

Global and Regional Variation in the Cumulative Risk of Death from Cancer: Rethinking the Age of Initiation of Screening and Preventive Surgery

Constanza Fabiola Gonzalez Gonzalez

Heidelberg University

Rajiv Kumar

Heidelberg University

Bruno Nervi

Escuela de Medicina Pontificia Universidad Católica de Chile

César Muñoz

Hospital Regional de Talca

Erik Morales

Hospital Regional de Talca

Hector Losada

Universidad de la Frontera

Gina Merimo Pereira

Heidelberg University

Pamela Salina Alvarez

Laboratory of Biostatistics for Precision Oncology

Justo Lorenzo Bermejo

lorenzo@imbi.uni-heidelberg.de

Heidelberg University

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Abstract

Cancer is the second leading cause of death globally, and population-based screening plays a crucial role in early cancer detection, significantly improving clinical outcomes. The current European Union guidelines recommend initiation of screening for colorectal cancer (CRC), and for breast cancer (BC) in women, at age 50 years. In Chile, surgical removal of the gallbladder (cholecystectomy) is performed to prevent gallbladder cancer (GBC) in persons aged 35–49 years with symptomatic gallstones. However, the best age for starting CRC and BC screening, as well as for preventive cholecystectomy, may vary depending on sex, geographic region and over time.

We calculated the cumulative risks of death from cancer based on data from the Global Cancer Observatory (GLOBOCAN) and the Chilean Ministry of Health. The 10-year cumulative risks at age 50 of dying from CRC in the general European population, from BC in European women, or from GBC in Chilean women were used as thresholds to inform the optimal age for initiation of screening and preventive cholecystectomy.

The cumulative mortality risk thresholds were reached in many countries before the age of 50 years. Worldwide, men typically reached the threshold for cumulative CRC mortality risk of 0.2% at age 41, while women reached this threshold at age 46. In most African countries, women reached the threshold for cumulative BC mortality risk of 0.33% between the ages of 32 and 36. In Chile, substantial regional and temporal heterogeneity was observed: women reached the threshold for cumulative BC mortality of 0.33% between the ages of 46 and 70, and the threshold for cumulative GBC mortality risk of 0.11% between the ages of 38 and 56.

These findings suggest that cancer screening and prevention guidelines could benefit from adjusting the age of initiation to reflect variations by sex, geographic region and temporal trends. Such risk-adapted approaches could improve early cancer detection and help reduce cancer-related mortality.

Background

Cancer remains one of the leading causes of death worldwide among individuals aged 45 and older.¹ Population-based cancer screening is a cornerstone of cancer prevention, enabling early tumour detection and substantially improving treatment outcomes and survival. However, most current guidelines for cancer prevention have been developed primarily using data from populations of European descent. This reliance underscores the need for prevention strategies that better reflect global diversity in geographic, demographic, ethnic and genetic risk profiles.²

Colorectal cancer (CRC) is a malignancy with high incidence for which there are well-established prevention strategies. European clinical guidelines recommend CRC screening for individuals aged 50–74 years using quantitative faecal immunochemical testing, a non-invasive tool that identifies individuals at increased risk and facilitates referral for confirmatory diagnostic procedures, such as endoscopy.³ According to data from the Global Cancer Observatory (GLOBOCAN), CRC has the highest incidence and mortality of all digestive tract cancers. The mortality rates are highest in South America, Eastern Europe and Asia, ranging from 11.2 to 20.2 deaths per 100,000 persons.⁴ Although overall CRC incidence has declined gradually since the mid-1990s, an alarming rise in incidence among adults under 50 has been documented in the USA.^{5,6} Between 2015 and 2019, the incidence increased by 80–100% among persons aged 15–50 years, compared with a 20–30% increase among those aged 55–59 years.⁷ Similar trends have been reported in Australia, Canada and several European countries, including Germany, Poland and Spain.^{8–10}

Evidence further suggests that trends in early-onset CRC vary by ethnicity and sex. In the USA, analyses of age-adjusted CRC incidence rates among men aged 20–49 years from 1992 to 2005 demonstrated the highest annual percentage change among Hispanic men (+ 2.7%), followed by non-Hispanic White (+ 2.0%), Asian American and Pacific Islander (+ 1.2%) and non-Hispanic Black men (–0.2%). Among women in the same age group, the ranking was as follows: non-Hispanic White (+ 2.2%), Hispanic (+ 1.1%), Asian American and Pacific Islander (+ 0.6%), non-Hispanic Black (–0.6%).¹¹

Breast cancer (BC) is another highly prevalent malignancy among women for which organised screening programmes exist. European guidelines recommend mammography screening for women aged 50–69 years, with extended suggested limits ranging from 45 to 74 years.³ Globally, BC mortality rates are highest in Africa, Latin America, Europe and Oceania, ranging from 19.3 to 38.9 deaths per 100,000.¹² Substantial racial and ethnic disparities in BC incidence and mortality have been documented. Despite a 44% overall mortality decline since 1989, BC mortality remains 38% higher in Black than among White women.^{13–15} Black women are also more likely to develop triple-negative breast cancer and experience poorer survival, whereas Hispanic women exhibit survival outcomes comparable with those of White women.¹⁶

Beyond these high-incidence cancers with established screening programmes, gallbladder cancer (GBC) represents a malignancy characterised by marked geographic heterogeneity in risk. High GBC incidence (1.3–8.4 cases per 100,000) and mortality (1.0–7.0 deaths per 100,000) in women have been reported in parts of South America, including Bolivia, Chile and Peru, as well as in Asian countries, including India, Korea and Japan.¹² GBC is associated with a particularly poor prognosis, with 5-year survival rates below 32%. Early identification and targeted interventions, including prophylactic surgical gallbladder removal (cholecystectomy) among high-risk individuals, are therefore critical to improving outcomes.^{17,18}

Chile has one of the highest GBC mortality rates worldwide and is the only country to have implemented a national GBC prevention programme.¹⁹ This programme, introduced in 2006, is based on a public health policy providing preventive cholecystectomy to reduce GBC mortality.^{20,21} The policy covers free surgery for individuals aged 35–49 years with symptomatic gallbladder disease, as well as for individuals with asymptomatic gallstones aged 40 and older who have specific risk factors, including multiparity, body mass index greater than 26 kg/m², fewer than 8 years of formal education and at least one Mapuche surname. (The Mapuche are the largest Indigenous people in Chile and experience a high prevalence of gallstones and GBC.).^{19,22} Although GBC mortality has declined overall during the past decade, persistently high mortality rates remain in southern regions of Chile.²³

Collectively, these findings suggest that the best age for starting screening for CRC and BC, as well as for preventive cholecystectomy to prevent GBC, may vary depending on sex, country and time. Accordingly, we calculated the 10-year cumulative risks of death from CRC, BC and GBC, defined mortality risk thresholds consistent with current recommendations for screening and preventive gallbladder surgery, and estimated the age at which mortality risk thresholds are reached according to sex, geographic region and calendar year, with the aim of informing more precise and tailored cancer prevention strategies.

Methods

To calculate the age at which the 10-year cumulative risk is reached, it was necessary to collect the mortality rates for the different types of cancer. Cancer mortality rates for men and women were obtained separately provided by GLOBOCAN (estimates for 2020; 5-year groups: 20–24, 25–29, ..., 75–79; worldwide calculations),^{12,24,25} and from mortality database provided by the Department of Statistics and Health Information of the Chilean Ministry of Health as part of a research collaboration with the Chilean Center for Cancer Prevention and Control (CECAN; data from 2004 to 2019, calculations for Chilean women). Information on the age distribution of the Chilean population for calculating standardised 5-year mortality rates was provided by the Chilean National Institute of Statistics (2017 census). The mortality rates for CRC, BC and GBC needed to reproduce all the results presented in this article, as well as the code used for data analysis, will be made publicly available at www.biometrie.uni-heidelberg.de/StatisticalGenetics/Software_and_Data at the time of publication.

First, we used the mortality rates provided by GLOBOCAN for Europe (40 countries in northern, southern, western and eastern Europe) for the age groups 50–54 and 55–59 years to calculate the 10-year cumulative risk of death from CRC (ICD-10-CM codes C18–C20) and BC (ICD-10-CM code C50) at age 50, and the annual mortality rates between ages 50 and 59 provided by the Chilean Ministry of Health to calculate the 10-year cumulative risks of death from GBC (ICD-10-CM code C23) at age 50. The 10-year cumulative risk of death at age 50 was 0.2% for CRC among Europeans, 0.33% for BC among European women, and 0.11% for GBC among Chilean women. We then used the 10-year cumulative risks of death as mortality thresholds, and calculated the age at which these thresholds were reached by cancer type, sex, country and geographic region, and calendar year. For example, the 10-year cumulative mortality rate at age 21 was calculated as follows:

$$10 - \text{year cumulative mortality rate at 21 years} = (\text{mortality rate at 20} - 24 \text{ years} \times 4 \text{ (for age 21 to 24)}) + (\text{mortality rate at 25} -$$

The 10-year cumulative mortality risk was:

$$10 - \text{year cumulative risk} = \left(1 - \exp^{(-10 - \text{year cumulative mortality rate})}\right) \times 100$$

For Chile, we also examined regional and temporal variations in the female cumulative risk of dying from BC and GBC between 2004 and 2019. We selected three regions based on the lowest and highest ages to reach the cumulative mortality thresholds between 2016 and 2019 (Supplementary Tables S1 and S2), along with the “Metropolitana de Santiago” region, where approximately 40% of the Chilean population lives. For each selected region, we fitted a cubic spline using the R package “lme4”, with the age at which the threshold was reached as the dependent variable, and the calendar year as the independent variable:

$$\text{predicted_age} < - \text{predict}(\text{lm}(\text{age} \sim \text{bs}(\text{year}, \text{degree} = 3)), x = \text{age})$$

Results

Cumulative mortality risk from colorectal cancer and breast cancer worldwide

First, in line with current European Union recommendations to start CRC and BC screening at age 50, we calculated the 10-year cumulative risks of death from CRC and BC at age 50, based on mortality rates for ages 50–54 and 55–59 years provided by GLOBOCAN for Europe (40 countries in northern, southern, western and eastern Europe). The 10-year cumulative risk of death from CRC at age 50 was 0.2% for Europeans, and the 10-year cumulative risk of death from BC at age 50 was 0.33% for European women. We then estimated the age at which these cumulative mortality risks were reached in each country worldwide. Figure 1 illustrates this procedure for CRC. The 10-year cumulative risk of dying from CRC in the general European population (black curve) was 0.2% at age 50 (horizontal red line). Among the 185 countries investigated, Puerto Rico (yellow curve) and Hungary (green curve) reached the threshold of 0.2% cumulative mortality risk at the youngest age, namely 41 and 42 years, respectively, while Rwanda (blue curve) and Sierra Leone (purple curve) reached the threshold at the oldest age (> 70 years).

Figure 2 shows the age at which each country worldwide reached the 0.2% threshold for cumulative CRC mortality risk. Among men (Fig. 2A), several eastern European countries (e.g. Hungary and Romania) reached the threshold between the ages of 42 and 44. The USA and Canada, Argentina, several European countries (e.g. Poland and Belarus) and some Asian countries (e.g. Kazakhstan and Korea) reached the 0.2% risk threshold risk between the ages of 45 and 49 years. In contrast, most African countries reached the threshold after the age of 50. Women reached the 0.2% threshold for cumulative CRC mortality risk at a higher age than men (Fig. 2B). Several eastern European countries (e.g. Hungary and Belarus) reached the threshold between the ages of 45 and 49, but unlike men, women in most countries worldwide reached the threshold after the age of 50. The left-hand side of Table 1 shows the 10 countries in the world that reached the 10-year cumulative risk of dying from CRC at the youngest ages. For example, men reached the 0.2% risk threshold at the youngest age in Puerto Rico (41 years) and Hungary (42 years), while women reached this threshold at the youngest age in Brunei (46 years), Barbados and Singapore (both 47 years).

The age at which women in each country reached the threshold of 0.33% for cumulative BC mortality risk is shown in Fig. 3. Many African countries (e.g. Ivory Coast, Central African Republic, Ethiopia, Cameroon, Djibouti, Equatorial Guinea and Eritrea), Jamaica, Fiji, Papua New Guinea and the Dominican Republic reached the threshold at the youngest ages (between 32 and 37 years, middle section of Table 1). In addition, numerous countries across Asia,

Africa, Europe and Latin America reached the threshold between 38 and 49 years of age. Countries where the threshold was not reached until after the age of 50 were rare worldwide. Exceptions were China, Korea and Mongolia, where the 0.33% 10-year cumulative risk of dying from BC was only reached after the age of 70.

Cumulative mortality risk from breast cancer and gallbladder cancer in Chile

We also examined regional and temporal changes in the cumulative risk of dying from BC and GBC within a single country (Chile), using cancer mortality rates from 2004 to 2019 provided by the Department of Statistics and Health Information of the Chilean Ministry of Health. Figure 4A shows the age at which women in Chile's 16 regions reached the 0.33% threshold for cumulative BC mortality risk during four periods (2004–2007, 2008–2011, 2012–2015 and 2016–2019). Overall, the age at which women reached the 0.33% risk threshold varied both among regions and over time. For example, in 2004–2007, there were five regions where women did not reach this threshold until after the age of 70, in 2008–2011 and 2012–2015 there was one region, and in 2016–2019 there were again five regions.

Over time, the age at which the threshold of 0.33% for cumulative BC mortality risk was reached generally increased. To better assess changes over time, we selected three regions for detailed analysis (Fig. 4B): the “Metropolitana de Santiago” region in the centre of the country, the “De los Ríos” region in the south, and the southernmost region of “De Magallanes y de la Antártica Chilena”. Women from the “De los Ríos” region (U-shaped pink curve) reached the threshold of 0.33% at the highest age. The age at which women from the “Metropolitana de Santiago” region (black curve) reached the threshold rose from 54 years in 2004 to 59 years in 2019. Of concern is the decline in the age at which women from the “De Magallanes y de la Antártica Chilena” (red curve) reached the 0.33% threshold for cumulative BC mortality: 55 years in 2004, 45 years in 2019. The current recommendation of the Chilean Ministry of Health is that mammography screening be initiated at the age of 50 for average-risk women.²⁶

Based on cancer mortality rates provided by the Chilean Ministry of Health, for Chilean women the 10-year cumulative risk of dying from GBC at age 50 was 0.11% between 2004 and 2019. Figure 5A shows the age at which Chilean women reached this threshold in four periods. The age at which the threshold was reached generally increased (more regions coded lighter green in 2016–2019 than in 2004–2007). Women in two southern regions of the country (“De los Ríos” and “De los Lagos”) reached the threshold between 38 and 45 years of age in 2016–2019. Figure 5B shows the changes over time for three selected regions. Women from the “De Tarapacá” region (U-shaped blue curve) reached the threshold of 0.11% at the highest age. The age curves for women from the “Metropolitana de Santiago” region (black curve) and the “De los Ríos” region (green curve) ran parallel – on average, women from the “De los Ríos” region reached the threshold of 0.11% for cumulative GBC mortality risk at the age of 44, i.e. 5 years earlier than women from the “Metropolitana de Santiago” region. Worldwide, other countries where women reached a 0.11% threshold for cumulative GBC mortality before the age of 50 were Nepal, Sao Tome and Principe, Bolivia and Libya (right-hand side of Table 1).

Discussion

Screening for CRC and BC in Europe usually begins at the age of 50 years. We calculated the risk of dying from these two types of cancer between the ages of 50 and 60 in Europe, and used these values (CRC: 0.2%, BC: 0.33%) as mortality thresholds to identify countries where initiation of screening earlier than recommended in current guidelines might be justified. This risk-based approach highlights the considerable heterogeneity across cancer types, sexes and countries, with important implications for screening strategies.

For CRC, marked geographic and sex-specific differences were observed. Men consistently reached the mortality risk threshold at a younger age than women, and in some countries the differences from the recommendations of the prevailing EU guidelines were pronounced. For example, men reached the threshold at the age of 42 in Hungary and at the age of 44 in Moldova and Romania, representing a gap of up to 8 years. For women, the deviation from the age recommended in the guidelines was smaller and was observed in fewer countries. The risk of CRC in men under 50 has increased in several countries, but evidence regarding the epidemiology of early-onset CRC in persons without a family history remains limited, including uncertainty about tumour aggressiveness and the benefits of earlier screening at the population level.²⁷ Modelling studies, such as simulations using the Canadian OncoSim-CRC model, suggest that lowering the screening age to 40 or 45 years could reduce CRC incidence and mortality while remaining cost-effective.²⁸ Our findings confirm the need for targeted research in this age group, and suggest that earlier initiation of screening may merit consideration in selected high-risk countries.

For BC, the age at which the 0.33% mortality threshold was reached was substantially lower than for CRC, particularly in African populations. African women experience both higher incidence and a greater likelihood of aggressive disease at younger ages than women of European descent.^{29,30} Supporting epidemiological evidence, a recent genome-wide association study in African women found that the polygenic BC risk score was higher than that derived from women of European ancestry, suggesting a potential genetic contribution to earlier disease onset.³¹ Although the very early threshold age observed in some populations may not be generalisable, several countries showed elevated BC risk at younger ages, consistent with a global downward shift in age at onset. This context, and evidence that mammography screening reduces BC mortality by approximately 20–30%, as reported in recent evaluations of national screening programmes, speaks in favour of continuous reassessment of age-based screening recommendations.^{32–34} Collectively, these results underscore the importance of incorporating ethnic and population-specific risk profiles into screening guidelines to maximise benefits and reduce inequalities.

To explore within-country variation, we examined regional trends in Chile, focusing on BC and GBC, two malignancies with established prevention policies.^{19,26} At the national level, the 0.33% threshold for BC mortality risk was typically reached between ages 55 and 59 years (Fig. 3), which is in line with current recommendations to initiate mammography screening at age 50. However, regional analyses revealed notable heterogeneity over time, with women

in the “De Magallanes y de la Antártica Chilena” region reaching the mortality threshold at the age of 45, suggesting that this region could benefit from earlier BC surveillance.

For GBC, Chile represents an exceptional case, as it is the only country where public policy provides for free cholecystectomy for symptomatic gallstones in persons aged 35–49 years, with a focus on women. Our analysis found that the 0.11% threshold for GBC mortality was reached within a narrower and generally younger age range than for BC: between 38 and 56 years of age, versus 46–70+ years. This raises the possibility that the current prevention policy may be excluding older individuals at high risk. Given that high-risk Indigenous women living in southern regions of Chile face substantial socioeconomic barriers to healthcare, extension of the upper age limit for coverage could yield significant benefits.^{35,36} At the same time, the Chilean health system is already stressed by the demand for surgical procedures, underscoring the need for careful evaluation of both resource allocation and the overall effectiveness of the Chilean cholecystectomy programme since its introduction.³⁷

It is important to note that setting the age for the start of prevention strategies based solely on cumulative cancer mortality has conceptual and clinical limitations:

(1) Cumulative mortality reflects fatal outcomes that manifest years after tumour initiation, especially in cancers with a positive prognosis. Thus, the sole use of mortality carries the risk of choosing a starting age that is systematically later than the optimal time for early detection.

(2) Mortality does not capture essential determinants of screening performance. Younger women are more likely to have dense breasts, which markedly reduces mammographic sensitivity. CRC screening effectiveness depends on the prevalence of adenomas and early-stage tumours, which rises with age before mortality becomes substantial. In the case of GBC, mortality-based thresholds ignore the prevalence of gallbladder dysplasia lesions, for which cholecystectomy is most effective.

(3) Mortality measures are also confounded by improvements in cancer prevention and treatment, which reduce mortality without altering the biological rationale for earlier detection.

(4) Focusing exclusively on mortality ignores the heterogeneity in terms of incidence, tumour biology, risk factors and comorbidity profiles across different ethnic, socioeconomic and genetic subgroups, and neglects aspects such as overdiagnosis and cost-effectiveness.³⁸ Consequently, while cumulative cancer mortality can serve as a guide, it does not alone provide a complete basis for determining the best age to begin screening for CRC and BC, or for cholecystectomy to prevent GBC.

Conclusions

Our results demonstrate substantial age variability in cumulative mortality by cancer type, sex, geography and time. Many countries and regions reach clinically relevant risk thresholds at ages younger than those specified in current guidelines. Incorporating dynamic, population-specific risk estimates into cancer surveillance, screening and preventive surgery may both improve cancer control and help to target measures at the persons and populations at highest risk.

Abbreviations

BC
breast cancer
CECAN
Center for Cancer Prevention and Control
CRC
Colorectal cancer
GBC
gallbladder cancer
GLOBOCAN
Global Cancer Observatory

Declarations

Ethics approval: The study was based on anonymised data, and ethical review was not required.

Availability of data and materials: The mortality rates from CRC, BC and GBC to reproduce all the results presented in this article, as well as the code used for data analysis, will be made publicly available at www.biometrie.uni-heidelberg.de/StatisticalGenetics/Software_and_Data at the time of publication.

Competing interests: The authors declare that no conflict of interest exists.

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Authors' contributions:

Conceptualisation: Lorenzo Bermejo. Resources: Lorenzo Bermejo, Nervi, Munoz, Morales, Losada, Merino-Pereira, Salinas. Methodology: Lorenzo Bermejo, Gonzalez. Formal analysis: Gonzalez. Writing-original draft: Gonzalez, Kumar, Lorenzo Bermejo. Writing-review and editing: all coauthors. Visualisation: Gonzalez. Supervision: Lorenzo Bermejo. Funding acquisition: Lorenzo Bermejo. All authors have read and agreed to the published version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Table 1

Table 1. Top ten countries in the world that reached the 10-year cumulative risk of death from colorectal, breast and gallbladder cancer at the youngest ages.

Age at which the 10-year cumulative risk of death from colorectal cancer reaches 0.2%				Age at which the 10-year cumulative risk of death from breast cancer reaches 0.33%		Age at which the 10-year cumulative risk of death from gallbladder cancer reaches 0.11%	
Men		Women		Women		Women	
Country	Age	Country	Age	Country	Age	Country	Age
Puerto Rico	41	Brunei	46	Jamaica	32	Nepal	43
Hungary	42	Barbados	47	Fiji	33	Sao Tome and Principe	43
Barbados	44	Singapore	47	Ivory Coast	33	Bolivia	44
Guadeloupe	44	Hungary	48	Central African Republic	34	Chile	45
Moldova	44	Belarus	49	Ethiopia	34	Libya	49
Romania	44	Bulgaria	49	Barbados	35	Algeria	53
Serbia	44	Cyprus	49	Cameroon	35	Bhutan	54
Bulgaria	45	Jordan	49	Djibouti	35	Qatar	55
Croatia	45	Moldova	49	Equatorial Guinea	35	Pakistan	56
North Macedonia	45	Serbia	49	Eritrea	35	Peru	56

Figures

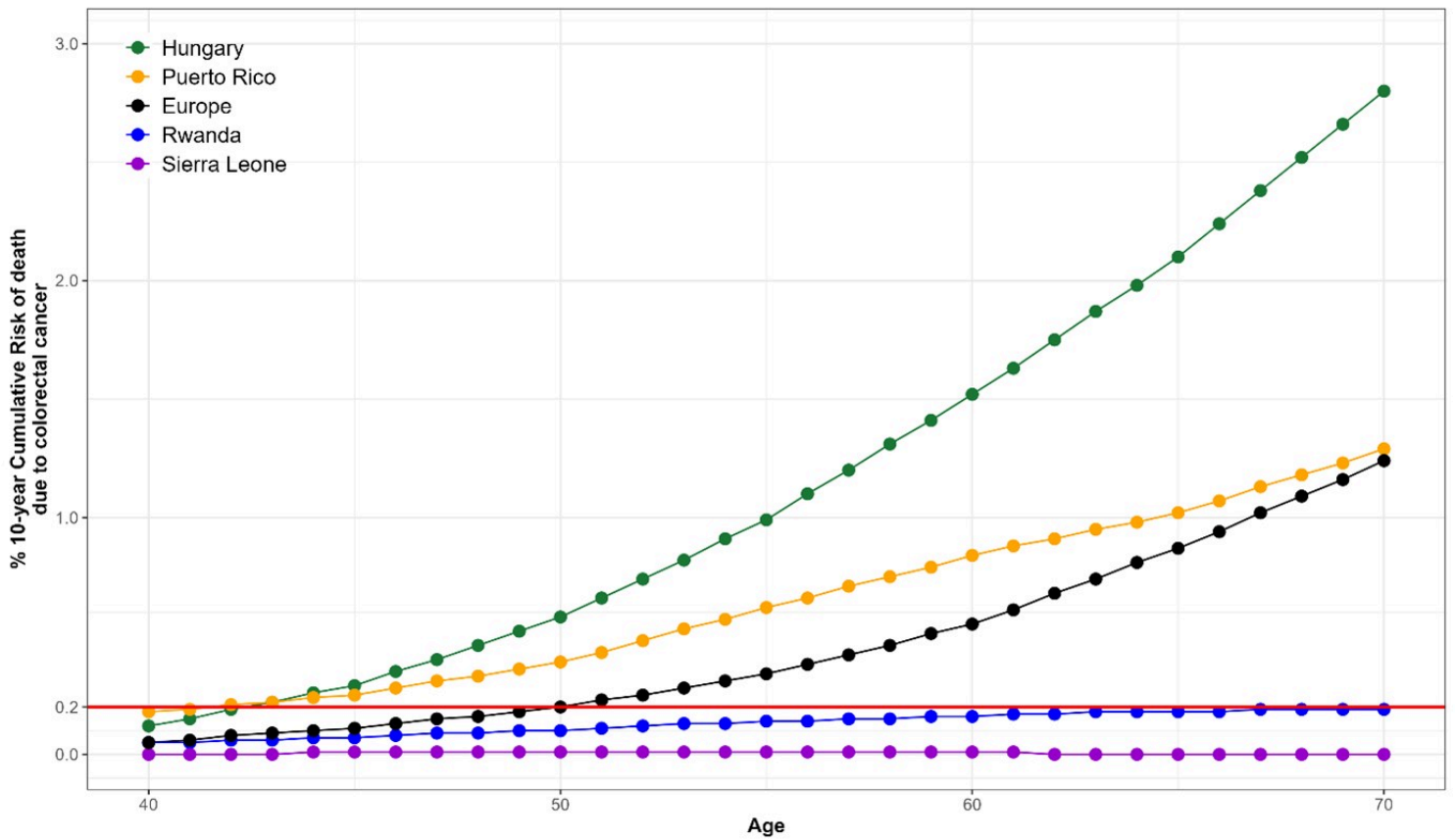


Figure 1

10-year cumulative risk of death from colorectal cancer in men by age. The black curve represents the cumulative risk in Europe, which was 0.2% at age 50 (horizontal red line), and was used as the cumulative risk threshold. Hungary (green) and Puerto Rico (yellow) reached the cumulative risk threshold at the youngest age, while Rwanda (blue) and Sierra Leone (purple) reached the threshold at the oldest age among the 185 countries investigated.

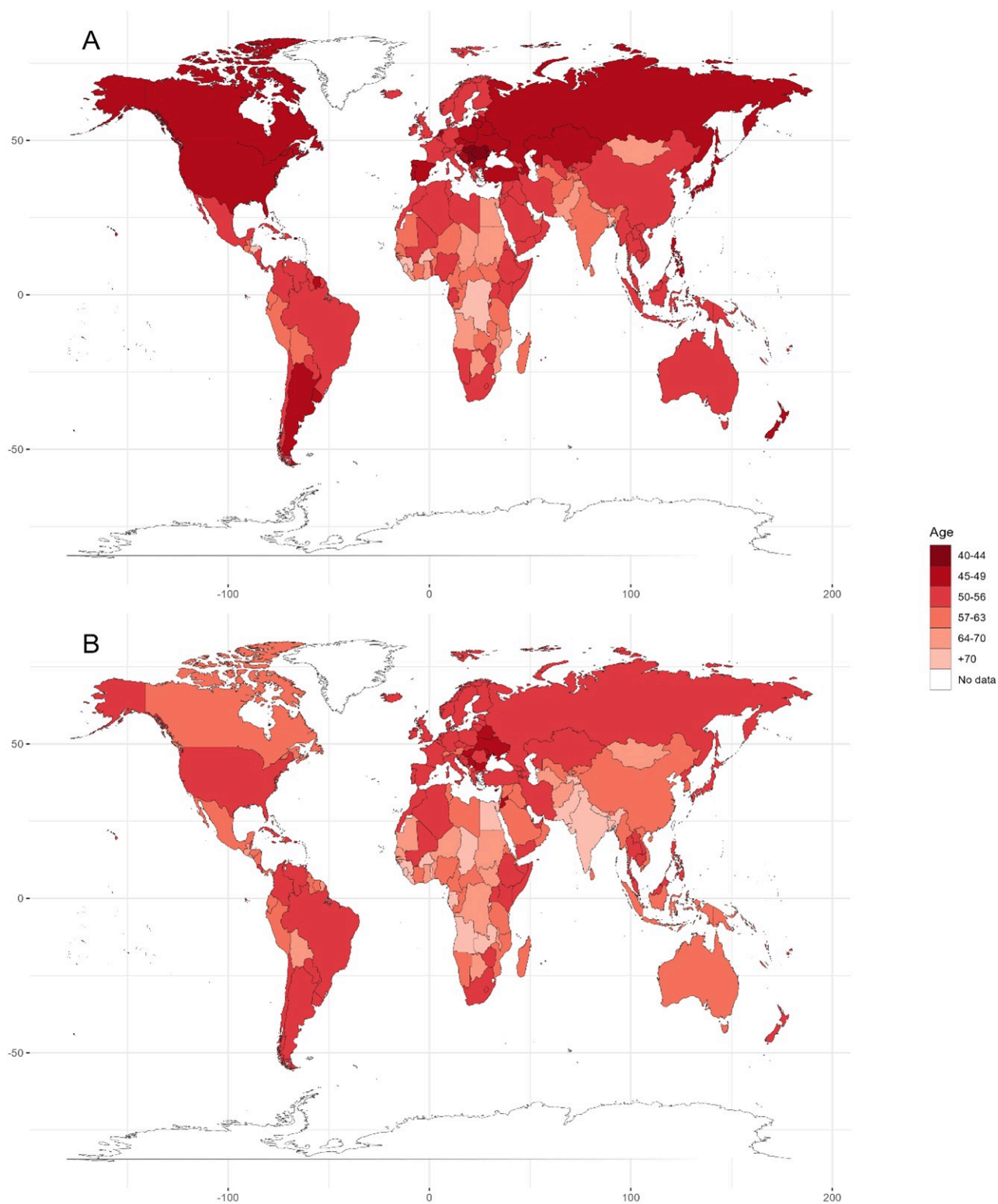


Figure 2

Age at which the 10-year cumulative risk of death from colorectal cancer reached the threshold of 0.2% worldwide. Figure 2A shows the age for men, and Figure 2B displays the age for women. The darker the red colouring, the younger the age at which the 0.2% mortality risk threshold was reached.

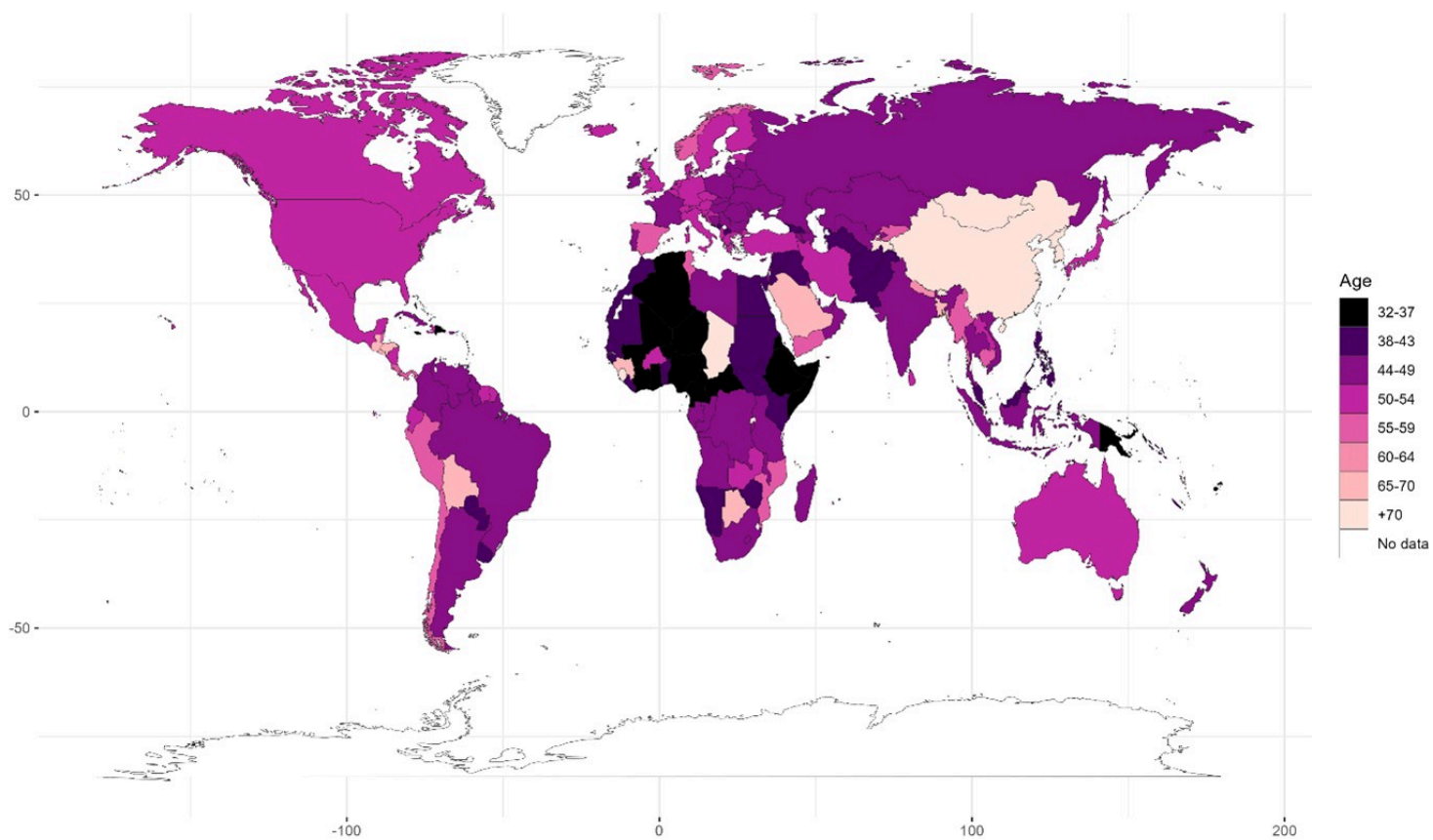


Figure 3

Age at which women worldwide reached the threshold of 0.33% for a 10-year cumulative risk of death from breast cancer. The darker the purple colouring, the younger the age at which the 0.33% mortality risk threshold was reached.

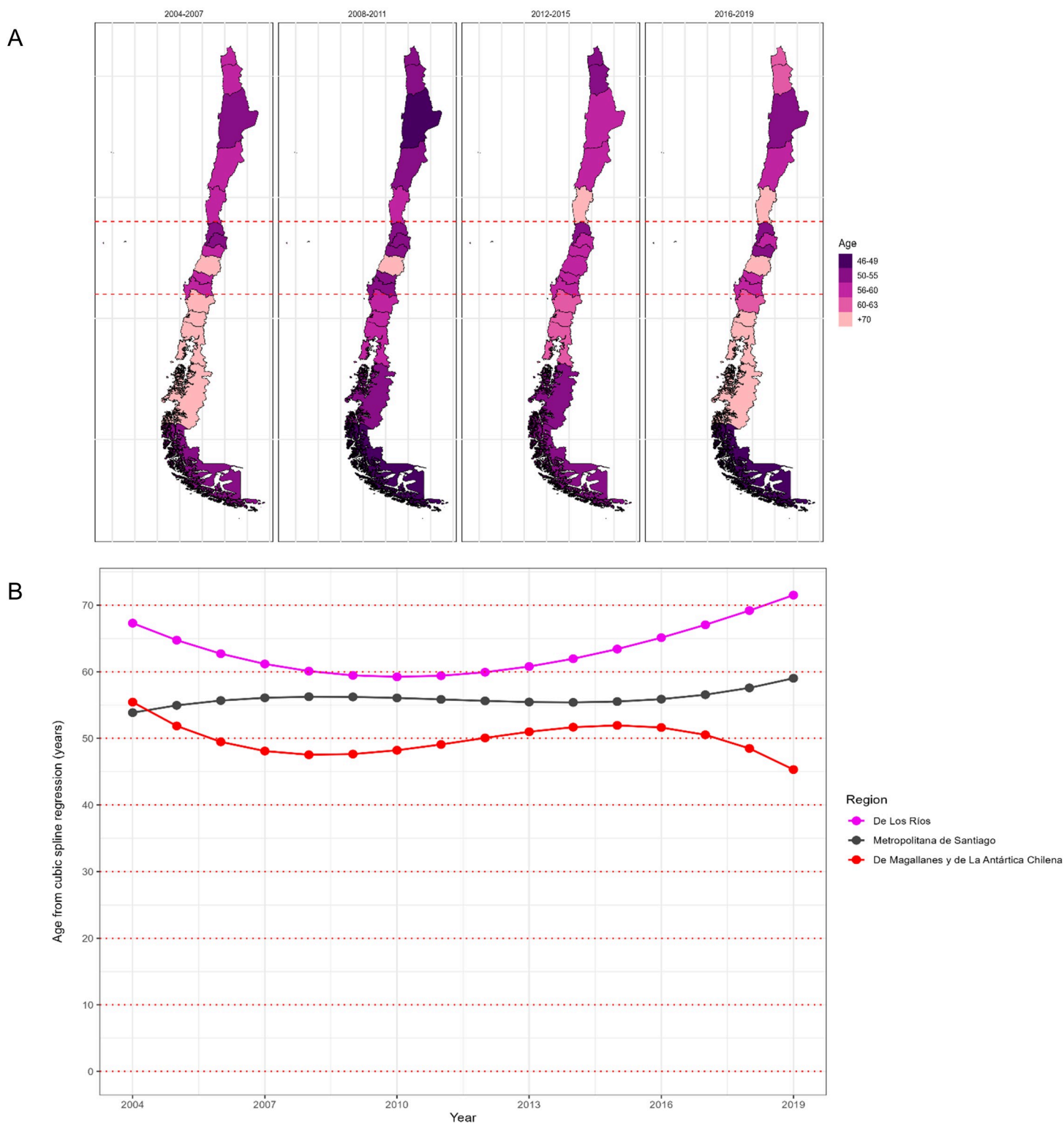


Figure 4

Age at which Chilean women reached the threshold of 0.33% for a 10-year cumulative risk of death from breast cancer, in different regions and over the years. Figure 4A shows the age over four calendar periods (2004-2007, 2008-2011, 2012-2015, 2016-2019). Figure 4B displays the age at which women reached the mortality risk threshold between 2004 and 2019 in three Chilean regions: the “Metropolitana de Santiago” region in the centre of the country (black curve), the “De los Ríos” region in the south (pink curve), and the southernmost region of “De Magallanes y de la Antártica Chilena” (red curve). The curves were derived using cubic spline regression and point to both regional and temporal differences in the age at which the threshold for breast cancer mortality was reached.

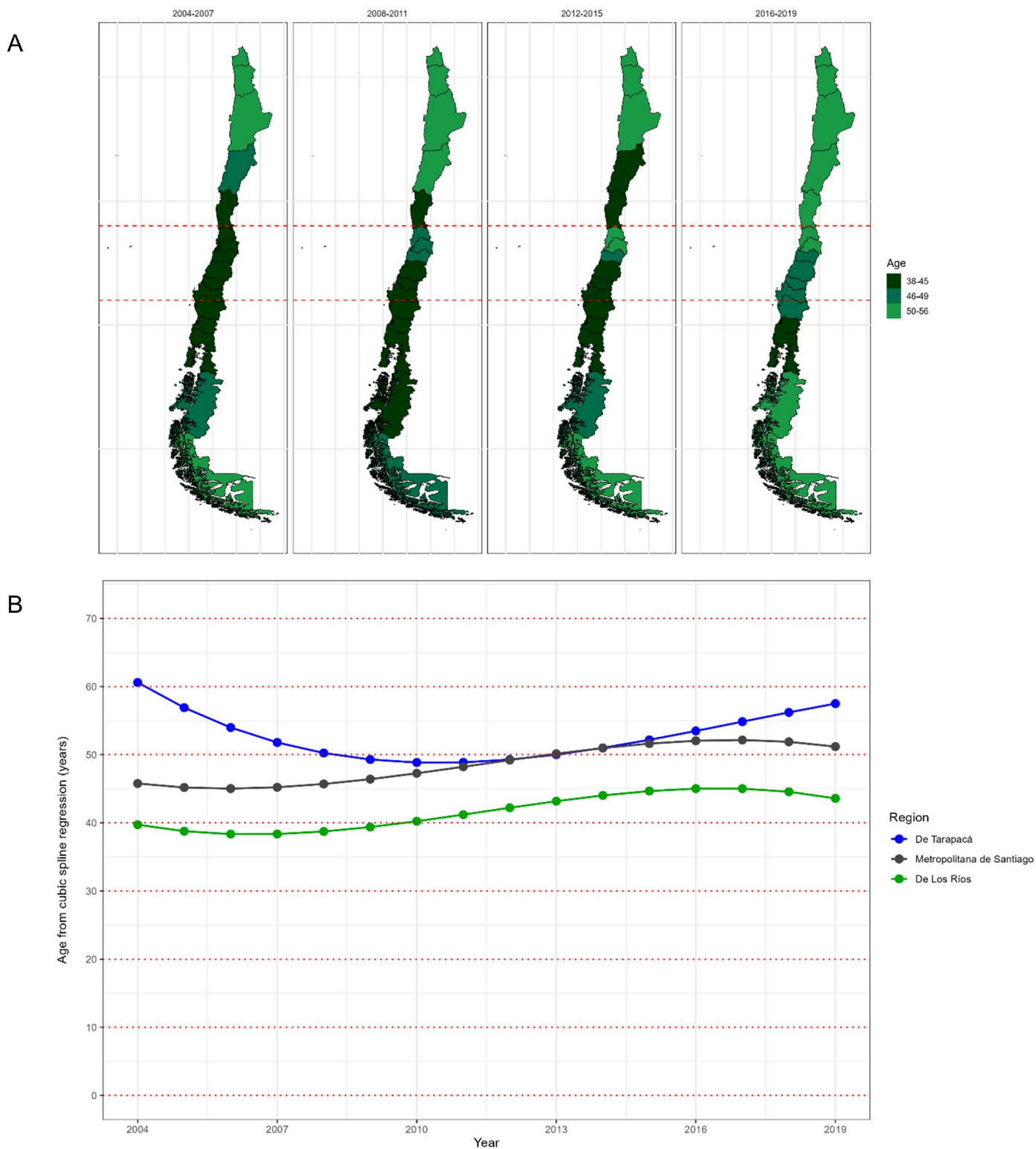


Figure 5

Age at which Chilean women reached the threshold of 0.11% for a 10-year cumulative risk of death from gallbladder cancer, in different regions and over the years. Figure 4A shows the age over four calendar periods (2004-2007, 2008-2011, 2012-2015, 2016-2019). Figure 4B displays the age at which women reached the mortality risk threshold between 2004 and 2019 in three Chilean regions: the “De Tarapacá” region in the north of the country (blue curve), the “Metropolitana de Santiago” region in the centre (black curve), and the “De los Ríos” region in the south (red curve). The curves were derived using cubic spline regression and point to both regional and temporal differences in the age at which the threshold for gallbladder cancer mortality was reached.