Age-Period-Cohort Modeling of Colorectal Cancer Incidence and Mortality in Spain

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Abstract

Spain registers a much lower rate of colorectal cancer incidence and mortality than do other European countries, yet the rises observed in the adjusted rates over recent decades led us to attempt to monitor the trends over time using Poisson log-linear models. Incidence data were furnished by the Zaragoza and Navarre population-based cancer registries, whereas mortality data corresponded to Spain as a whole. For trend evaluation purposes, we made use of invariant parameters from age-period-cohort models (net drift and curvature) and a restriction of the cohort-effect slope range. The results suggest the presence of a marked rise in incidence of colorectal cancer for both sexes and across all age groups in the provinces studied. The rise in mortality was less pronounced than the rise in incidence and seemed to coincide with a marked cohort effect present throughout the study period. Both in incidence and mortality, the increases were more pronounced among men. When studied jointly, incidence and mortality trends tend to be complementary, rendering an approach of this nature especially important in sites with better survival, such as the case in point.

Introduction

Colorectal cancer is the third leading cancer affecting both sexes worldwide. Incidence and mortality vary widely between countries, depending on their degree of development. Estimates put the global number of incident cases in 1980 at 572,000, with approximately 11% occurring in Spain, providing a population coverage of 71% and enabling incidence figures and trends over recent years to be ascertained. There are a number of instances in which the use of available mortality and incidence data has been recommended for evaluation of time trends in cancer (2, 3). The primary reason for carrying out such analyses (apart from monitoring the trend) is to detect possible shifts in the prevalence of risk factors. In 1981–1982, colorectal cancer survival at 5 years of diagnosis already stood at around 40% for both sexes, so that mortality may not reflect evolution in the incidence rates.

Relatively speaking, Spain registers a much lower rate of colorectal cancer incidence and mortality than do other European countries (4), yet the rises observed in the adjusted rates over recent decades spurred us to attempt to characterize the disease’s pattern of evolution. Evaluation of this disease’s time trend was based on the following available information: (a) incidence in those provinces having a population-based register with over 15 years of experience, namely, Zaragoza and Navarre; and (b) Spanish mortality data. The aim of this study was to compare time trends for colorectal cancer incidence and mortality and to investigate age, time period, and birth cohort as determinants of such trends.

Materials and Methods

Incidence Statistics. Incidence data were furnished by the Zaragoza and Navarre Provincial Cancer Registries, originally set up in 1960 and 1973, respectively; both registers are population-based, with the former covering 824,776 inhabitants and the latter covering 512,512 inhabitants. The provinces are contiguous and lie in the north of the Iberian peninsula. Study of incidence rates covers the period 1963–1991 in Zaragoza and 1973–1991 in Navarre. A more detailed description of both registries can be found in Ref. 5.

Mortality Statistics. The national population figures, together with data (duly broken down by age and sex) on the number of deaths due to colorectal cancers, were obtained from the official annual reports of the Instituto Nacional de Estadística (National Statistics Institute). During the period under study, four consecutive revisions of the ICD were in use. In all four ICD revisions, rubrics 153 and 154 corresponded to colon and rectum cancer, respectively. In 1980, coinciding with the introduction of the ninth ICD revision, there was a marked decline in cases coded under rubric 153 (malignant neoplasm of colon), due to the classification of a considerable proportion of cases falling within the rubric “other specified sites of large intestine” (rubric 153.8) as “intestinal tract, part unspecified” (rubric

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3 The abbreviations used are: ICD, International Classification of Diseases and Causes of Death; df, degrees of freedom.
Incidence (Zaragoza)  
1963–1967 7.23 10.71 0.82 6.34 9.50 0.70 1.13  
1968–1972 9.94 14.78 1.15 7.12 10.78 0.75 1.37  
1973–1977 10.42 15.52 1.21 9.70 14.38 1.06 1.08  
1978–1982 13.59 20.76 1.51 10.68 16.01 1.16 1.30  
1983–1987 20.77 30.97 2.47 15.02 22.20 1.70 1.40  
1988–1990 25.97 39.44 3.05 17.15 25.51 1.89 1.55  
Incidence (Navarre)  
1973–1977 19.10 29.22 2.27 12.96 18.77 1.54 1.56  
1978–1982 22.78 34.39 2.63 15.82 23.30 1.81 1.48  
1983–1987 25.99 39.36 2.91 18.55 27.33 2.08 1.44  
1988–1991 31.15 47.47 3.46 19.84 28.11 2.18 1.69  
Mortality (Spain)  
1953–1957 6.03 9.13 0.73 6.62 10.08 0.74 0.91  
1958–1962 7.86 12.03 0.91 8.05 12.37 0.89 0.97  
1963–1967 8.80 13.46 1.01 8.74 13.63 0.91 0.99  
1968–1972 9.36 14.34 1.05 8.60 13.32 0.92 1.08  
1973–1977 10.64 16.34 1.20 9.16 14.14 0.98 1.16  
1978–1982 10.23 16.65 1.11 7.84 13.98 0.83 1.31  
1983–1987 11.51 20.34 1.23 8.17 14.79 0.84 1.43  
1988–1992 14.01 23.37 1.51 9.31 15.69 0.97 1.52

Table 1. Incidence and mortality for colorectal neoplasms

Men (age-adjusted rates)*

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<th>World</th>
<th>European</th>
<th>Cumulative*</th>
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<td>1968–1972</td>
<td>9.94</td>
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<td>10.42</td>
<td>15.52</td>
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<td>20.76</td>
<td>1.51</td>
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<td>1983–1987</td>
<td>20.77</td>
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<td>1988–1990</td>
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<td>39.44</td>
<td>3.05</td>
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Women (age-adjusted rates)*

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<td>9.50</td>
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<td>7.12</td>
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<td>1988–1990</td>
<td>17.15</td>
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Men:Women

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<td>1988–1990</td>
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* Age-adjusted rates per 100,000 person-years.

Cumulative risks (0–74) per 100.

159.0. As a consequence, in this analysis, rubric 159.0 has been included, along with rubrics 153 and 154.

As in many earlier studies and despite any implied loss of information, cases corresponding to cancer of the colon and cancer of the rectum were studied jointly. The reasons for this were as follows: (a) pinpointing the site and coding of tumors of the rectosigmoid junction classified as "rectum" (ICD 154) in ICD-8 and ICD-9 is difficult; and (b) until 1980, other unspecified sites of the large intestine were assigned to the colon.

Specific and Adjusted Rates. Age- and sex-specific mortality and incidence rates were calculated for 5-year periods. Rates were adjusted for age using the world and European populations as standard. Male:female mortality ratios were computed from age-adjusted rates. Population estimates used were those standing at the midpoint of each quinquennium studied, as calculated from available censuses and municipal rolls.

Poisson Models. On the assumption that the number of new cases and deaths in each age group and period would be distributed as a Poisson variable, a log-linear model was used to assess the effect of age, period, and cohort as independent variables. Bearing in mind the problem of identifiability of the parameters, we used cohort-effect curve analysis as proposed by Holford (6) and a restriction of the possible range of cohort-effect slopes (7). Cohort-effect curvature is the deviation from a model with age, period, and cohort variables didn't exceed its degrees of freedom by more than 10%.

Extra-Poisson dispersion was tested, evaluating that the deviance from a model with age, period, and cohort variables didn't exceed its degrees of freedom by more than 10%.

Whereas the same models were fitted for studying the trend in incidence and mortality, in the case of incidence, models including the registry identifier variable were additionally considered to check for the presence of register-related differences. Because the interaction between the register variable and the remaining variables proved significant in men, the results for the two registries have been shown separately.

Results

Table 1 and Fig. 1 show the trend in the adjusted incidence and mortality rates. A marked rise in incidence rates was observed in both sexes and for both registers, with a steepening of the slope in the last 10 years of the study period. The increase in incidence was far greater than that in mortality, with increases in both cases proving higher in men than in women.

Average age-adjusted colorectal cancer incidence rates in the final period studied were 24.49 and 16.39 per 100,000 person-years in men and women, respectively, in Navarre (Fig. 1). The interval between the periods 1978-1982 witnessed a 37.8% increase in male mortality. The sex ratio of mortality seemed to remain more stable.

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Fig. 1. Trends in age-adjusted incidence rates (European standard population) in Navarre and Zaragoza (left) and mortality in Spain (right). Thick lines, men; thin lines, women.

Fig. 2. Trends in age-specific incidence rates for Zaragoza and Navarre (jointly). Left, men; right, women.

In Fig. 2, the trend in age-specific incidence rates in men and women is depicted jointly for the two registries. Incidence was observed to increase for all age groups in both sexes, without any signs of stabilization in any one group. Goodness of fit of the age-period-cohort models is shown in Table 2. Both registers showed a trend over time, evinced by the statistical significance of any one of the terms added to the first model, with the presence (for both registers) of a net drift per 5-year period in men and women of 0.243 and 0.197, respectively, corresponding to annual increases of 4.98 and 4.01%. In the comparison of the three-term model against the two-term models nested therein, the only variable to attain statistical significance was the period effect in Zaragoza in men. Nevertheless, to facilitate comparison among incidence, mortality, and prov-
Table 2  Goodness of fit in age, period, and cohort models for colorectal cancer incidence in Zaragoza and Navarre and for mortality in Spain

<table>
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<th>Women</th>
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<td></td>
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<td>61.41</td>
<td>60</td>
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* Overdispersion was corrected. Without the correction for the three-factor model, the deviance was 30.95 and 30.87 with 28 df for men and women, respectively.

* Overdispersion was corrected. Without the correction for the three-factor model, the deviance was 123.98 and 134.5 with 60 df for men and women, respectively.

ince trends, both effects have been depicted in Figs. 3 and 5. The cohort effects proved very similar, irrespective of sex and register.

There is a little evidence of extra-Poisson dispersion in Zaragoza incidence data. The \( \chi^2 \) test for the period effect was 20.96 (4 df), being 22.51 (4 df) in the uncorrected model. In contrast, the effect of such correction was more clear in the cohort effect, 1.77 (12 df) versus 13.02 (12 df). Although, in the case in point, conclusions are not affected by controlling for overdispersion, we believe its use is motivated.

Fig. 4 shows the trend in age-specific mortality rates in men and women. In men, a rise in mortality was observed for all except the youngest age groups (25–34 years), something that seemed to correspond to a marked cohort effect that held steady up to generations born in and around 1948 and subsequently declined. In women, the trend was not quite as well defined, but a shift in trend was also observable for post-1948 generations.

The results plotted in Fig. 5 and taken from the mortality analysis based on age-period-cohort models better illustrate the
points made above with reference to the graph depicting age-specific rates. In men, a cohort effect was observed, which peaked in the 1948 generation and declined thereafter. The changes in the ICD revision can be seen in the period effect. In women, the cohort effect was less pronounced, with four stages being distinguishable: (a) an initial rise, which has been observed for other tumor sites (11) and possibly corresponds to the consolidation of mortality statistics in Spain; (b) a period of discreet rise from the 1888 generation through 1938; (c) a penultimate stage that reached a peak in 1948 (as with men); and (d) a subsequent decline. The cohort and period components were significant, with the three-factor model proving the best fitting (Table 2). Net drift for the mortality of men and women per 5-year period was 0.081 and 0.028, respectively (an increase of 1.62 and 0.55% per annum).

Discussion

The results suggest the presence of a marked rise in the incidence of colorectal cancer for both sexes and across all age groups in the provinces studied. The rise in mortality is less pronounced than the rise in incidence and seems to coincide with a marked cohort effect present throughout the study period. Both in incidence and mortality, the increases are more pronounced among men.

Shown in Table 3 is the trend in quality indicators (percentages of cases with histological confirmation and cases registered on the basis of death certificates) for the Navarre and Zaragoza colorectal cancer registers over the study period. The improvement in quality is evident in both cases and, moreover, is possibly associated with an improvement in diagnostic techniques, such as the use of flexible endoscopes, thereby implying that part of the steep rise in incidence may well be artifact-induced. The low incidence rates in Zaragoza during the first two 5-year periods for both sexes (Table 1 and Fig. 1) suggest possible underregistration during these years.

Implicit in this discussion is the assumption that, in part, incidence trends in Navarre and Zaragoza are representative of Spain as a whole. During the period 1978–1992, male mortality rates in Navarre and Zaragoza were 21.6 and 19.7 per 100,000 inhabitants, respectively, whereas the overall rate for Spain was 18.7 per 100,000. For women, the equivalent values were 13.2 and 13.9 per 100,000 for Navarre and Zaragoza and 13.1 per 100,000 for Spain overall (12). We are therefore of the opinion that incidence trends in these two provinces can indeed be taken as a good indicator of the prevailing situation countrywide.

In the mortality analysis, tumors of the “intestinal tract, part unspecified” (ICD 159.0) were included along with those of the colon and rectum. The reason for this lay in the changes introduced in the ICD in 1980, which led to a considerable number of tumors of the colon of unspecified site ceasing to be classified under rubrics 153.8 and 153.9. Parallel analyses were run with and without inclusion of rubric 159.0, and, as was to be expected, its inclusion failed to affect the cohort effects and caused a marked period effect detected in that year to disappear, hence better reflecting the real trend in mortality.

The results point to a marked increase in the incidence of colorectal cancer in both sexes and for both registries. On the basis of the data available, this could be attributed to a steady rise, one in which the role of the cohort and period components cannot be differentiated. The fact that the analysis covered only two provinces and that there was only a short period eligible for study renders a clean separation of the two components difficult.

The increase in mortality is more pronounced in men than in women (Fig. 1), with a birth cohort-associated component that holds steady until the 1948 generation (Fig. 5). In women, the cohort effect is more discreet, and the difference between the sexes increases with time. The decline in risk of death in post-1948 generations could be explained by enhanced survival deriving from advances in early detection (particularly with the aid of flexible endoscopes) and improved survival among the young (13). In the period 1979–1984, relative survival, as
reported by all European cancer registries, rose from 39 to 45% for colon cancer and from 36 to 41% for cancer of the rectum (13). Nevertheless, because these figures refer to younger age groups (age groups in which there would logically be a low number of cases), this shift in the cohort-effect trend should be interpreted with caution.

The disparity between men and women in incidence and mortality has been observed in a number of studies (14–17) and supports the existence of different etiologies. It has been suggested that sex-related differences in risk could be attributed to: (a) hormonal effects in the composition of the bile generating bile-acid cancer promoters; (b) a difference in bowel transit times determining different contact times between carcinogenic fecal substances and the mucous membrane; (c) use of exogenous hormones; and (d) differences in dietary habits (18). In the case of Spain, the first three explanations cannot account for the fact that in the period 1955–1965, colorectal cancer mortality was higher among women (Fig. 1 and Table 1). The subsequent trend in rates would seem to be better explained by the increase in exposure to risk factors and differences in dietary habits. Gradual introduction of such exposures into the population would have given rise to the cohort effect shown, with men undergoing more intensive exposure or, alternatively, women proving less susceptible or enjoying some element of protection.

Dietary risk factors described in colorectal cancer are high ingestion of animal fats and meat and total dietary calorie intake. Protective factors, such as consumption of vegetables, fruit, fiber, calcium, and aspirin, have been described previously (19–22). Hereditary factors are present in 10–15% of cases (23). Although results are not wholly consistent, in most cases, consumption of alcohol is reported to be a risk factor (24). Compared to consumption of other alcoholic drinks (wine and spirits), beer shows a stronger association with colorectal cancer and adenomas (24–26) and with cancer of the rectum in particular (25).

Food consumption patterns in Spain have been studied using different sources that agree as to their assessment of the trend in dietary habits (27, 28). In short, the transition from the 1960s to the 1990s has been accompanied by a fall in consumption of bread, cereals, legumes, potatoes, and olive oil and a considerable rise in the consumption of milk and dairy products, meat and poultry (beef, pork and chicken), and fruit and fish. Vegetable consumption has not changed substantially.

The higher male mortality and incidence seem likely to be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors. Sex-related differences in risk could be attributed to greater exposure to risk factors.
mented by recourse to nutritional surveys; in general terms, and taking women as reference, Spanish men consume more meat, eggs, sausage meats, and alcoholic beverages, whereas women consume more wholemeal bread, dairy products, butter and margarine, coffee, salads, pastries, fruit juices, and fruit (29–32).

In the more northern European countries (Finland, Sweden, Austria, Switzerland, Belgium, Denmark, and the United Kingdom), a plateau is observed with a downward mortality trend. France, Italy, and Portugal show a flattening out in their trends (4). Mortality in Spain is substantially lower than that for the rest of Europe, with Greece being the only country with better indicators, and this difference has itself been ascribed to dietary habits. In addition, Italy and Portugal show a period effect due to changes in ICD coding between 1977 and 1982 (4). In general, incidence of colorectal cancer is on the increase, which contrasts with the downward trend in mortality observed for the northern European countries (4).

Despite the difficulties implicit in the incidence analysis due to both the short study period and the consequences of consolidation of the cancer registers, the results suggest the presence of a marked increase in colorectal cancer incidence in both sexes in Spain, a finding further supported by the trend in mortality. A phenomenon of cohort-effect stabilization might be present in mortality and is something that would affect the youngest generations, although confirmation of any such shift in trend would have to be furnished by subsequent studies. When incidence and mortality trends are studied jointly, the information tends to be complementary, rendering an approach of this nature especially important in sites with better survival, such as the case in point.

Acknowledgments

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References

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