast	South-Inland
No. counties	28	101	67	137
<b>Characteristic</b>				
Chilean pop. %	12	49	14	24
Mean percentage of Mapuche in pop (range)	1.0% (0.3% – 3.0%)	2.6% (0.0% – 10.6%)	6.5% (0.2% – 64.7%)	6.5% (0.0% – 59.5%)
Mean percentage of population living in poverty (range)	16.7 (8.2 – 41.9)	16.7 (1.4 – 42.0)	26.5 (4.5 – 59.9)	27.4 (10.9 – 59.5)
Mean percentage of urbanization (range)	78% (0% – 99%)	71% (0% – 100%)	45% (0% – 99%)	47% (0% – 97%)
Typhoid incidence rate 1999–2004, mean per 100,000 population (range)	4.2 (0.0 – 10.5)	5.2 (0.0 – 54.9)	7.5 (0.0 – 38.3)	7.0 (0.0 – 104.1)
Gallbladder disease hospital discharges. 1992–2003, average rate per 100,000 inhab. (range)	290.8 (50.5 – 757.1)	316.1 (0.0 – 628.3)	352.5 (0.0 – 747.2)	441.1 (65.2 – 1,207.7)
Mean Cholecistectomy 1992–2003 <sup>a</sup> , (range)	74% (39% – 100%)	81% (47% – 100%)	56% (22% – 100%)	59% (17% – 100%)
Ratio of gallbladder diseases hospital discharges over gallbladder cancer death <sup>b</sup> (range)	42 (19 – 78)	37 (0 – 78)	43 (0 – 102)	37 (13 – 111)
Age-sex Adjusted Gallbladder cancer mortality rate per 100,000 inhab. (range)	8.22 (0.0 – 11.3)	8.53 (0.0 – 23.7)	10.41 (0.0 – 38.3)	12.44 (0.0 – 26.6)
RR for gallbladder cancer mortality (95% CI)	0.83 (0.77 – 0.88)	0.93 (0.89 – 0.98)	0.98 (0.91 – 1.06)	1.18 (1.14 – 1.23)
$\beta$ factor (%) for the temporal trend of RR gallbladder cancer mortality, 1985–2002 (IC95%)	–0.20% (–0.4 – 0.0)	–0.19% (–0.4 – 0.0)	0.21% (0.0 – 0.4)	0.30% (0.12 – 0.4)

<sup>a</sup> prepared by the authors from Ministry of Health hospital statistics, number of major surgery per 100 gallbladder diseases hospitalizations

<sup>b</sup> a proxy for access to hospital care among gallbladder disease people.

TABLE II

Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for Gallbladder Cancer Mortality Risk in Relation to Selected Factors in 333 Counties in Chile, 1985–2002. Multivariable Logistic Regression.

Characteristics	No. Counties	% of counties with RR>1 <sup>a</sup>	OR <sup>b</sup> (95% CI)	P
Geographic Location				
North-Coast	28	11	1.0	
North-Inland	101	37	<b>10.13 (2.4 – 42.2)</b>	<b>0.001</b>
South-Coast	67	43	<b>5.19 (1.1 – 24.5)</b>	<b>0.04</b>
South –Inland	137	67	<b>26.10 (6.0 – 114.2)</b>	<b>&lt;0.001</b>
Mapuche population				
Low (<3.7%)	227	41	1.0	
High (≥3.7%)	106	64	<b>3.92 (1.8 – 8.7)</b>	<b>0.001</b>
Typhoid incidence rate <sup>d</sup>				
Low (<7.2)	281	44	1.0	
High (≥7.2)	52	69	<b>2.92 (1.2 – 6.9)</b>	<b>0.014</b>
Poverty				
Low	105	25	1.0	
Medium	192	56	<b>3.20 (1.6 – 6.4)</b>	<b>0.001</b>
High	36	78	<b>5.05 (1.6 – 15.9)</b>	<b>0.006</b>
Urbanization				
Low (<40%)	121	45	1.0	
Medium (40–75%)	101	67	<b>5.29 (2.5 – 11.2)</b>	<b>&lt;0.001</b>
High (>75%)	111	36	<b>8.01 (3.4 – 18.7)</b>	<b>&lt;0.001</b>
Cholecistectomy <sup>c</sup>				
High (>80%)	115	31	1.0	
Medium (50–80%)	130	50	<b>2.01 (1.0 – 4.0)</b>	<b>0.048</b>
Low (<50%)	88	68	<b>3.86 (1.5 – 10.1)</b>	<b>0.006</b>
Hospital care for gallbladder diseases <sup>d</sup>				
High	34	21	1.0	
Medium	188	47	<b>5.16 (1.7 – 15.8)</b>	<b>0.004</b>
Low	111	59	<b>14.25 (4.2 – 48.7)</b>	<b>&lt;0.001</b>

<sup>a</sup>RR: relative risk of gallbladder cancer > 1 from the Poisson Regression Analysis

<sup>b</sup>Odds ratios for comparisons between two strata within each characteristics, adjusted for geographical location

<sup>c</sup>number of major surgery per 100 gallbladder diseases hospital discharge

*p* Ratio of gallbladder diseases hospital discharges over gallbladder cancer deaths