



Gallbladder cancer mortality in Chile: has the government program targeting young gallstone patients had an impact?

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Introduction

Chile has among the highest rates of gallbladder cancer (GBC) mortality worldwide.¹ Gallstones are strong risk factors for GBC. On pathological review, 2%-4% of the gallbladders with gallstones removed via cholecystectomy in Chile have been found to have cancer.^{2,3}

In July 2005, Chile reformed its universal health plan through a benefits package called Universal Access with Explicit Guarantees (Acceso Universal con Garantías Explícitas, or AUGE).^{4,5} The AUGE benefits package focuses on priority health problems, including cholecystectomy for the prevention of GBC. AUGE prioritizes cholecystectomy among individuals aged 35-49 with gallstones, including some without symptoms.⁶ Although this approach might effectively eliminate risk of developing GBC in young individuals, it could lead to delayed treatment of older patients at higher GBC risk and overtreatment of patients at low risk.

While mortality from cholecystectomy is low (0%-0.6%),^{7,8} complications (bile duct injury, biliary leak, postoperative bleeding, and wound infection) occur in 5% of patients, and bile duct damage occurs in approximately 1/200 patients.⁷ In addition, cholecystectomy has been associated with increased risk of gastrointestinal cancers⁹ and fatty liver disease,¹⁰ bringing into question the long-term consequences of preferentially cholecystectomizing young individuals, particularly those without symptoms from gallstones.

We analyzed the magnitude and trends in GBC mortality in Chile as an indirect assessment of the potential impact of the AUGE program on GBC mortality.

Methods

We accessed publicly available data from 1990-2021 through the Chilean Ministry of Health mortality database.¹¹ Given concerns over data accuracy during the SARS-CoV-2 pandemic, we excluded 2020-2021. Ethical review was not required as anonymized data are publicly available. We conducted a descriptive analysis to indirectly evaluate how the AUGE program might have affected GBC mortality.

For each year of the study period, we identified individuals who died from GBC using *International Classification of Diseases, Tenth Revision*, code C23. Cause-specific mortality was calculated by sex and age group. Crude and age-adjusted mortality rates per 100 000 were plotted by year using a 3-year moving average. We conducted joinpoint analysis to examine trends over time and calculate annual percent change (APC) and 95% confidence intervals (CIs) by sex and age group in 1992-2019, projecting populations using the 2017 population census, the best data available. We investigated trends among those aged 35-49 years (ages covered by the AUGE program beginning in July 2005), 50-59 years (individuals aged 37-47 in July 2005 would be 50-59 by the end of 2019), and ≥60 years (most of whom would not have been covered by AUGE).

For women, where the number of cases was larger, we evaluated mortality rates by approximately 5-year age group from ages 30-79 years for the 1946-1950, 1951-1956, 1957-1961, 1962-1968, 1969-1974, and 1975-1980 birth cohorts. The 1946-1950 and 1951-1956 birth cohorts were not covered by the AUGE program; 1957-1961 was partially covered, and 1962-1968, 1969-1974, and 1975-1980 were covered for 5-15 years.

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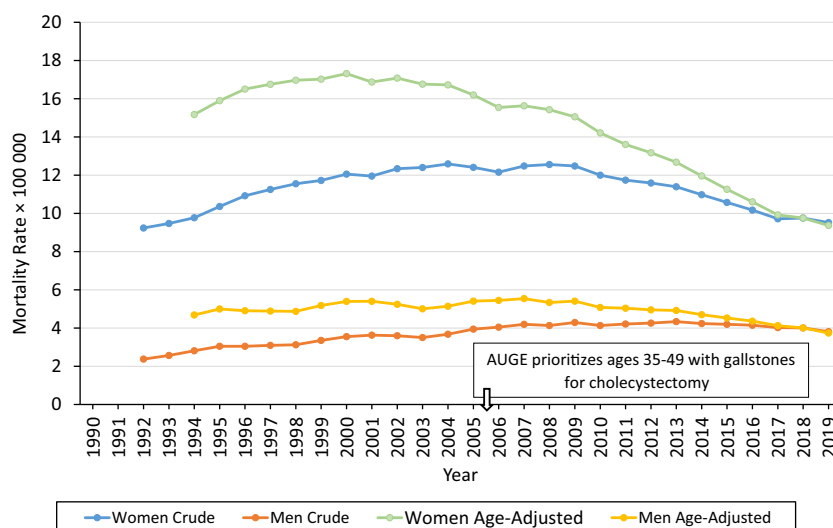


Figure 1. Crude and age-adjusted mortality rates using a 3-year moving average for gallbladder cancer among men and women in Chile, 1990-2019. Acceso Universal con Garantías Explícitas (AUGE) guidelines recommend that women aged 40 be given a questionnaire to assess risk factors (history of biliary colic, history of gallstones, multiparity, education < 8 years, body mass index of > 27, aboriginal ethnicity). If positive, they should be referred for ultrasound and to cholecystectomy if the ultrasound revealed gallstones of ≥ 3 cm, volume of gallstones of > 10 mL, or polyps of ≥ 1 cm. Otherwise, men or women aged 35-49 years with symptomatic gallstones should be referred for cholecystectomy.

Since GBC mortality has been declining for some time, we needed to understand whether AUGE led to a more-recent acceleration in the declining mortality rate. Thus, we first estimated the expected rate by approximately 5-year age groups based on the mortality rate experienced by the 2 previous 5-year age cohorts. For example, for age group 40-44 years we calculated the ratio of mortality rates for the 1951-1956 vs 1946-1950 cohorts and multiplied the number of GBC deaths observed in the 1946-1950 cohort by that ratio to determine the expected number of cases for age group 40-44 years in the 1957-1961 cohort. We then divided the observed rate of GBC deaths by the expected rate to determine whether the observed number was higher or lower than expected based on the difference in mortality rates in the previous two cohorts.

We hypothesized that if AUGE reduced GBC mortality, the relative risk (RR) of observed-to-expected mortality rates would be lower among AUGE-eligible individuals compared with those not covered by AUGE.

Results

As expected, the GBC mortality rates were highest in women (Figure 1). In women aged 35-49 years, the mortality rate decreased in 1992-2007 (APC = -1.5% ; 95% CI, -2.7 to -0.1) and then decreased more sharply in 2007-2019 (APC = -8.9% ; 95% CI, -10.8 to -7.5) (Figure 2A). In women aged 50-59 years, the rate increased in 1992-1999 (APC = 4.8% ; 95% CI, 3.2 - 7.1), decreased in 1999-2010 (APC = -3.4% ; 95% CI, -4.3 to -1.7), and decreased more steeply in 2010-2019 (APC = -6.0% ; 95% CI, -9.0 to -5.0) (Figure 2B). In women aged ≥ 60 years, the rate increased in 1992-1997 (APC = 3.4% ; 95% CI, 1.7 - 7.0), plateaued (APC = -0.7% ; 95% CI, -1.6 to 0.0), and then decreased in 2007-2019 (APC = -4.1% ; 95% CI, -4.7 to -3.6) (Figure 2C).

In men aged 35-49 years, GBC mortality increased in 1992-1996 (APC = 21.7% ; 95% CI, 6.7 - 64.7), plateaued (APC = -2.0% ; 95% CI, -4.9 to 0.8), and then decreased in 2011-2019 (APC = -12.7% ; 95% CI; -25.8 to -8.3) (Figure 2D). In men aged 50-59 years, the

rate was stable in 1992-2013 (APC = -0.7% ; 95% CI, -1.7 to 14.9) and decreased in 2013-2019 (APC = -6.9% ; 95% CI, -28.0 to -1.6) (Figure 2E). In men aged ≥ 60 years, the rate increased until 2007 (APC = 1.5% ; 95% CI, 0.9 - 2.2) and then decreased (APC = -3.0% ; 95% CI, -4.1 to -2.2) (Figure 2F).

Among women, cohorts born before 1957 were not covered by AUGE, so age-specific mortality rates decreased due to secular trend rather than AUGE (Table S1). Comparing observed with expected rates, women aged < 49 years in the 1957-1961 cohort (partially covered by AUGE) had higher than expected rates based on the secular trend (RR = 1.44; 95% CI, 1.11-1.85 for women aged 40-44 years; and RR = 1.29; 95% CI, 1.08-1.55 for those aged 45-49 years). However, those 40-44 years in the 1969-1974 and 1975-1980 cohorts, in which almost everyone had at least some AUGE coverage, tended to have lower than expected rates (RR = 0.58; 95% CI: 0.44-0.76, and RR = 0.82; 95% CI, 0.43-1.54, respectively). In the 1962-1968 cohort, those aged 45-49 years and 50-54 years, who had substantial AUGE coverage, also tended to have lower than expected mortality rates (RR = 0.74[95% CI, 0.63-0.86] and RR = 0.88[95% CI, 0.77-1.02], respectively).

Discussion

The age-specific mortality rates for GBC began dropping in Chile prior to the introduction of AUGE in July 2005. The rates declined more rapidly in women aged 35-59 years in 2007-2010, consistent with the hypothesis that the introduction of AUGE contributed to a greater decrease in mortality. In 35-59-year-old men, rates dropped from 2011-2013, potentially reflecting a slower uptake in men. Rates also declined in men and women aged ≥ 60 years in 2007, potentially reflecting public health interventions to control typhoid fever in the mid-1980s and 1990s.^{12,13} Younger female cohorts with more years of AUGE coverage tended to have larger drops in GBC mortality than expected based on the decrease in mortality observed in prior cohorts. This post-AUGE reduction in observed rates suggests that prioritizing individuals aged 35-49

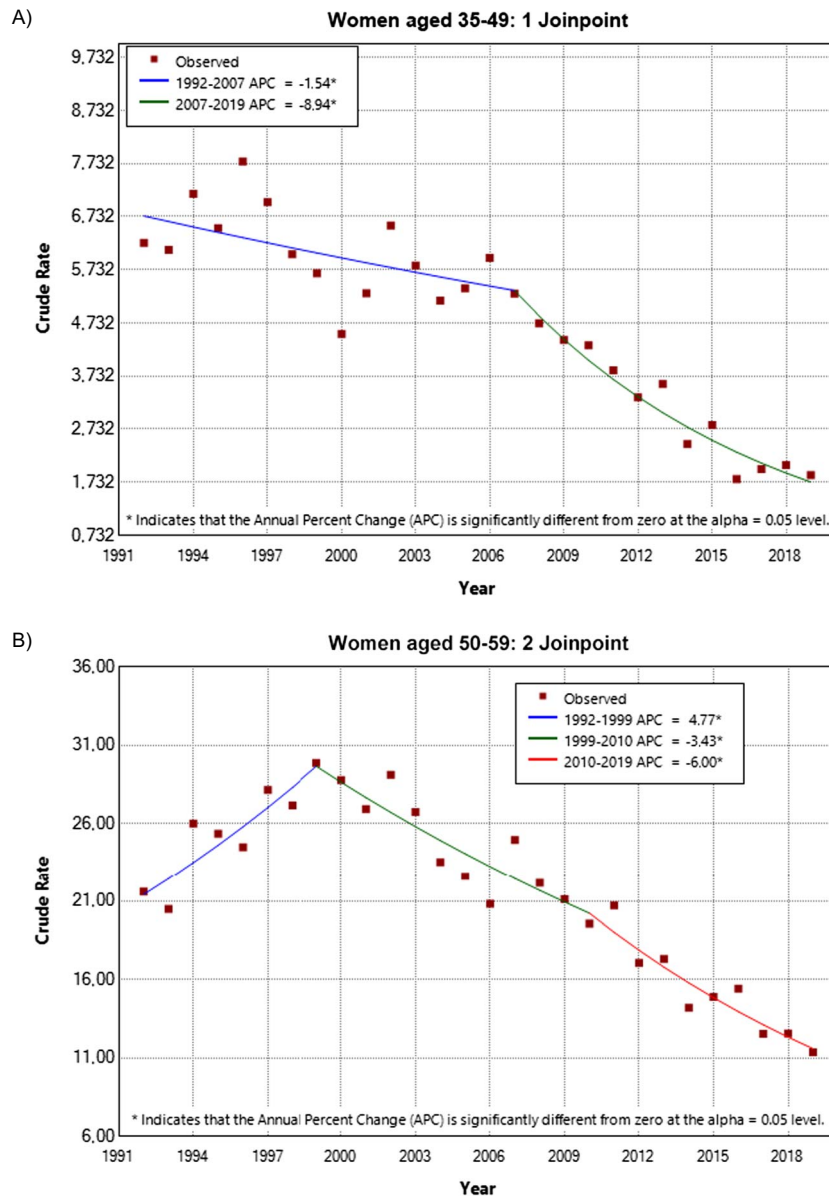


Figure 2. Continues

years with gallstones for cholecystectomy might have contributed to a faster decline in GBC mortality.

This finding is consistent with previous reports from Chile (2002-2014) and Australia (1982-2018), suggesting that prioritizing younger individuals can reduce GBC incidence and mortality.^{14,15} This strategy might be effective because it removes the gallbladder before the average age of cancer invasion. If true, the effect will become more pronounced as cohorts reach peak ages for GBC incidence, while primary prevention measures to reduce gallstone incidence (eg, decreasing obesity, improving metabolic and inflammatory conditions, controlling chronic infections) might take decades to have an effect. However, primary prevention approaches are important to consider since surgery is not without risk, and prioritizing younger individuals for cholecystectomy extends the wait time for surgery among older individuals. Additionally, if living without a gallbladder increases the risk of other digestive cancers and fatty liver disease,^{9,10} cholecystectomy at younger ages lengthens the period of increased risk.

The reasons for the decline in GBC mortality prior to initiation of the AUGE program are unclear. One factor that is often proposed as an explanation is increasing cholecystectomy rates. However, hospital discharge data showed that cholecystectomy rates decreased in Chile through the 1980s and did not begin to increase until the 2000s,^{14,16,17} largely after the AUGE program began, in July 2005. In addition, GBC mortality rates decreased among women from an older birth cohort prior to the time when cholecystectomy rates began to increase. Thus, it seems unlikely that increasing cholecystectomy rates completely account for the decline in GBC mortality. Reductions in exposure to *Salmonella enterica* serovar Typhi might have contributed prior to the increase in cholecystectomies and AUGE.¹²

Administrative data have limitations, requiring cautious interpretation. For example, we assumed that GBC cases not covered by AUGE had lower access to surgery, while AUGE-eligible individuals had higher access. However, only individual-level data could confirm whether GBC cases not covered by AUGE had to wait longer

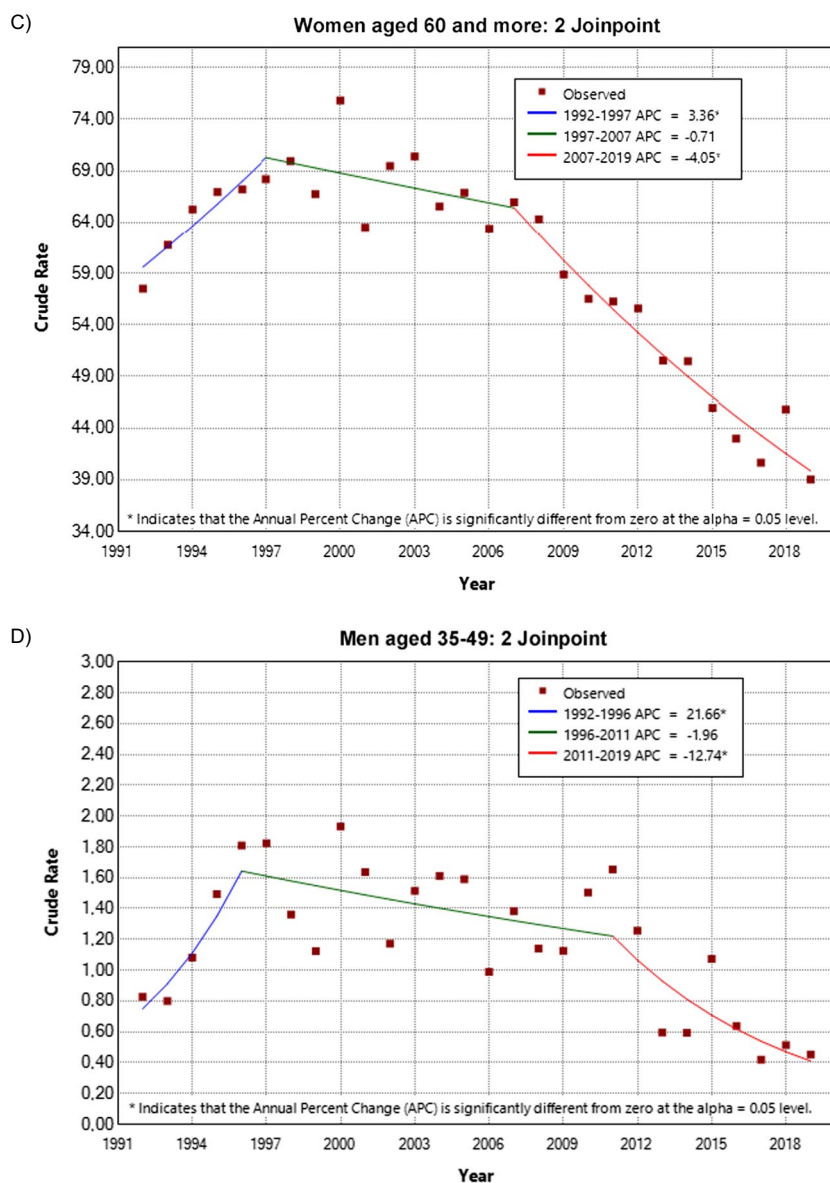


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for surgery than AUGE-eligible cases. In addition, it is possible that to facilitate programmatic evaluation the AUGE initiative led to more stringent criteria for diagnosis of GBC as opposed to other biliary tract cancers, potentially artificially reducing the rate of GBC, particularly in AUGE-covered ages.

This study also has strengths. We analyzed nearly 30 years of data. The Chilean Ministry of Health mortality database covers the entire country, allowing us to indirectly assess the potential impact of AUGE on GBC mortality in Chile.

We observed a strong decline in GBC mortality in Chile. Additional studies are needed to fully understand the reasons for this decline. However, the acceleration of the decline among age groups and cohorts covered by the AUGE program suggests that prioritizing younger individuals for surgery might have contributed.

Supplementary material

Supplementary material is available at *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

Data are publicly available through the Chilean Ministry of Health (MoH) mortality database (<https://deis.minsal.cl/>).

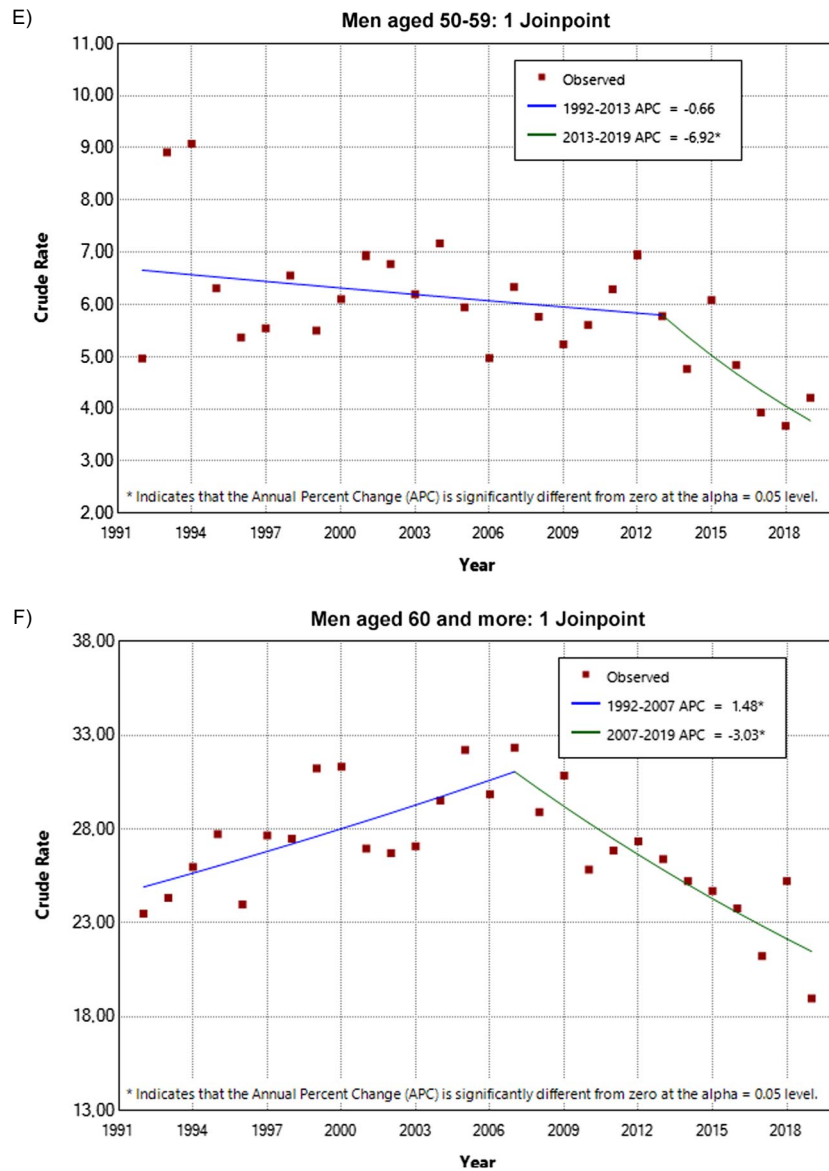


Figure 2. Joinpoint analysis of gallbladder cancer mortality in Chile, 1992-2019. A) Women aged 35-49 years, B) women aged 50-59 years, C) women aged 60 years or older, D) men aged 35-49 years, E) men aged 50-59 years, and F) men aged 60 years or older.

References

- Miranda-Filho A, Piñeros M, Ferreccio C, et al. Gallbladder and extrahepatic bile duct cancers in the Americas: incidence and mortality patterns and trends. *Int J Cancer*. 2020;147(4):978-989. <https://doi.org/10.1002/ijc.32863>
- Koshiol J, Bellolio E, Vivallo C, et al. Distribution of dysplasia and cancer in the gallbladder: an analysis from a high cancer-risk population. *Hum Pathol*. 2018;82:87-94. <https://doi.org/10.1016/j.humpath.2018.07.015>
- Roa I, de Aretxabala X, Araya JC, et al. Preneoplastic lesions in gallbladder cancer. *J Surg Oncol*. 2006;93(8):615-623. <https://doi.org/10.1002/jso.20527>
- Bitran R. *Explicit Health Guarantees for Chileans: The AUGE Benefits Package*. UNICO Studies Series. Washington DC: World Bank, 2013:i-30.
- Chilean Government. 10 years of AUGE: achievements, guarantees and how the health plan works. 2015. Accessed March 17, 2023. <https://www.gob.cl/en/news/10-years-of-auge-achievements-guarantees-and-how-the-health-plan-works/>
- Health Ministries, Chilean Government. *Clinical Guide: Preventive Cholecystectomy in Adults Between the Age of 35 and 49*. Clinical Guide Series 2010. Santiago, Chile: Chilean Government; 2010.
- Dooley JS. Gallstones and benign biliary diseases. In: Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ, eds. *Sherlock's Diseases of the Liver and Biliary System*. Hoboken, NJ: Blackwell Publishing Ltd., 2011:257-293. <https://doi.org/10.1002/9781444341294.ch12>
- Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver*. 2012;6(2):172-187. <https://doi.org/10.5009/gnl.2012.6.2.172>
- Nogueira L, Freedman ND, Engels EA, et al. Gallstones, cholecystectomy, and risk of digestive system cancers. *Am J Epidemiol*. 2014;179(6):731-739. <https://doi.org/10.1093/aje/kwt322>
- Ruhl CE, Everhart JE. Relationship of non-alcoholic fatty liver disease with cholecystectomy in the US population. *Am J Gastroenterol*. 2013;108(6):952-958. <https://doi.org/10.1038/ajg.2013.70>
- Departamento de Estadísticas e Información de Salud, División de Planificación Sanitaria, Subsecretaría de Salud Pública.

- Defunciones por Causa 1990—2020 CIFRAS OFICIALES. Accessed January 27, 2022. <https://deis.minsal.cl/#datosabiertos>
12. Ferreccio C. *Salmonella typhi* and gallbladder cancer. In: Khan AA, ed. *Bacteria and Cancer*. Dordrecht, the Netherlands: Springer; 2011:117-137.
 13. Marco C, Delgado I, Vargas C, et al. Typhoid fever in Chile 1969-2012: analysis of an epidemic and its control. *Am J Trop Med Hyg*. 2018;99(3 suppl):26-33. <https://doi.org/10.4269/ajtmh.18-0125>
 14. Mardones ML, Frenz P. Changes in gallbladder cancer mortality and hospital discharges due to preventive cholecystectomy in Chile. *Rev Med Chil*. 2019;147(7):860-869. <https://doi.org/10.4067/S0034-98872019000700860>
 15. Mollah T, Chia M, Wang LC, et al. Epidemiological trends of gallbladder cancer in Australia between 1982 to 2018: a population-based study utilizing the Australian cancer database. *Ann Hepatobiliary Pancreat Surg*. 2022;26(3):263-269. <https://doi.org/10.14701/ahbps.21-169>
 16. Chianale J, Valdivia G, del Pino G, et al. Gallbladder cancer mortality in Chile and its relation to cholecystectomy rates. An analysis of the last decade. *Rev Med Chil*. 1990;118(11):1284-1288.
 17. Serra I, Calvo A, Maturana M, et al. Biliary-tract cancer in Chile. *Int J Cancer*. 1990;46(6):965-971. <https://doi.org/10.1002/ijc.2910460603>