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Cholecystectomy and digestive cancer in Chile: Complementary results from interrupted time series and aggregated data analyses

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Abstract

Gallbladder cancer (GBC) mortality in Chile is among the highest worldwide. In 2006, the Chilean government launched a programme guaranteeing access to gallbladder surgery (cholecystectomy) for patients aged 35–49 years. We evaluated the impact of this programme on digestive cancer mortality. After conducting an interrupted time series analysis of hospitalisation and mortality data from 2002 to 2018 publicly available from the Chilean Department of Health Statistics and Information, we calculated the change in the proportion of individuals without gallbladder since 10 years. We then estimated age, gender, region, and calendar-year standardised mortality ratios (SMRs) as a function of the change in the proportion of individuals without gallbladder. The cholecystectomy rate increased by 45 operations per 100,000 persons per year (95%CI 19–72) after the introduction of the health programme. Each 1% increase in the proportion of individuals without gallbladder since 10 years was associated with a 0.73% decrease in GBC mortality (95% CI −1.05% to −0.38%), but the negative correlation was limited to women, southern Chile and age over 60. We also found decreasing mortality rates for extrahepatic bile duct, liver, oesophageal and stomach cancer with increasing proportions of individuals without gallbladder. To conclude, 12 years after its inception, the

Chilean cholecystectomy programme has markedly and heterogeneously changed cholecystectomy rates. Results based on aggregate data indicate a negative correlation between the proportion of individuals without gallbladder and mortality due to gallbladder and other digestive cancers, which requires validation using individual-level longitudinal data to reduce the potential impact of ecological bias.

KEYWORDS
cancer prevention, cholecystectomy, digestive tract cancer, interrupted time series

What's new?

Taking advantage of the introduction of a Chilean health program in 2006 that guarantees access to gallbladder surgery for gallstone patients, here the authors investigated the relationship between cholecystectomy and digestive cancer mortality. Gallbladder cancer mortality decreased by 0.73% for every 1% increase in the proportion of individuals living without a gallbladder for the last 10 years, but the negative correlation was limited to women, patients in southern Chile, and individuals over 60. The increasing proportions of Chileans without a gallbladder were also associated with lower mortality rates from extrahepatic cholangiocarcinoma, liver, esophageal, and gastric cancer.

1 | INTRODUCTION

The mortality due to gallbladder cancer (GBC) in Chile is one of the highest in the world, proving to be a major health problem in the country.[1] GBC mainly affects women—in 2002 it was the first cause of cancer death (15.3 per 100,000 women) and in 2010 it became the second cause (11.9 per 100,000 women).[2,3] In 2021, GBC was the third type of cancer in women that caused the most years of life lost, and 935 Chilean women and 493 Chilean men died from GBC.[4]

GBC usually develops asymptomatically in the early stages and is diagnosed at advanced stages with very limited treatment options, presenting the worst prognosis of all gastrointestinal and hepatobiliary cancers: <10% first-year survival in advanced stages and a five-year survival rate of <32% for patients with intramucosal tumours.[5]

One of the main risk factor for GBC is the presence of gallstones (cholelithiasis).[6] Gallstones are hard accumulations of cholesterol and other substances in the gallbladder that can cause chronic inflammation.[7] Relative GBC risks of 9.2–10.1 have been reported for gallstones larger than 3 cm, and 2.4 for gallstones 2.0–2.9 cm in diameter.[8–10] Another important risk factor for both GBC and gallstones is female gender: depending on age, women have double to triple the risk of developing gallstones than men,[11] and some studies suggest that pregnancy is a pathogenic factor for gallstone formation.[12,13] Other factors strongly associated with GBC risk are age, overweight and obesity and, in Chile, the individual proportion of indigenous American Mapuche ancestry (the Mapuche are the largest ethnic group in Chile),[14] as well as interactions between these risk factors. Overweight and obesity, for example, have a particularly strong effect on GBC risk for Chileans with a high proportion of Mapuche ancestry.[15]

Due to the high prevalence of GBC and gallstones, since 2006 the Chilean government's legally guaranteed health services include the performance of an abdominal ultrasound within 30 days for patients aged 35–49 years and, if gallstones ≥3 cm or volume >10 ml and/or polyps ≥1 cm are detected, the surgical removal of the gallbladder (cholecystectomy) within 90 days (Garantía Explícita de Salud 26—GES-26). In addition to symptomatic gallstone disease with biliary colic or cholecystitis, women over the age of 40 with several children, a body mass index (BMI) >25 kg/m^2, <8 years of education and at least one Mapuche surname can also benefit from this programme. The GES-26 programme aims to increase the number of cholecystectomies performed in high-risk individuals and thus hopefully reduce mortality from GBC.

However, in addition to the costs and perioperative risks associated with cholecystectomy (related to general anaesthesia and surgical complications such as bile duct injury), an increased risk of cancer, particularly digestive tumours in the stomach, liver, small intestine and pancreas, has been reported.[16] Recent studies based on the Swedish population-based registries have also found an increased risk of kidney, endometrial and breast cancer after gallbladder removal.[17,18]

In this study, we apply interrupted time series analysis to investigate the change in the number of cholecystectomies and GBC-related deaths after the introduction of the GES-26 programme based on publicly available data. We then use cholecystectomy and all-cause mortality data to calculate the change in the proportion of individuals without gallbladder since 10 years, and examine its relationship with GBC and digestive cancer mortality using age, gender, region and calendar-year standardised mortality ratios.

2 | MATERIALS AND METHODS

2.1 | Data sets analysed

The investigated datasets are publicly available on the website of the Chilean Department of Health Statistics and Information, which is

responsible for the collection and dissemination of health data and statistics in Chile. We downloaded the available information from 2002 to 2018 in two independent, anonymised datasets: (1) the hospitalisation dataset, which contains cholecystectomy information and (2) the mortality dataset, which contains the number of deaths related to cancer and other diseases. We selected specific pathologies based on International Classification of Diseases (ICD-10) codes: Cholelithiasis (K80), cholecystitis (K81) and other diseases of the gallbladder and biliary tract (K82 and K83), as well as cancer of the gallbladder (C23X), oesophagus (C15), stomach (C16), colon (C18), liver (C22.0), intrahepatic bile duct (C22.1), extrahepatic bile duct (C24), and pancreas (C25), and all cancers (CXX) except GBC. Chile was divided into 13 regions in the downloaded datasets, but we decided to exclude regions 11 and 12 due to the low number of GBC deaths (<10), and classified the remaining regions according to their proportions of indigenous American ancestry into southern regions with high Mapuche-Huilliche ancestry (Regions: VIII, IX and X), northern regions with high Aymara-Quechua ancestry (Regions: I, II and III), and central regions with high European ancestry proportions (Regions: IV, V, VI, VII and the metropolitan region). The regional ancestry proportions were provided by the Statistical Genetics Research Group of Heidelberg University, and the age distribution for males and females was taken from the 2017 Population and Housing Census reported by the Chilean National Institute of Statistics.

2.2 | Interrupted time series analysis

Cholecystectomy and mortality rates from 2002 to 2018 were age-standardised using the direct method based on the age distribution of the Chilean population in 2017. In addition to the overall analyses, analyses were stratified by gender, region (south, centre and north) and age-group (under 35 years, 35–49 years [age range considered by the GES-26 programme], and 50+ years).

Interrupted time series regression was used to examine and predict the effect of the cholecystectomy programme on cancer mortality at the start of the intervention and over the years of the policy. The period analysed was 2002–2018, with 2006 considered as an interruption in the time series. The earthquake in Chile in 2010, which mainly affected the central and southern regions, was also considered in the regression model. We performed overall, gender, region and age-group stratified analyses using the regression model:

$$y_i = \text{Intercept} + \text{Year} + \text{Programme begin}_{2006} + \text{Programme impact} + \text{Earthquake impact}_{2010} + e_i.$$

where y_i represents the age-standardised cholecystectomy and cancer mortality rates for the year $i = 2002$ to 2018. If autocorrelation was detected using the Durbin–Watson test (p value <0.05), we performed a Prais–Winsten first-order autocorrelation regression, and used standard or Prais–Winsten interrupted time series regression models to predict the cholecystectomy and mortality rates for the period 2019 to 2022.

2.3 | Standardised mortality ratios as a function of the change in the proportion of gallbladder-free individuals

We then estimated age (8 categories), gender, region (North, Centre, South), and calendar-year standardised mortality ratios (SMRs) as a function of the change in the proportion of individuals without gallbladder. First, we calculated the change in the proportion of individuals without gallbladder since 10 years (or 5 years in the sensitivity analyses). For example, women who underwent a cholecystectomy in 2007 at the age of 60, reached the age of 70 and had been without gallbladder for 10 years in 2017, provided they were still alive.

The change in the proportion of individuals without gallbladder was therefore estimated by considering both the probability of being cholecystectomised and the probability of remaining alive, which depended on age, gender, region and calendar-year in the hospitalisation and mortality datasets. For example, let's assume that three people aged 60 underwent a cholecystectomy in 2006. Over time, these persons get older and have a certain probability of dying each year. It is therefore to be expected that not all of them will still be alive after 10 years. Taking this factor into account, age-, gender-, region- and calendar year-specific all-cause mortality rates were used to calculate survival probabilities. Assuming that the probability of survival for 60-year-olds in 2006 was 0.9995, it is expected that $3 \times 0.9995 = 2.998$ 61-year-olds will still be alive in 2007. Similarly, age-, gender-, region- and calendar year-specific cholecystectomy rates were used to calculate the probabilities of undergoing cholecystectomy. The change in the proportion of individuals without gallbladder was then calculated as:

Proportion without gallbladder$_j$ = Persons alive without gallbladder$_j$/Persons alive$_j$, for the age, gender, region and calendar-year category $j = 1$ to 144.

To assess the relationship between the proportion of individuals without gallbladder since 10 years (5 years in the sensitivity analyses) and cancer mortality rates, the 144 age, gender, region and calendar year categories were grouped into quartiles according to their proportion of gallbladder-free individuals. We then calculated SMRs for Q2 vs. Q1, Q3 vs. Q1 and Q4 vs. Q1, with SMRs below 1.00 and decreasing with increasing proportions of gallbladder-free individuals, indicating a negative association. Finally, to estimate the reduction in cancer mortality for each 1% increase in the proportion of individuals without gallbladder since 10 years (5 years in the sensitivity analyses), we grouped the age, gender, region and calendar-year categories from the mortality database into deciles according to the change in the proportion of individuals without gallbladder, excluded the first and tenth deciles, and fitted a linear regression model to deciles 2 to 9, with SMR as the response variable and the mid-decile proportion of gallbladder-free individuals as the explanatory variable. Figure S1 illustrates this procedure for GBC.

3 | RESULTS

Figure 1A shows the age-standardised cholecystectomy rates in Chile from 2002 to 2018. After its minimum value in 2005, the

cholecystectomy rate increased from 172 surgeries per 100,000 person-years (pyrs) in 2006 to 317 operations per 100,000 pyrs in 2017, with a decrease in 2018 (blue curve). The interrupted time series model predicted an increase in cholecystectomy rates between 2019 and 2022 (red line with corresponding 95% confidence band).

Figure 1B shows cholecystectomy rates in women (higher) and men (lower). In women, 247 gallbladders were surgically removed

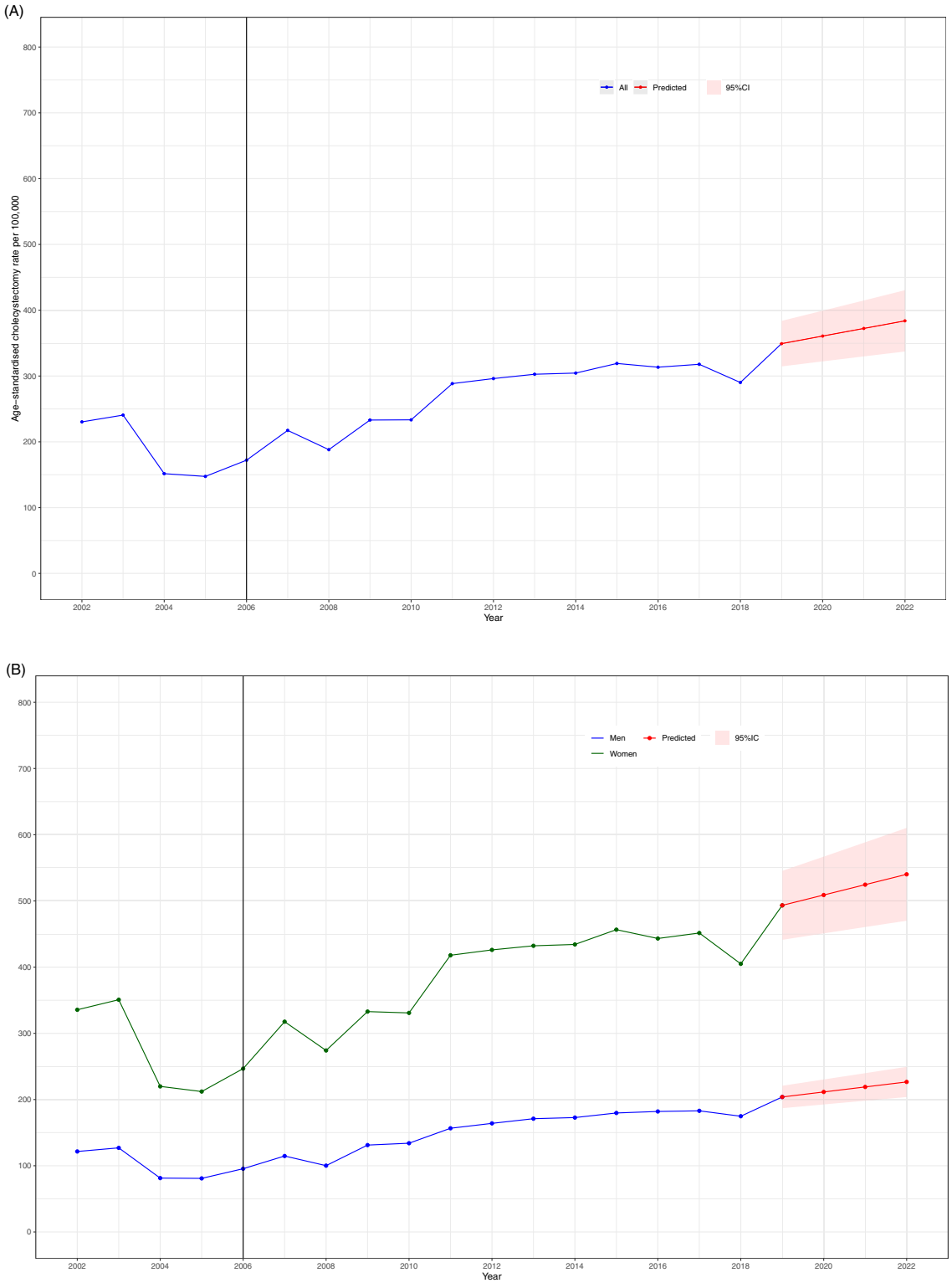

FIGURE 1 Age-standardized cholecystectomy and mortality rates per 1,00,000 persons in Chile from 2002 to 2022. [Color figure can be viewed at wileyonlinelibrary.com]

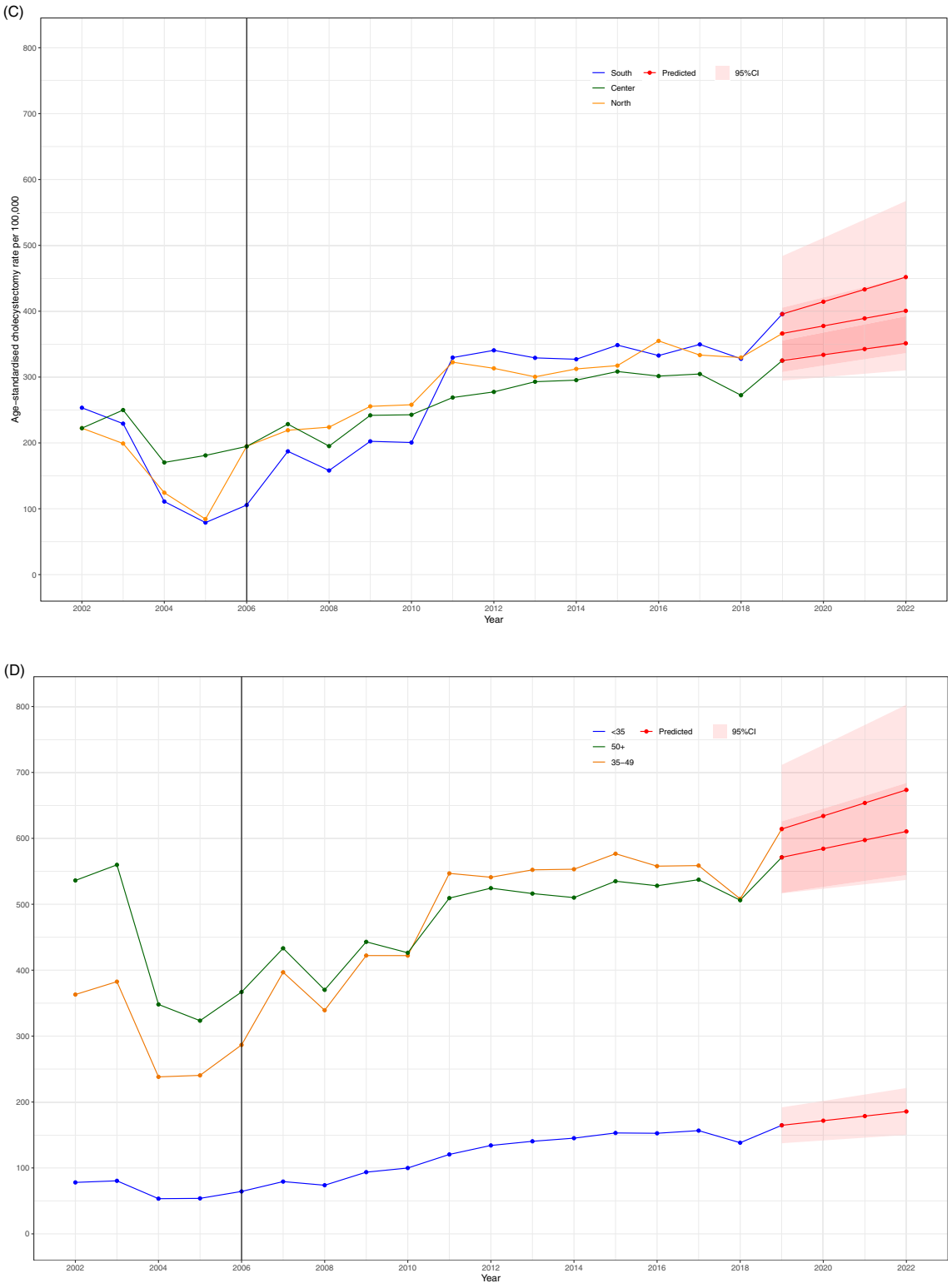

FIGURE 1 (Continued)

per 100,000 pyrs in 2006, and the cholecystectomy rate peaked (456 operations per 100,000 pyrs) in 2015. In men, 96 gallbladders were surgically removed per 100,000 pyrs in 2006, and the cholecystectomy rate peaked in 2017 (182 operations per 100,000 pyrs).

In the starting year of the GES-26 programme, the cholecystectomy rate was lower in southern Chile than in the central and northern regions (Figure 1C), but this situation was reversed after 2011. Stratified analyses by age group revealed an increase in cholecystectomy rates in all three age categories (under 35 years, 35–49 years

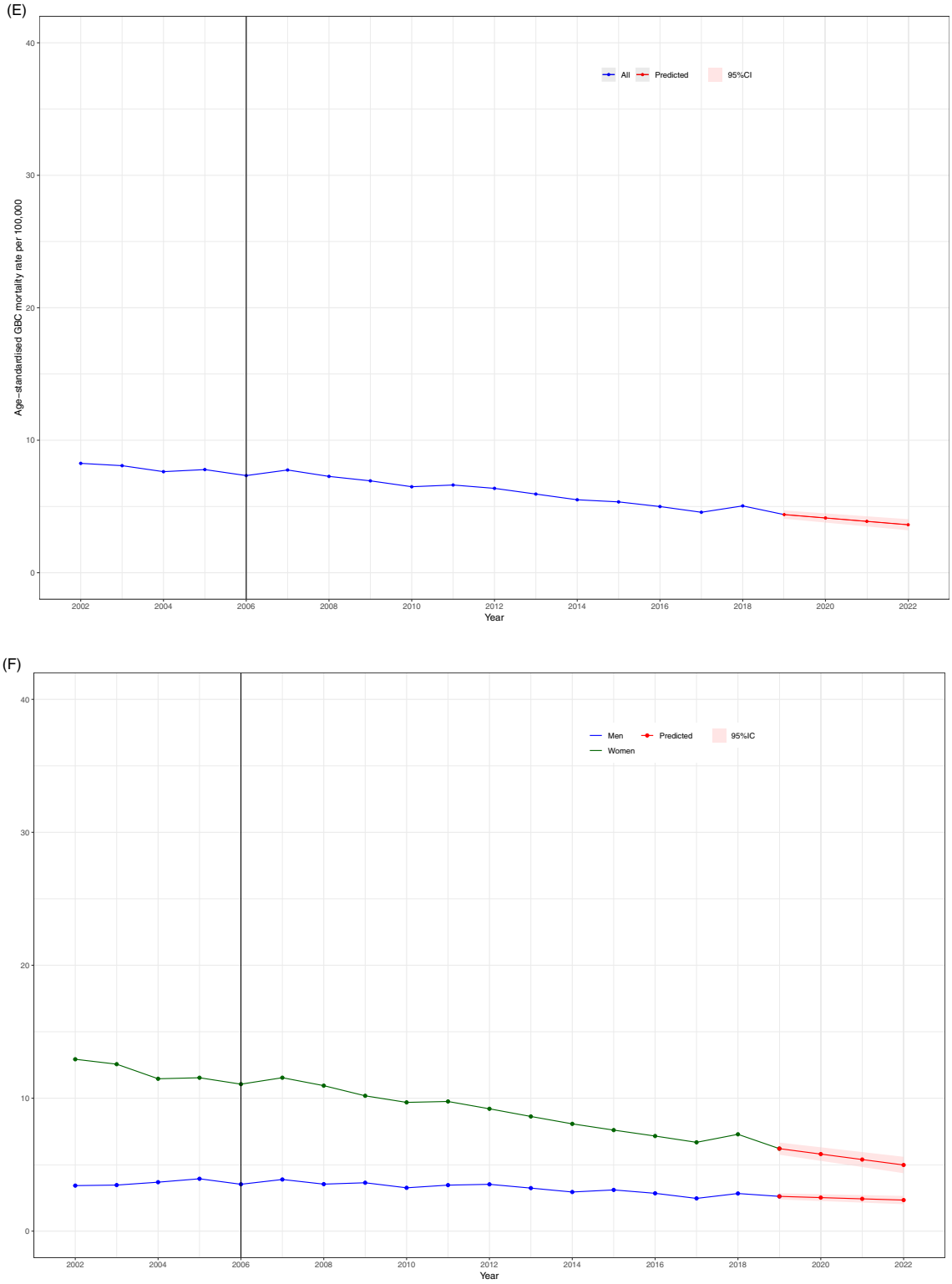

FIGURE 1 (Continued)

[age range considered by the GES-26 programme], and over 50 years, Figure 1D). Virtually no differences in cholecystectomy rates were observed between the 35–49 and over-50 age groups in 2018, but the interrupted time series model predicted a higher rate in the GES-26 age range than after age 50.

The age-standardised GBC mortality rate was declining prior to the implementation of the GES-26 programme, and continued to decline thereafter (Figure 1E): from 8.3 deaths in 2002 to 3.6 predicted deaths in 2022 per 100,000 pyrs. Analyses stratified by gender (Figure 1F) revealed a steeper decline in GBC mortality in women than

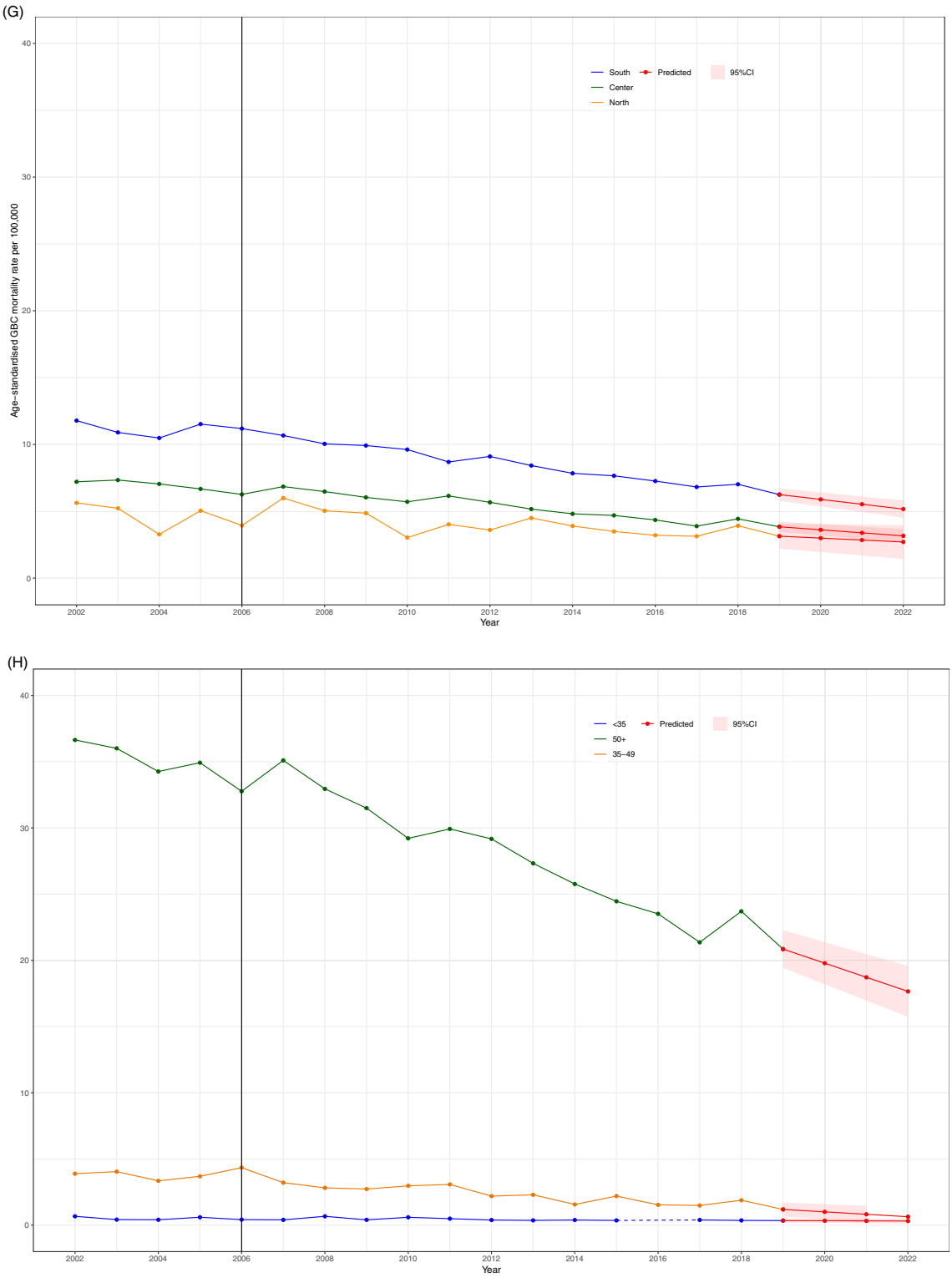

FIGURE 1 (Continued)

in men, and analyses stratified by region (Figure 1G) showed higher GBC mortality in southern, then central, and then northern Chile, with a somewhat steeper decline in GBC mortality in southern regions. As expected due to its age distribution, mortality due to GBC was notably higher, and declined particularly steeply, after age 50: from 37 deaths in 2002 to 24 deaths in 2018 per 100,000 pyrs (Figure 1H). In comparison, GBC mortality between 35 and 49 years of age decreased from 3.9 deaths in 2002 to 1.9 deaths in 2018 per 100,000 pyrs. The predicted standardised mortality due to GBC followed this downward trend for all age categories, for example,

TABLE 1 Cholecystectomy and gallbladder cancer mortality rates, standardised by age, gender and region based on an interrupted time series analysis.

Stratum	R^2	Year	95% CI		*p* value	Programme start	95% CI		*p* value	Programme impact	95% CI		*p* value	2010 earthquake	95% CI		*p* value
Cholecystectomy																	
All	0.85	**−33.78**	−60.06	−7.50	0.02	45.61	−15.24	106.47	0.13	**45.33**	18.69	71.98	0.003	−11.79	−73.70	50.11	0.69
Men	0.90	**−16.76**	−29.62	−3.89	0.01	20.28	−9.51	50.07	0.16	**24.33**	11.29	37.37	0.002	−1.69	−31.99	28.61	0.91
Women	0.82	**−50.14**	−89.70	−10.57	0.02	70.13	−21.50	161.75	0.12	**65.76**	25.64	105.88	0.004	−21.80	−115.01	71.40	0.62
South[a]	0.71	**−51.80**	−94.50	−9.10	0.02	26.92	−66.96	120.80	0.54	**70.50**	23.42	117.59	0.01	−61.28	−132.56	10.00	0.09
North[a]	0.88	**−43.76**	−65.53	−21.99	0.0009	**109.31**	59.94	158.68	0.0004	**55.25**	31.76	78.74	0.0003	−25.99	−65.34	13.35	0.18
Centre	0.79	−20.37	−43.55	2.81	0.08	27.01	−26.66	80.68	0.29	**29.13**	5.63	52.63	0.02	−3.42	−58.02	51.17	0.89
<35 years[a]	0.67	−6.87	−19.60	5.85	0.26	7.18	−20.54	34.91	0.58	13.86	−0.25	27.97	0.05	−6.68	−27.50	14.14	0.50
35–49 years[a]	0.64	−35.55	−94.47	23.36	0.21	71.92	−63.63	207.48	0.27	**55.30**	−7.36	117.97	0.08	−49.04	−161.21	63.13	0.36
50+ years	0.77	**−84.99**	−126.49	−43.50	0.0008	73.42	−22.67	169.51	0.12	**98.09**	56.02	140.17	0.0003	−26.86	−124.60	70.89	0.56
Gallbladder cancer mortality																	
All	0.97	−0.19	−0.42	0.05	0.11	0.32	−0.23	0.86	0.23	−0.07	−0.31	0.17	0.54	−0.20	−0.76	0.35	0.44
Men	0.85	0.18	6.E-04	0.35	0.05	0.02	−0.38	0.43	0.90	**−0.27**	−0.45	−0.09	0.01	−0.19	−0.60	0.22	0.33
Women	0.98	**−0.53**	−0.87	−0.18	0.01	0.61	−0.19	1.42	0.12	0.12	−0.24	0.47	0.48	−0.21	−1.03	0.61	0.59
South	0.96	−0.12	−0.48	0.24	0.48	0.32	−0.51	1.15	0.42	−0.24	−0.61	0.12	0.17	0.12	−0.73	0.96	0.77
North	0.53	−0.37	−1.08	0.34	0.28	0.94	−0.72	2.59	0.24	0.22	−0.50	0.95	0.51	−1.41	−3.10	0.27	0.09
Centre	0.94	−0.19	−0.49	0.11	0.19	0.25	−0.44	0.94	0.44	−0.04	−0.34	0.26	0.78	−0.19	−0.88	0.51	0.57
<35 years	0.39	−0.02	−0.12	0.08	0.63	0.00	−0.23	0.23	0.98	0.01	−0.09	0.11	0.80	0.15	−0.08	0.39	0.17
35–49 years	0.85	−0.13	−0.52	0.27	0.49	0.21	−0.70	1.13	0.62	−0.05	−0.46	0.35	0.77	0.13	−0.80	1.06	0.77
50+ years	0.96	−0.69	−1.77	0.39	0.19	1.34	−1.17	3.85	0.27	−0.38	−1.47	0.72	0.47	−1.22	−3.78	1.33	0.32

Note: The "Year" column shows the rate trend prior to the cholecystectomy programme. "Programme start" shows the estimated immediate effect of the programme. "Programme impact" shows the long-term impact of the programme, and "2010 earthquake" the effect of the Chilean earthquake in 2010. 2010 Earthquake: Effect of the 2010 earthquake in the south-central zone of Chile.

Abbreviations: CI, confidence interval; *p* value, probability value; programme start, immediate effect after the start of the cholecystectomy programme in 2006; programme impact, annual effect of the programme after its start; R^2, coefficient of determination, year, calendar year from 2002 to 2018.

[a]Autocorrelation was detected using the Durbin Watson test (*p* value <0.05), and Prais–Winsten first-order autocorrelation regression was performed to estimate the coefficients and 95%CIs. Bold type indicates *p* values <0.05.

17 predicted deaths in 2022 (95% CI 15 to 19) per 100,000 pyrs in the 50+ age group.

Table 1 shows the results of the interrupted time series analysis of cholecystectomy and GBC mortality rates. Consistent with Figure 1, prior to the implementation of GES-26, the nationwide cholecystectomy rate was decreasing by 34 interventions (95%CI 7.5 to 60). In 2006 (start of the GES-26 programme), an immediate increase in the cholecystectomy rate was only noticed in the north of Chile (109 operations per 100.000 pyrs, p value $= 4 \times 10^{-4}$).

In contrast, the long-term effect of the GES-26 programme (Programme impact) was clear in most subgroup analyses. Nationwide, the cholecystectomy rate increased by 45 surgeries per 100,000 persons per year (95%CI 19–72). In women, this increase was 66 operations, compared to 24 surgeries per 100,000 pyrs in men, but the difference did not reach the 5% level of statistical significance (overlapping 95%CIs). Consistent with Figure 1C, the long-term effect of the GES-26 programme was greatest in the southern regions (70.5 operations), then in the north (55 surgeries), and then in the central regions of Chile (29 interventions per 100,000 pyrs, 95% CIs overlap). Interestingly, stratified analyses by age group revealed a larger long-term effect of the programme after age 50 (98 operations) than between 35 and 49 (55 operations per 100,000 pyrs). We also investigated the effect of the 2010 earthquake, which particularly affected the central-southern regions of Chile, but did not detect any impact.

As depicted in Figure 1E, GBC mortality was decreasing in Chile before the implementation of GES-26, resulting in an annual decrease estimated by the interrupted time series model of 0.19 deaths (95%CI −0.42 to 0.05) per 100,000 pyrs. The GES-26 programme did not show an immediate effect on overall GBC mortality, but did show a long-term effect in men: reduction of 0.27 deaths (95%CI 0.09–0.45) per 100,000 pyrs.

Categorisation of the hospitalisation and mortality databases by age (eight age intervals), gender (2 levels), region (North, Central and South) and calendar-year (2016–2018, to be able to calculate the change in the proportion of individuals without gallbladder since 10 years) resulted in 144 categories. These categories were grouped into quartiles (Q1: change in the proportion of individuals without gallbladder since 10 years below 18%; Q2: 18%–34%; Q3: 35%–55%; Q4: more than 55%, Table 2). Note that in Chile (estimated population 19.7 million) approximately 50,000 gallbladders are surgically removed each year, resulting in a significant proportion of the population without the gallbladder.

The number of GBC deaths in Q1 was 176 compared to 405 deaths in Q2, resulting in a standardised mortality ratio (SMR) of 0.76 (95% 0.73 to 0.80), indicating a 1–0.76 = 0.24% lower GBC mortality risk in Q2 than in Q1. The corresponding SMR was 0.61 (95%CI 0.58 to 0.65) for Q3 vs. Q1, and 0.55 (95%CI 0.52 to 0.59) for Q4 vs. Q1. This trend of reduced mortality risk (24%, 39% and 45%) suggests that an increasing proportion of gallbladder-free individuals translates into lower GBC mortality.

To estimate the reduction in GBC mortality for each 1% increase in the proportion of individuals without gallbladder since 10 years, we also grouped the age, gender, region and calendar-year categories

TABLE 2 Number of GBC deaths (n_1–n_4) and standardised GBC mortality ratios (SMR) as a function of the change in the proportion of individuals without gallbladder since 10 years.

	n_1	n_2	SMR		n_3	SMR		n_4	SMR				
Stratum	<18%	18%–34%	18%–34% vs. <18%	95% CI	35%–55%	35%–55% vs. <18%	95% CI	>55%	>55% vs. <18%	95% CI		per 1%	95% CI
All	176	405	0.76	0.73 0.80	798	0.61	0.58 0.65	662	0.55	0.52 0.59		**−0.73**	−1.07 −0.38
Men	119	288	0.80	0.71 0.89	156	0.96	0.86 1.07	13	0.68	0.60 0.76		−0.23	−0.57 0.10
Women	57	117	0.75	0.71 0.80	642	0.53	0.49 0.56	649	0.52	0.49 0.56		**−0.55**	−0.71 −0.36
South	128	176	0.88	0.80 0.97	245	0.79	0.72 0.87	185	0.55	0.49 0.61		**−0.76**	−0.97 −0.50
North	14	21	1.56	1.12 2.17	34	2.29	1.68 3.11	59	2.26	1.66 3.08		0.67	−0.02 1.35
Centre	34	208	1.21	1.07 1.36	519	2.45	2.21 2.72	418	2.06	1.85 2.29		**1.74**	1.06 2.48
50–59 years	30	72	0.42	0.37 0.47	86	0.40	0.30 0.40	184	0.32	0.28 0.36		−0.09	−0.18 0.00
60–69 years	73	167	0.70	0.65 0.76	296	0.60	0.60 0.70	224	0.47	0.42 0.51		**−1.03**	−1.17 −0.86
70–80 years	53	157	1.03	0.94 1.12	379	0.70	0.70 0.80	234	0.86	0.78 0.94		**−0.50**	−0.75 −0.26

Note: n_1: Number of gallbladder cancer deaths in the age, gender, region and calendar-year categories of the mortality database with a change in the proportion of individuals without gallbladder since 10 years of <18% (first quartile), n_2, n_3, n_4: Number of deaths corresponding to the second, third and fourth quartiles, respectively. SMR per 1%: Change in GBC mortality for every 1% increase in the proportion of individuals without gallbladder since 10 years. Bold type indicates the 95%CI for the SMR per 1% does not include zero.

TABLE 3 Number of deaths due to several types of digestive cancer (n_1–n_4) and standardised mortality ratios (SMR) as a function of the change in the proportion of individuals without gallbladder since 10 years.

Cancer site	n_1 <18%	n_2 18%–34%	SMR 18%–34% vs. <18%	95% CI		n_3 35%–55%	SMR 35%–55% vs. <18%	95% CI		n_4 >55%	SMR >55% vs. <18%	95% CI		SMR per 1%	95% CI	
Oesophagus	137	305	0.54	0.50	0.59	243	0.39	0.35	0.43	115	0.38	0.35	0.42	**−0.74**	−0.87	−0.59
Stomach	821	1787	0.91	0.88	0.95	1385	0.80	0.77	0.84	657	0.72	0.69	0.75	**−0.19**	−0.27	−0.10
Colon	299	748	1.29	1.21	1.36	920	1.31	1.24	1.39	583	1.25	1.18	1.33	0.10	−0.11	0.30
Liver	97	273	0.99	0.89	1.10	263	1.03	0.93	1.14	140	0.99	0.89	1.10	**−1.32**	−1.54	−1.09
Intrahepatic bile duct	41	105	1.18	1.02	1.37	144	1.25	1.08	1.45	89	0.65	0.55	0.78	−0.25	−0.63	0.13
Extrahepatic bile duct	52	131	0.85	0.76	0.95	177	0.60	0.53	0.68	111	0.52	0.45	0.59	**−1.53**	−1.94	−1.13
Pancreas	226	622	1.08	1.01	1.15	800	1.24	1.16	1.32	549	1.09	1.02	1.16	−0.02	−0.22	0.16
All sites (excl. GBC)	4054	10,727	1.03	1.02	1.05	12,248	1.05	1.04	1.07	7612	1.01	0.99	1.02	**−0.37**	−0.41	−0.33

Note: n_1: Number of cancer deaths in the age, gender, region and calendar-year categories of the mortality database with a change in the proportion of individuals without gallbladder since 10 years of <18% (first quartile). n_2, n_3, n_4: Corresponding number of deaths for the second, third and fourth quartiles, respectively. SMR per 1%: Change in GBC mortality for every 1% increase in the proportion of individuals without gallbladder since 10 years. excl. GBC: Excluding gallbladder cancer. Bold type indicates the 95%CI for the SMR per 1% does not include zero.

from the mortality database into deciles according to the change in the proportion of individuals without gallbladder, excluded the first and tenth decile, and fitted a linear regression model to deciles 2 to 9 (Figure S1). The three rightmost columns of Table 2 indicate that each 1% increase in the proportion of individuals without gallbladder since 10 years correlates with a 0.73% reduction in GBC mortality (95%CI −1.05% to −0.38%).

Analyses stratified by gender revealed a larger reduction in GBC mortality with increasing changes in the proportion of individuals without gallbladder in women (0.55% reduction in GBC mortality for every 1% increase in the proportion of women without gallbladder) than in men (23% risk reduction and the 95%CI included zero). Analyses stratified by region showed that the negative association was limited to the south of Chile (0.76% GBC mortality reduction), while there was a positive trend in the northern regions, and a positive association in the centre of the country. Analyses stratified by age-group revealed the strongest negative correlation for individuals aged 60–69 years (1.03% reduction in GBC mortality for every 1% increase in the proportion of gallbladder-free individuals).

Table 3 shows the SMR for various types of digestive cancer as a function of the change in the proportion of individuals without gallbladder since 10 years. The SMRs for oesophageal cancer were 0.54 for Q2 vs. Q1, 0.39 for Q3 vs. Q1, and 0.38 for Q4 vs. Q1, suggesting that an increasing proportion of individuals without gallbladder is also associated with a decreasing mortality from oesophageal cancer. Each 1% increase in the proportion of gallbladder-free individuals correlated with a 0.74% reduction in oesophageal cancer mortality (95%CI 0.59% to 0.87%).

The relationship between the change in the proportion of individuals without gallbladder and mortality was weaker for stomach cancer: 0.19% mortality reduction (95%CI 0.10% to 0.27%) for every 1% increase in the proportion of gallbladder-free individuals. Colon cancer mortality increased with increasing proportion of individuals without gallbladder, but this increase did not reach the 5% level of statistical significance (the 95%CI included zero).

The association between the proportion of gallbladder-free individuals and mortality was stronger for extrahepatic bile duct cancer (1.53% reduction) and liver cancer (1.32% reduction). No association was found between the proportion of gallbladder-free individuals and mortality from intrahepatic cholangiocarcinoma or pancreatic cancer. For every 1% increase in the proportion of individuals without gallbladder since 10 years, the overall cancer (excluding GBC) mortality rate decreased by 0.37% (95%CI 0.33% to 0.41%).

4 | DISCUSSION

The present study takes advantage of the implementation in 2006 of a Chilean health programme that guarantees access to cholecystectomy for patients with gallstone disease aged 35–49 years (GES-26) to investigate the association between cholecystectomy and mortality rates from GBC and other digestive cancers. We applied two complementary approaches: an interrupted time series analysis and an

aggregated-data analysis of the correlation between cancer mortality rates and the change in the proportion of individuals without gallbladder since 10 years. An increase in the proportion of individuals without gallbladder was associated with a decrease in GBC mortality, but the negative correlation was limited to (1) women and (2) southern Chile. Mortality rates from extrahepatic bile duct, liver, oesophageal and gastric cancers also decreased with increasing proportions of individuals without gallbladder.

In a previous study, Mardones and Frenz evaluated the Chilean cholecystectomy programme between 2002 and 2014 by comparing hospitalisations for biliary pathologies (ICD10: K80-K83) and mortality due to biliary cancer (ICD10: C23 and C24).[19] We considered a longer time period (until 2018), restricted our analyses to hospitalisations for cholecystectomy, examined GBC and bile duct cancer separately, and accounted for time trends in the data through interrupted time series analyses. An interrupted time series analysis with few observations before the intervention (only 4 years before programme implementation) may have low statistical power to detect intervention effects,[20–23] but we also performed the analyses considering months instead of years (taking into account the autocorrelation between observations) and results were practically identical (data not shown). The downward trend in GBC mortality before implementation of the programme, the limited time of follow-up (the average age at GBC diagnosis in Chile is 75 years, but 35–49 year old beneficiaries of the health programme in 2006 were 52–66 years old in 2018), and potential confounding factors (e.g., poverty in Chile has been decreasing since 2002 and may be a risk factor for GBC mortality) may lead to low statistical power of the interrupted time series analysis, which prompted us to apply a more sophisticated approach using aggregated data.

In a more recent study, Cid et al. examined the magnitude and trends of GBC mortality in Chile to indirectly assess the impact of the cholecystectomy programme on GBC mortality.[24] Our approach differed markedly: we considered cholecystectomy in addition to mortality rates, and investigated the relationship between cholecystectomy and mortality rates using SMRs of GBC and other digestive cancers as a function of the change in the proportion of individuals without gallbladder. To examine trends in SMR with increasing proportions of gallbladder-free individuals, we classified the age, gender, region and calendar-year groups of individual into quartiles and, to estimate the SMR per 1% increase in the proportion of individuals without gallbladder since 10 years, we classified the groups of individuals into deciles. This approach may have greater statistical power than interrupted time series analyses due to the higher granularity of the data, but results may be more strongly affected by the ecological study biases—the results identified for groups of individuals may not be true for individuals (ecological fallacy). We hope that publication of the present results will motivate the responsible teams at the Chilean Ministry of Health to timely release anonymised longitudinal data at the individual level to reduce the potential impact of ecological bias on the results of future studies.

When examining the relationship between the SMR and the change in the proportion of gallbladder-free individuals, the negative trend was evident for GBC: SMR of 0.76 for Q2 vs. Q2, 0.61 for Q3 vs. Q1, and 0.55 for Q4 vs. Q1. We also investigated in sensitivity analyses the association between GBC mortality and the proportion of individuals without gallbladder since 5 years, but did not observe any trend overall (Table S1), suggesting that the association becomes stronger with increasing time without gallbladder. However, the onset of the Covid19 pandemic in 2019 limits the possibility to considering periods longer than 10 years (e.g., considering 12 years without gallbladder limits the analysis to the 2006–2018 cohort, and the present 10-year analyses considered the 2006–2016, 2007–2017 and 2008–2018 cohorts). Using a very different assessment approach, our results were generally consistent with the findings of Cid et al. For example, we observed the strongest negative correlation between the proportion of gallbladder-free individuals and GBC mortality in the 60–69 age group, and Cid et al. reported that cohorts with more years of programme coverage tended to have a greater decline in GBC mortality than would be expected from the mortality decline in earlier cohorts.

Cholecystectomy alters the reflux of bile into the digestive tract, and it has been shown that patients who have undergone cholecystectomy have a greater bile reflux during fasting periods.[25–27] This could be related to more inflammation of the digestive mucosa and more frequent occurrence of biliary gastritis, which are considered risk factors for cancer development.[28] However, we found that mortality from cancers of extrahepatic biliary duct, liver, oesophagus and stomach decreased with increasing changes in the proportion of individuals without gallbladder and, interestingly, overall cancer (excluding GBC) mortality decreased by 0.37% for every 1% increase in the proportion of individuals without gallbladder over 10 years. In agreement with previous publications, colon cancer mortality increased with increasing proportion of gallbladder-free individuals, but without reaching the 5% level of statistical significance.[29,30]

The biliary system consist of the liver, the gallbladder and intrahepatic and extrahepatic bile ducts, which have a common embryonic origin and the same epithelium, and are responsible for the production, storage and secretion of bile.[31] Gallstones can cause chronic inflammation of the epithelium and have been identified as a major risk factor for biliary cancer,[32,33] and we found a strong decrease in mortality from extrahepatic cholangiocarcinoma and liver cancer with increasing proportions of cholecystectomised individuals. Interestingly, sensitivity analyses of the association between cancer mortality and the proportion of individuals without gallbladder since 5 years confirmed the strong impact of cholecystectomy on mortality from liver cancer, followed by oesophageal, extrahepatic bile duct, and gastric cancers (Table S2). The results for gallbladder cancer and extrahepatic cholangiocarcinoma (stronger mortality reduction for 10 years than for 5 years without gallbladder) are consistent with those of a Korean retrospective study, which reported a lower risk of biliary system cancer with increasing time after cholecystectomy.[34] Removal of the gallbladder in patients with gallstone disease reduces the risk of biliary pancreatitis, but we found no association between mortality from pancreatic cancer and the proportion of gallbladder-free individuals.

We noticed that the mortality from oesophageal cancer decreased with increasing proportions of individuals without gallbladder since 10 and even 5 years. The literature on the association between cholecystectomy and oesophageal cancer is contradictory: most studies report no association, but one Japanese study found a trend towards protection.[35] The negative correlation identified in the present study may be due to obesity, an important risk factor for oesophageal cancer, which is mechanistically related to greater reflux from the stomach into the oesophagus and chronic inflammation in obese individuals,[36] who also have an increased risk of gallstone disease.[37] Future mediation and Mendelian randomisation studies could help to distinguish between statistical correlation due to confounding and a potential causal effect of gallstones and/or cholecystectomy on the risk of oesophageal cancer.[17,18]

In conclusion, the present results, if validated in future studies based on individual-level longitudinal data, provide important evidence to optimise the use of cholecystectomy for cancer prevention in regions with high prevalence of GBC and other digestive tract cancers. We found that every 1% increase in the proportion of individuals without gallbladder since 10 years was associated with a 0.73% decrease in GBC mortality, but this negative correlation was restricted to women and to the South of Chile, giving important clues for the personalisation of prophylactic cholecystectomy. The effect of cholecystectomy on mortality from digestive cancers other than GBC probably depends on regional epidemiological and genetic characteristics. For example, in addition to the established associations with extrahepatic cholangiocarcinoma, we found that mortality from liver, oesophageal and gastric cancer decreased with increasing proportions of Chileans without gallbladder since 10 years.

AUTHOR CONTRIBUTIONS

Constanza Gonzalez: Conceptualization; formal analysis; methodology; visualization; writing – original draft. **Alfonso García-Pérez:** Conceptualization; methodology; writing – review and editing. **Bruno Nervi:** Resources; writing – review and editing. **César Munoz:** Resources; writing – review and editing. **Erik Morales:** Resources; writing – review and editing. **Hector Losada:** Resources; writing – review and editing. **Gina Merino-Pereira:** Resources; writing – review and editing. **Francisco Rothhammer:** Resources; writing – review and editing. **Justo Lorenzo Bermejo:** Conceptualization; funding acquisition; methodology; resources; supervision; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was based on anonymised, publicly available data, and ethical review was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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