Breast Cancer in Latin American and Caribbean countries: An Age-Period-Cohort analysis (Preliminary Results)

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Where do this analysis fall in the GSK ERI Breast Cancer Grant Proposal?

- Part 1: Identify the *age specific distribution of diagnosis and death*, comparing LAC to other regions of the developed and developing world.

- Part 2: Determine the degree to which these *can be explained by patterns and trends in demographic transition, family formation, reproductive health, nutrition, labor force participation and education, among others*.
  - Evaluation of *age-period and cohort effects* that may be related to differences in age patterns of breast cancer mortality in LAC countries

Questions for the analyses we present here:

1. Are there differences in the age specific distribution of breast cancer incident cases between countries, that are not explained by population structure?

   if so, do they reflect differential susceptibility to one type of breast cancer (Pre vs. Post menopausal)

2. In LAC countries with both incidence and mortality data, are there discrepant results/conclusions when modeling age-period-cohort effects?

Employed Data Sources

- IARC CI5plus database which contains annual BC **incidence** for selected cancer registries published in CI5
  - 87 cancer registries in 35 countries
  - Information since early 80s in most countries up to 2002
  - 4 LAC countries (Costa Rica, Brazil, Ecuador and Colombia)
  - Incidence counts by 5 year age groups and year
  - Denominator data provided for each registry

- WHO Mortality Database
  - Death counts by cause and age groups for most Latin American and Caribbean countries since the 1980s
  - Denominator data from the UN Population Division

First analysis:
CI5 plus database analysis:
Differences in the age specific distribution of breast cancer incident cases, between countries, not explained by population age structure

What determines the number and age distribution of breast cancer **incident cases** in a population?

- Population age structure
- BC Incidence rates
- Breast cancer screening programs (Mammography)
- Data quality

What determines breast cancer incidence rates? (Risk Factors)

- *Reproductive factors*
  - Early age at menarche
  - Late age at first birth
  - Null parity
  - No Breastfeeding
  - Late Age at menopause

- *Non-reproductive lifestyle factors*
  - Breast density
  - Previous breast disease
  - Family history, Genetics
  - Overweight and obesity
  - Diet
  - Low Physical activity
  - Alcohol consumption
  - Smoking and secondhand smoke
  - Chemicals in the environment …

Breast Carcinoma Presents a Decade Earlier in Mexican Women than in Women in the United States or European Countries

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BACKGROUND. In Mexico, breast carcinoma is the second most frequent malignancy, representing 10.6% of all cases and 16.4% of all cancers in women, with an increase in breast carcinoma mortality rates from 3.6 per 100,000 women in 1985 to 6 per 100,000 women in 1994. Most of the tumors are diagnosed in advanced stages with little chance of cure.

METHODS. To determine the age of patients in Mexico at presentation of breast carcinoma, the authors analyzed the cases registered from 1993 to 1996 from the database of the Histopathological Registry of Malignant Neoplasms in Mexico.

RESULTS. There were 29,075 cases of breast carcinoma. The median age of Mexican women with breast carcinoma is 51 years, and 45.5% of all breast carcinomas develop before patients reach age 50 years. The most frequently affected age group is that of 40–49 years (29.5%), whereas the groups from 30 to 39 and from 60 to 69 years of age have a similar percentage (14%) of frequency. This contrasts with women from the United States, as well as with women from European countries, where the median age at presentation is 63 years, and only one-fourth of the patients are younger than 50 years of age, and three-fourths are postmenopausal. Similar to Mexico, in Venezuela and in Japan nearly one-half of women with breast carcinoma are younger than 50 years of age, and this resembles rates in many Latin American countries.

CONCLUSIONS. It is necessary to change the guidelines of breast carcinoma screening in Mexican women, to increase the possibility of early diagnosis and better survival. *Cancer* 2001;91:863–8. *© 2001 American Cancer Society.*

KEYWORDS: breast carcinoma, age, Mexico, screening.

Mexico Study Results and limitations

- Data analyzed correspond to 1991-1996
- Average age at presentation: 50 years (45% cases present before age 50), compared to 63 in developed countries
- Authors conclude that Mexican women may be more susceptible to breast cancer occurring at early ages
- Main Limitation: Based on biopsy data and data from a major specialized treatment center:
  - Duplicate patients
  - Selected patients

Breast cancer age distribution in the Mexico Study (Biopsy data)

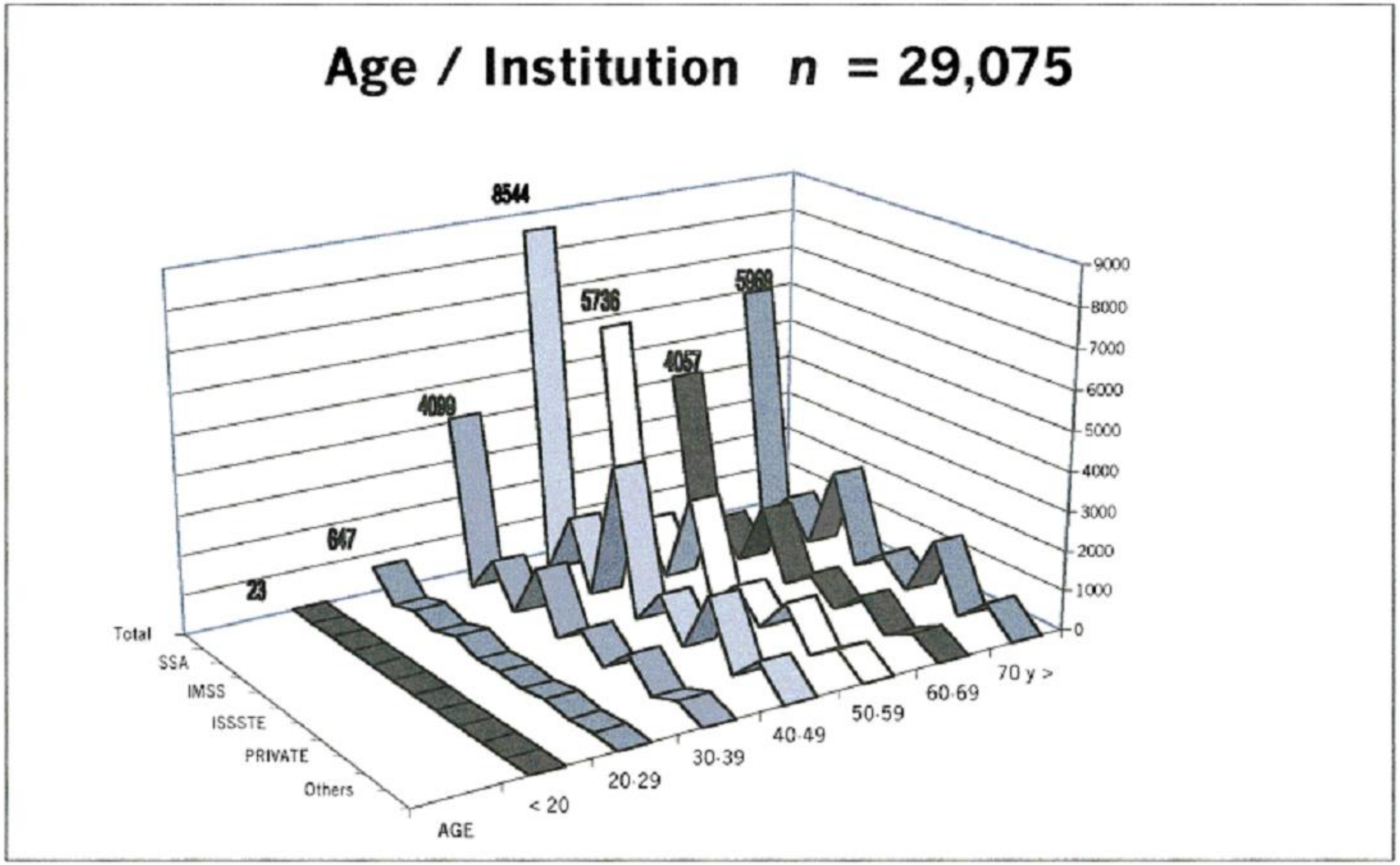


FIGURE 1. Distribution by age and institution of Mexican patients with breast carcinoma.

Breast cancer age distribution in the Mexico Study (Major treatment referral hospital)

TABLE 1
Age Distribution by Stage of Women with Breast Carcinoma at the Hospital de Oncología, CMN, IMSS, Mexico City, 1995

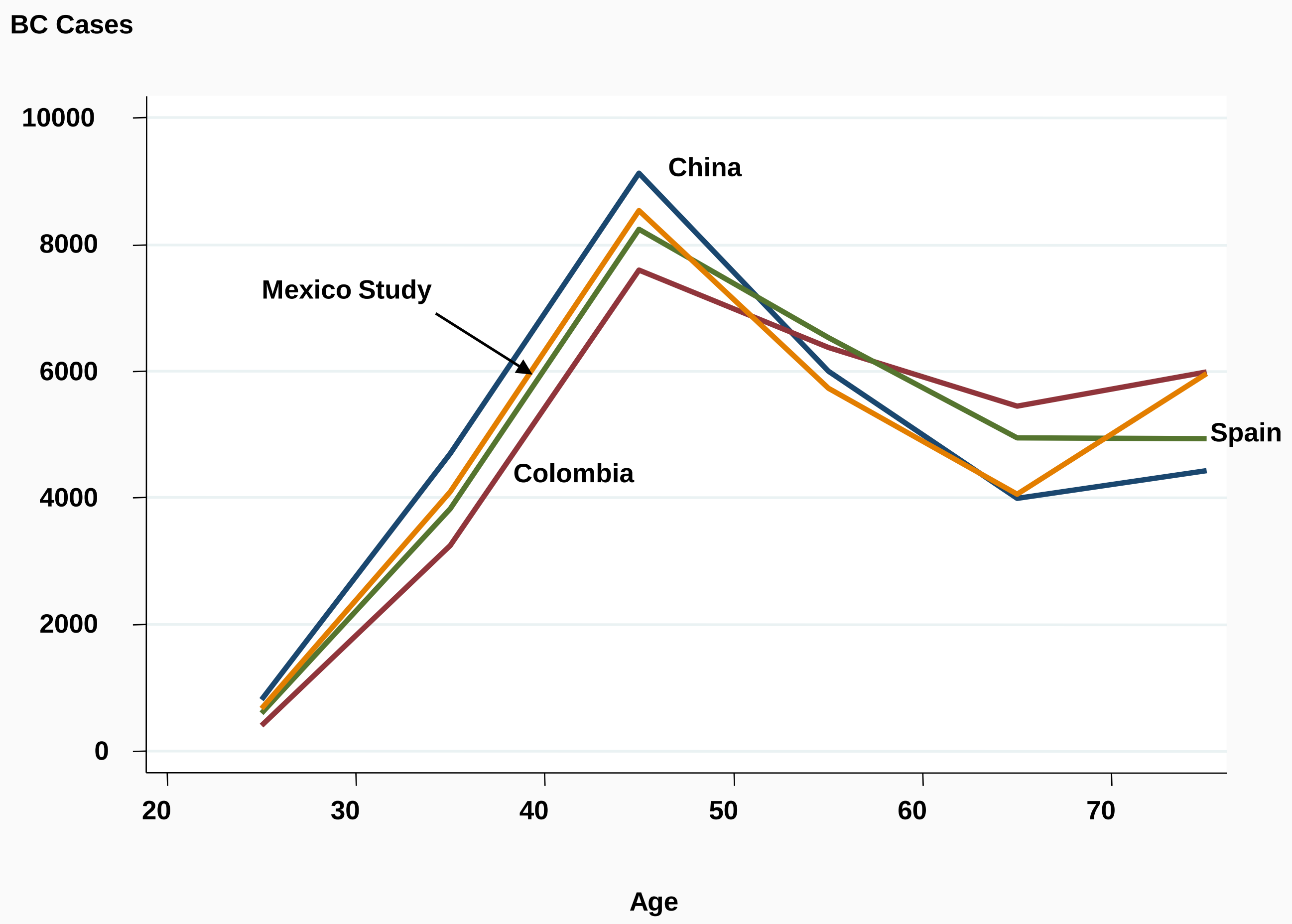
Stage	Mean age (yrs)	Median age (yrs)	SD (yrs)	Range (yrs)	n
I	50.0	48.0	13.5	19–83	128
II	48.0	50.9	13.0	24–92	748
III	48.6	48.0	10.7	25–80	370
IV	56.3	58.0	9.0	36–69	11
Total	50.1	49.0	12.5	19–95	1257

SD: standard deviation.

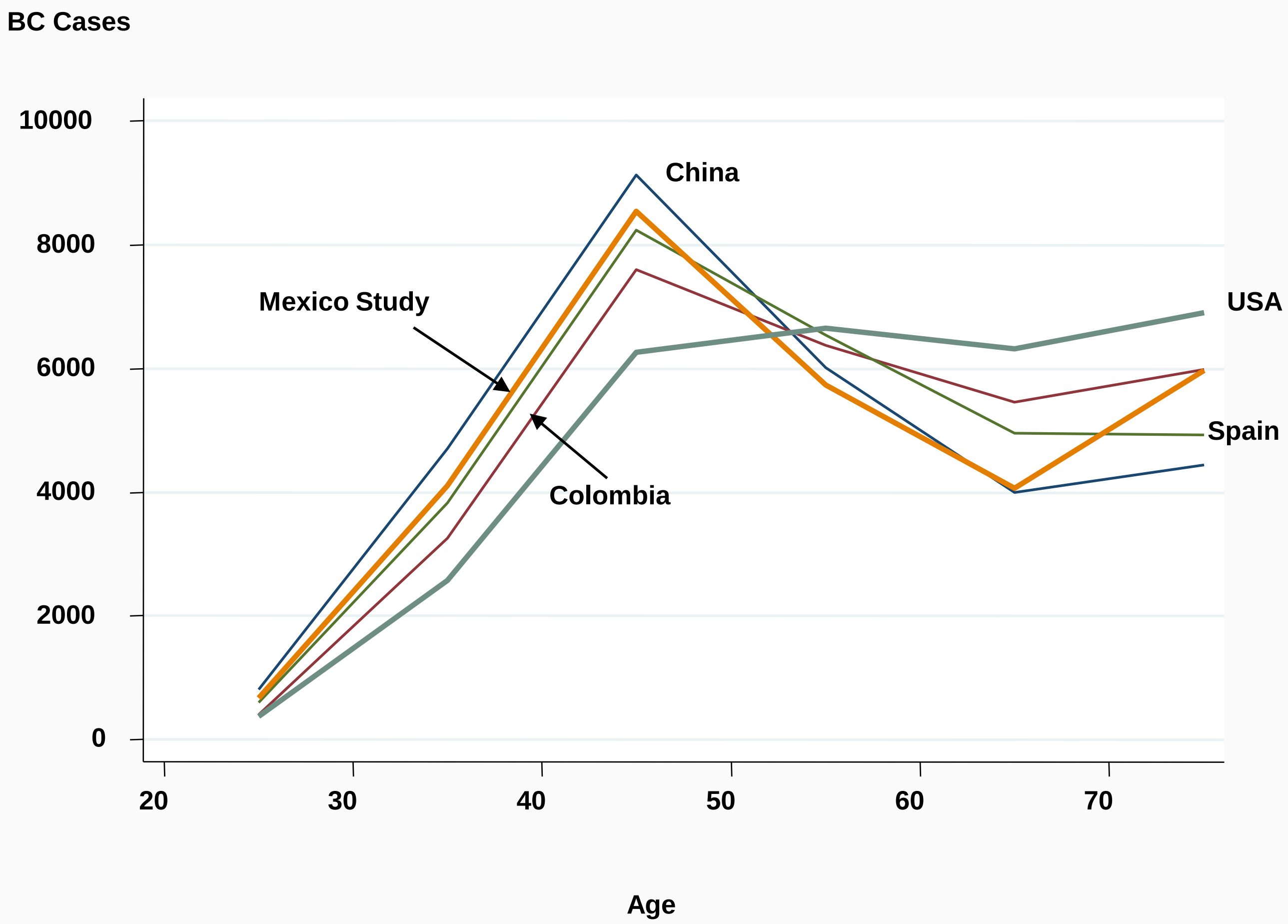
CI5 plus database analysis

- To find the closest age distribution of cases to that reported in the Mexico Study, once population age structure differences are removed, we:
  - Applied age specific incidence rates, averaged for the 1990s, observed in the included in the CI5 plus database, for each country, to a population age structure similar to the Mexican population in the 1990s
  - Rescaled the expected incidence counts obtained in previous step to 29,075
  - Compared the obtained counts to those published in the Mexico Study

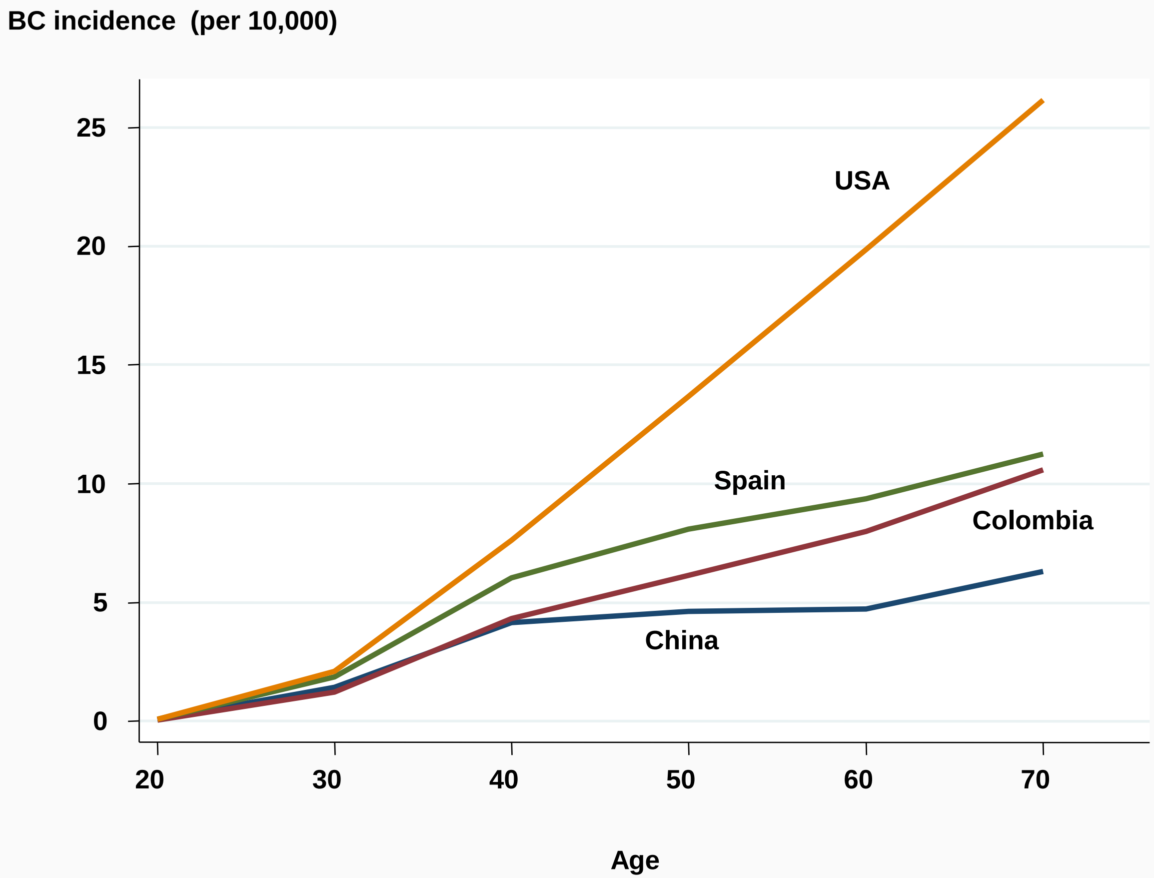
Closest incidence count matches to the Mexico study "incident cases" age distribution (CI5 plus, 1991-2000 aggregated data)



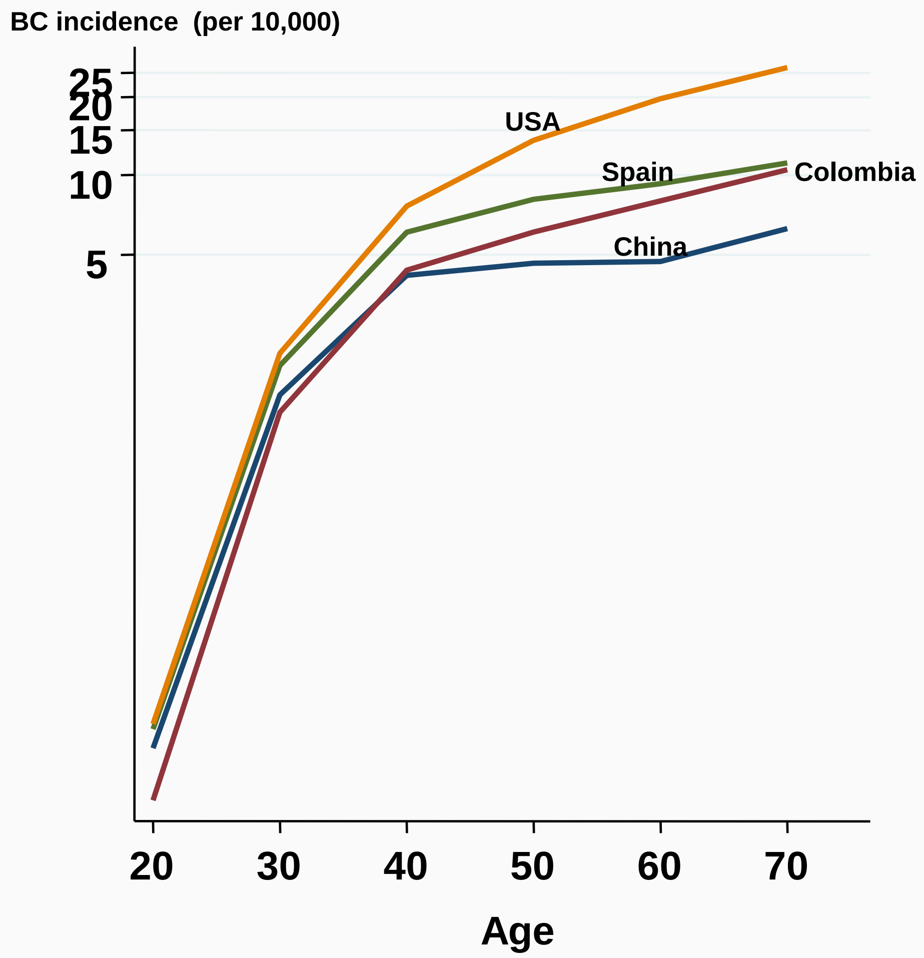
Closest incidence count matches to the Mexico study "incident cases" age distribution PLUS USA (CI5 plus, 1991-2000 aggregated data)



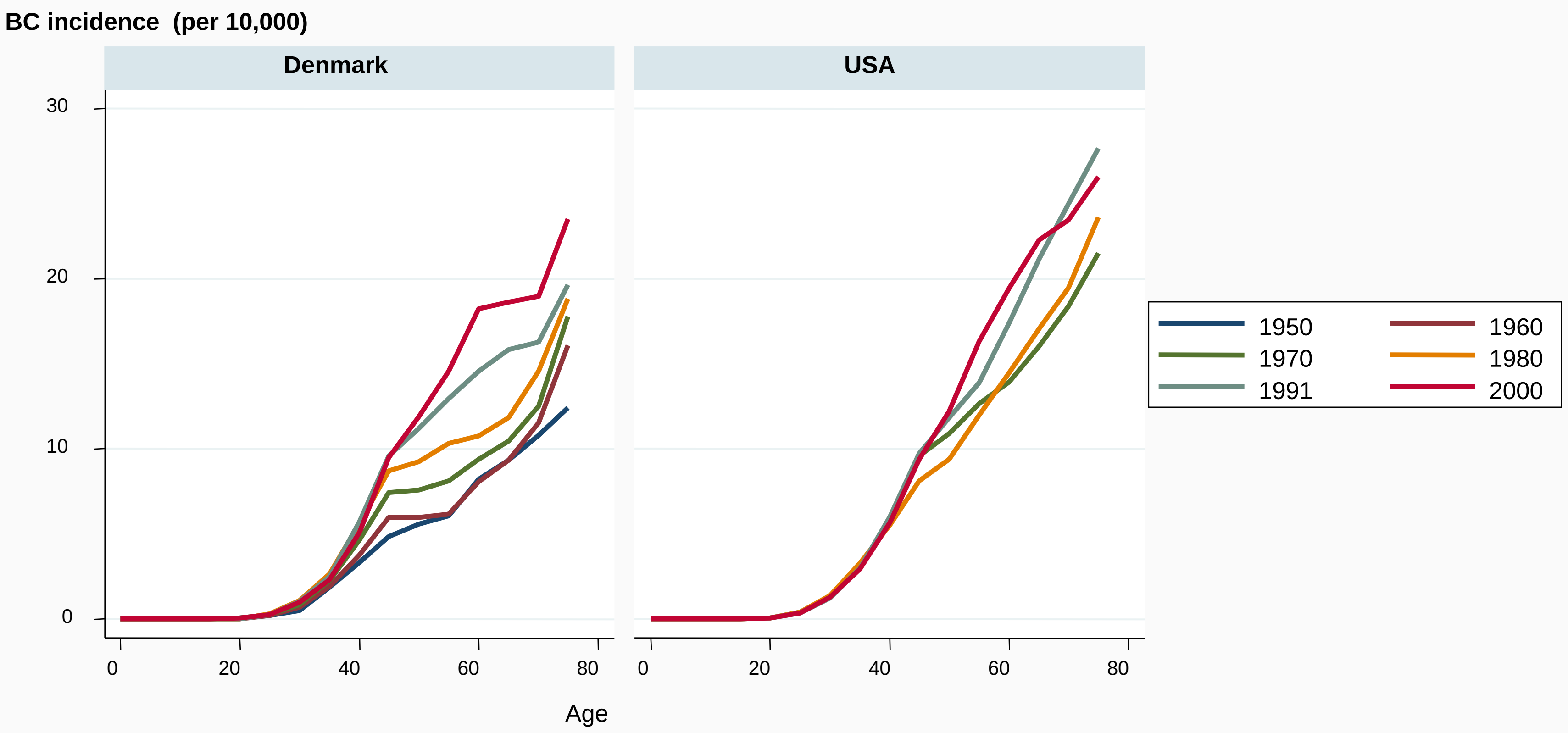
Breast cancer incidence rates in countries with earlier age at presentation and the US (CI5 plus, 1991-2000 aggregated data)



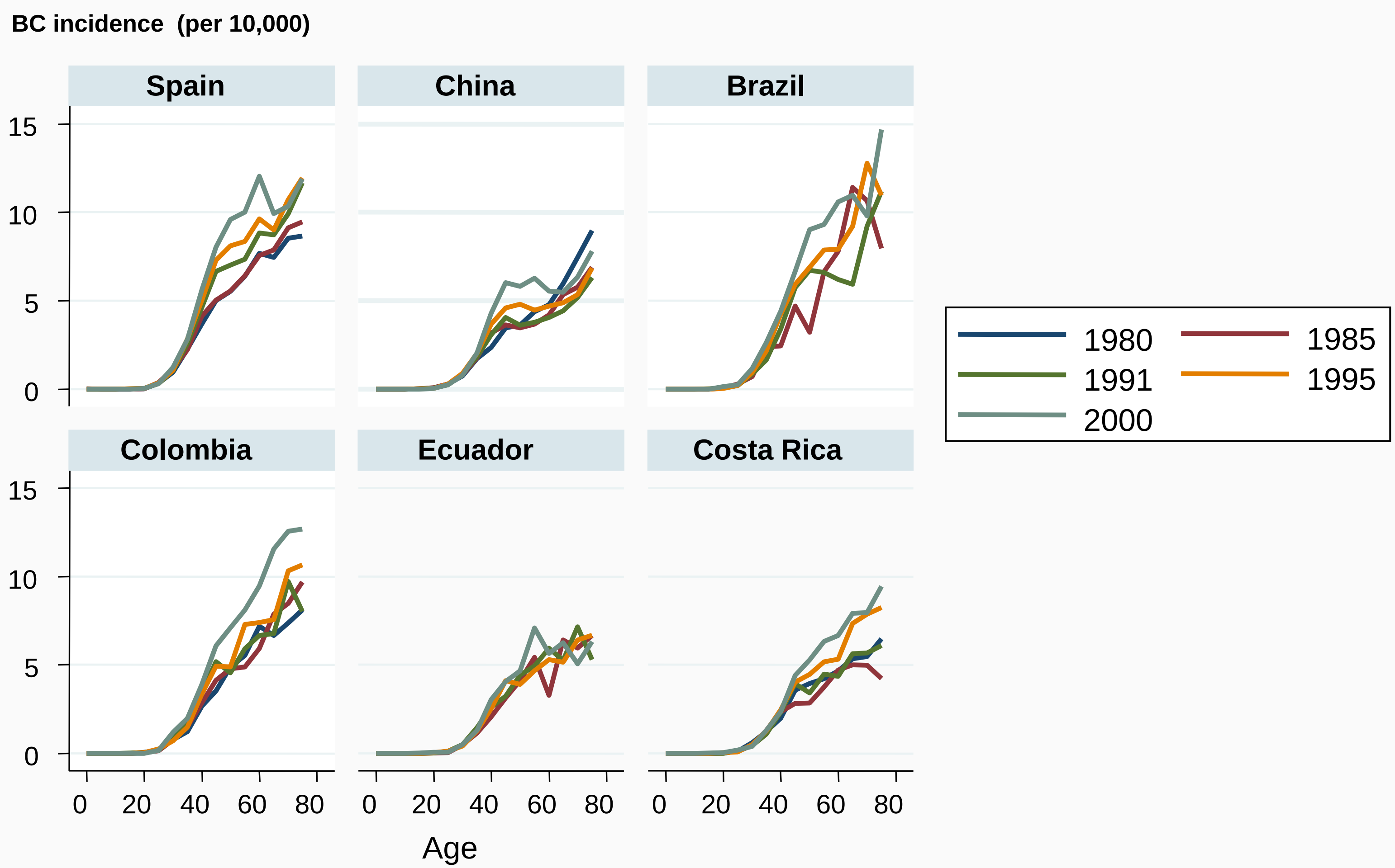
Breast cancer incidence rates in countries with earlier age at presentation and the US, log scale (CI5 plus, 1991-2000 aggregated data)



Changes overtime in age specific Breast Cancer incidence rates in 2 developed countries (CI5 plus data)



Changes overtime in age specific Breast Cancer incidence rates in countries with an earlier age at presentation (CI5 plus data)



First analysis conclusions

- In some countries Breast Cancer incident cases occur at an earlier average age than in developed countries (China, Spain, Brazil, Colombia and other Latin American Countries)

- Earlier presentation in these countries is not only due to age structure (younger population) but also to lower age specific incidence rates compared to developed countries

- Countries with high Breast Cancer incidence rates have higher rates at all ages, therefore data do not support that earlier presentation in some countries is due to increased susceptibility at younger ages

- In the last decades, countries with an earlier age at presentation present important increases in age specific incidence rates at all ages but these are sharper in women 50 and older

Second analysis:
CI5 plus and WHO mortality database analysis:
Are there discrepant results/conclusions when modeling age-period-cohort effects in LAC countries with both incidence and mortality data?

What determines the number and age distribution of breast **cancer deaths** in a population?

- Incidence Determinants
  - Age structure
  - Incidence rates
  - Breast cancer screening programs (Mamography)

- **Access to effective treatment**

- Data Quality

Age-Period-Cohort analysis

Data:

- Incidence and mortality annual counts, by five year age groups and year, between 1980 and 2002, were obtained for selected “countries” from CI5 Plus and WHO Mortality databases

- Denominators come from either CI5 Plus Database (incidence) or UN Population Office (mortality)

Holford's Age-Period-Cohort model employed

Age (a), period (p) and cohort (c) curvature trends for breast cancer mortality (λ) were estimated through the following Poisson Regression Age-Period-Cohort (APC) model, proposed by Holford:[9]

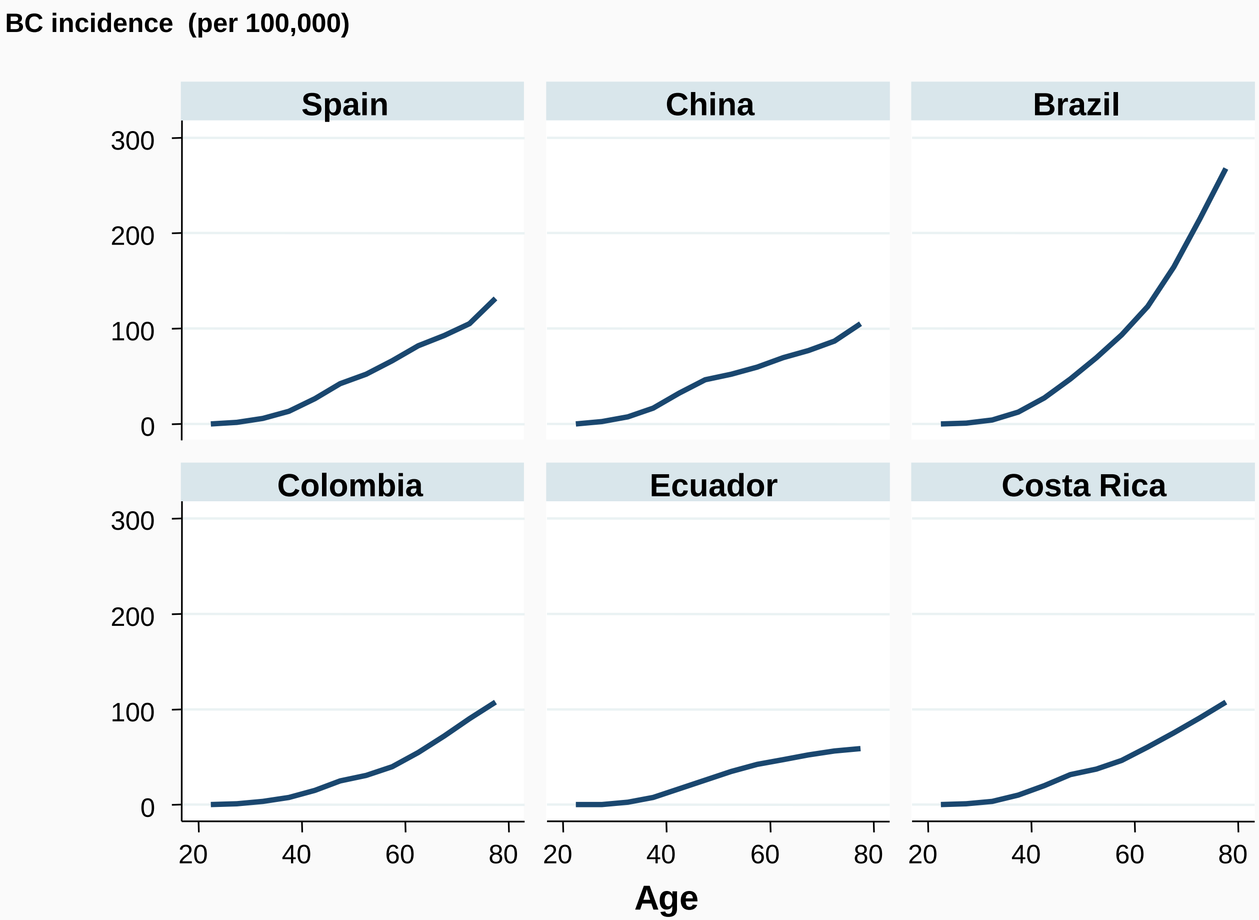
$$Log\lambda_{(a,p,c)} = \mu + [\beta a + \beta p]a' + [\beta p + \beta c]c' + \alpha(a) + \pi(p) + \gamma(c)$$

where a' and c′ are the curvature components of the age and cohort effects, [βp+βc] is called the "net drift parameter" indicating the overall direction in which the mortality trend is moving, and α, π and γ are the parameters describing the age, period and curvature trends.

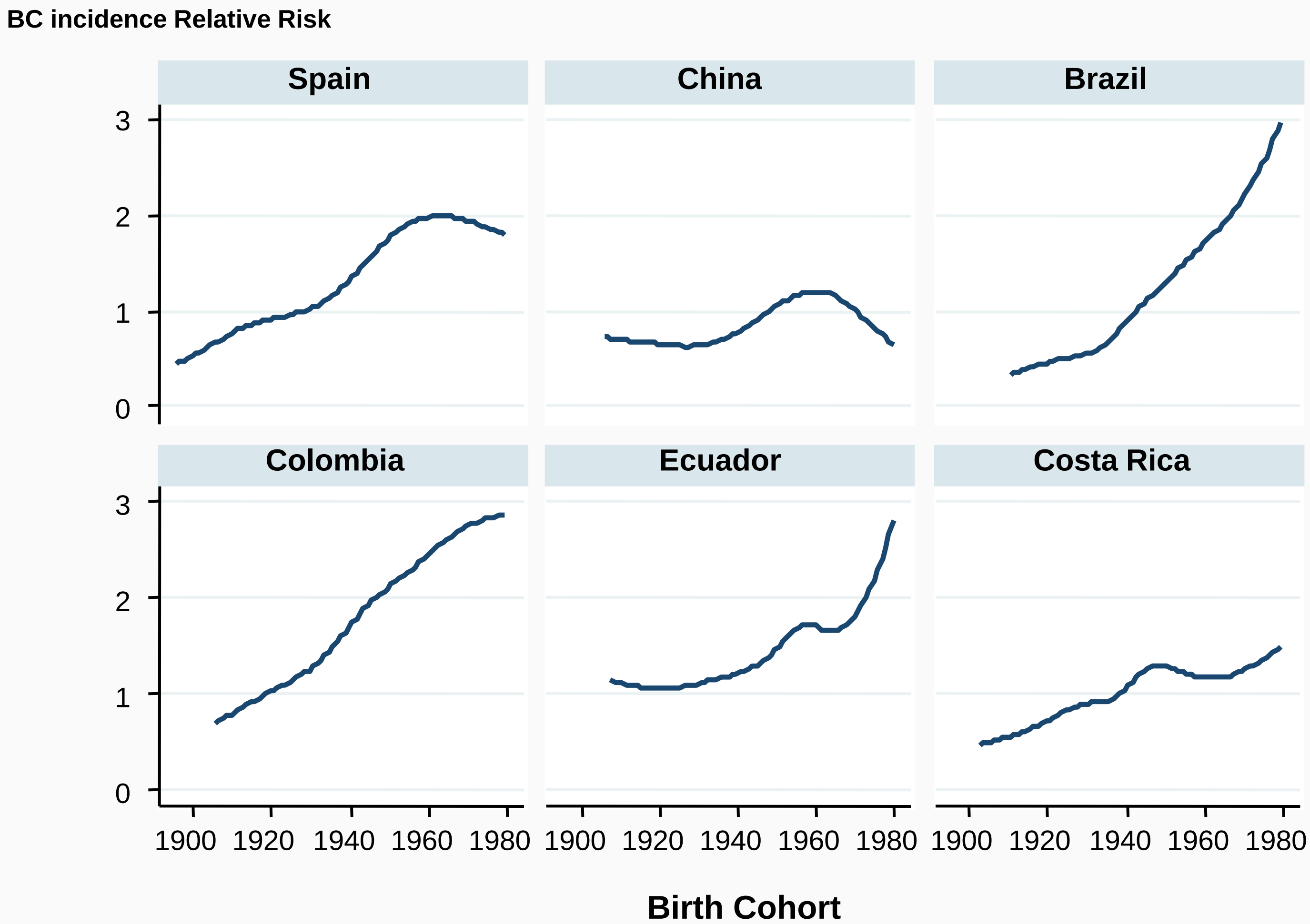
- This model assumes a constant age effect (no interactions)
- Modeling was done in the R Statistical Package (Carstensen, 2007)

Age-Period-Cohort analysis of breast cancer incidence data (CI5 plus data)

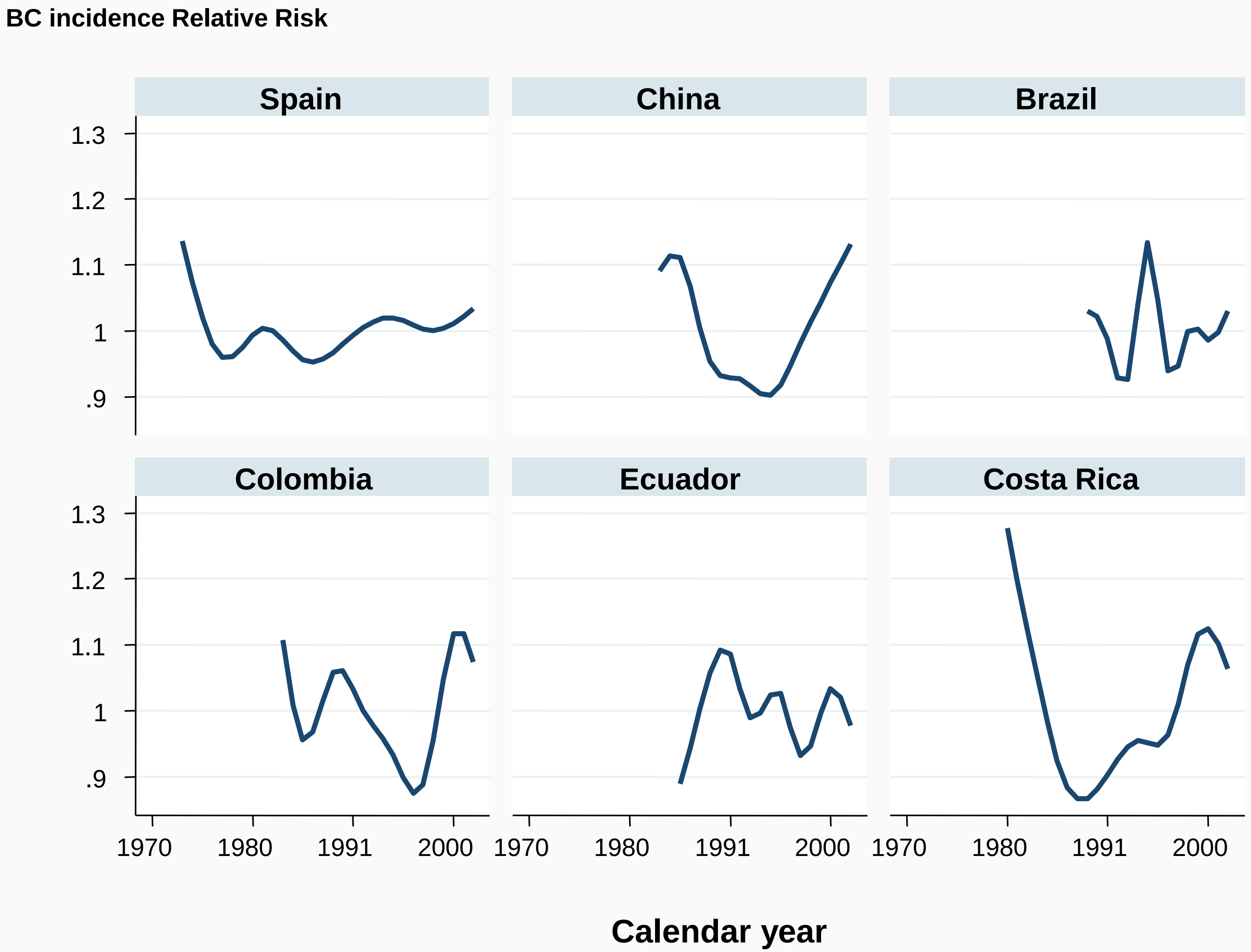
A-P-C incidence modeling: Age Effect



A-P-C incidence modeling: Cohort Effect

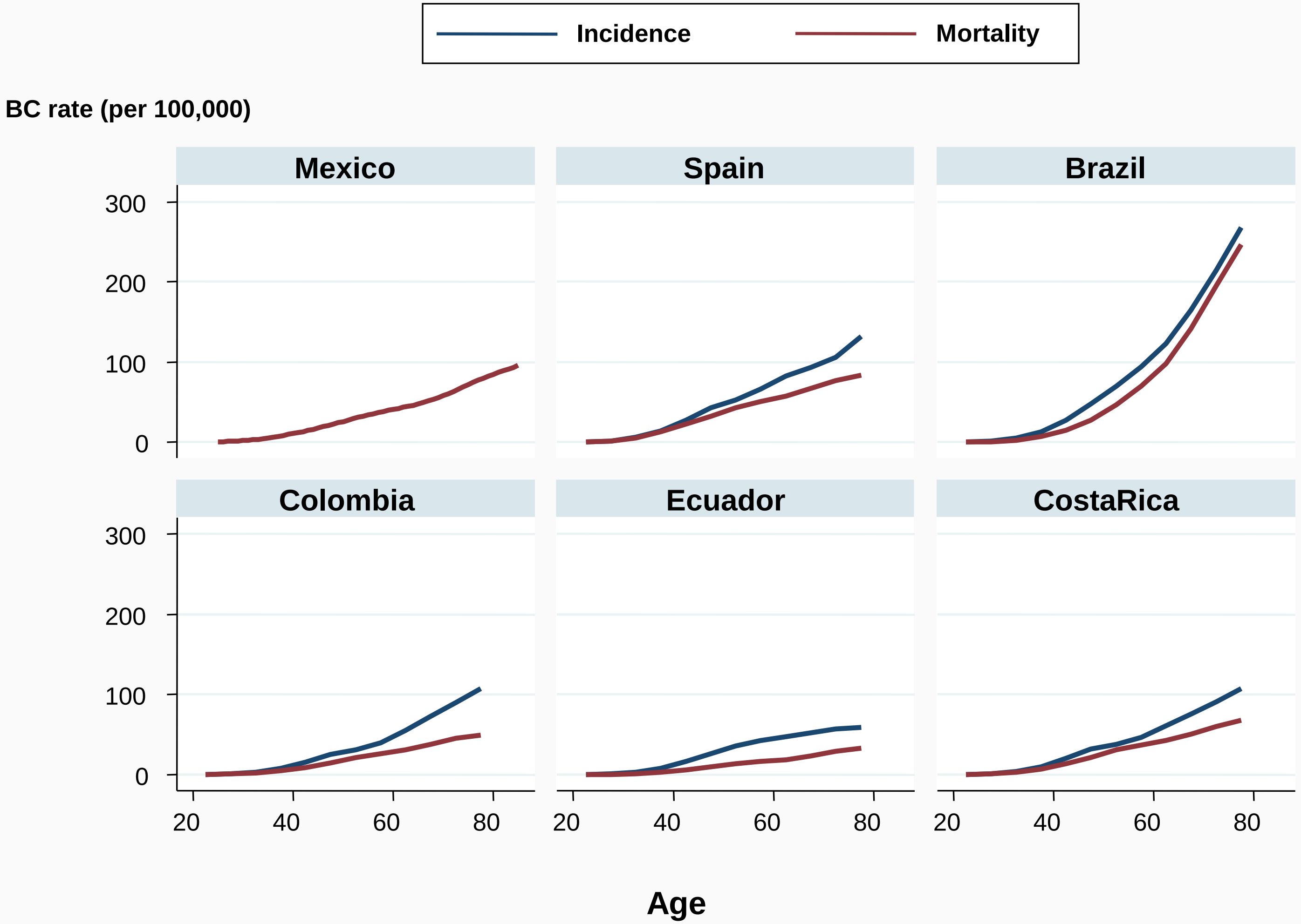


A-P-C incidence modeling: Period Effect

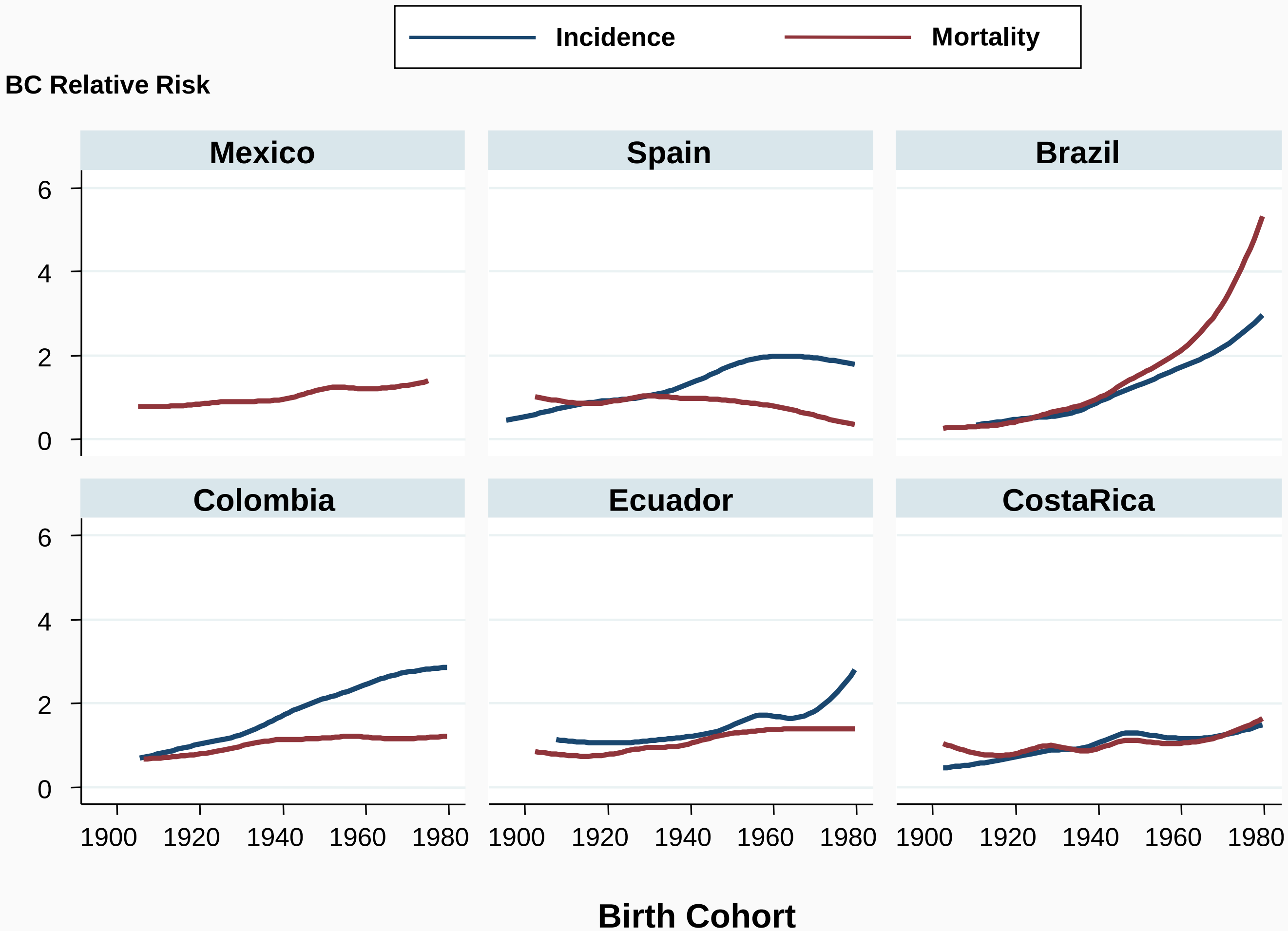


Age-Period-Cohort analysis of Breast Cancer incidence/ WHO Mortality data

A-P-C modeling: Age Effect



A-P-C modeling: Cohort Effect



Second analysis conclusions

- In some LAC countries results incidence and mortality A-P-C analysis may differ importantly
- Birth cohort effects detected by analyzing breast cancer mortality data could not directly reflect changes in incidence but also changes in access to effective treatment