GENDER DIFFERENCES IN THE TREND OF COLORECTAL CANCER INCIDENCE IN SINGAPORE, 1968-2002

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ABSTRACT

Background and aims: Over the past decades, incidence trends of colorectal cancer are sharply increased in Singapore. In this population-based study we describe changes in colorectal cancer incidence in Singapore and explore the reasons behind these changes through age-period-cohort (APC) modelling. **Methods:** We included all 22 609 colorectal cancer cases reported to the Singapore Cancer Registry between 1968-2002. Poisson regression, using age-period (AP) and age-cohort (AC) models was used to determine the effects of age at diagnosis, calendar period and birth cohort. **Results**: Male colorectal cancer rates between 1968-2002 from 20 to 40 per 100,000 person years. The increase was sharpest among older men, for whom there was a significant AC effect. Female colorectal cancer rates increased until 1992 (from 16 to 29 per 100,000 person years) and stabilised afterwards. For women under 65 years, we observed a significant AP effect, corresponding to a sudden rise in colorectal cancer incidence around 1978. **Conclusions:** This study demonstrates important gender differences in colorectal cancer incidence in Singapore, with increasing rates among men, and stabilized rates in women. The increase in men is mainly attributable to an incidence increase the oldest age groups, probably due to increased exposure to dietary and lifestyle risk factors earlier in life. The stabilization in female colorectal cancer risk could be due to lower exposure to life style risk factors and prophylactic removal of precancerous lesions.

Key words: age-period-cohort effect, colorectal cancer, gender, incidence, Poisson regression

INTRODUCTION

With almost 1 million new cases per year, colorectal cancer accounts for 9.4% of all new cancer cases worldwide.(1) In Singapore, colorectal cancer is the second most frequent type of cancer for both sexes. It accounts for 17% of all cancers in men and for 14% in women.(2)

It has been estimated that as much as 70-80% of colorectal cancer can be attributed to environmental and lifestyle factors, such as dietary habits (low intake of fruits and vegetables, high intake of red meat, daily consumption of alcohol), smoking and physical activity.(3-6) On the other hand, individual, genetically-determined susceptibility probably also plays a crucial role through its interaction with the other etiologic factors.(3, 7-10)

Over the past decades, incidence trends of colorectal cancer have differed considerably between populations. The incidence has been declining in the United States,(11) slightly increasing or stabilizing in Europe, and sharply increasing in many other parts of the world, including Singapore.(2, 12) These heterogeneous patterns suggest different effects of age, year of birth and period of diagnosis on colorectal incidence across populations. Recent changes in colorectal cancer incidence may have been induced by changes in exposure to risk factors several decades ago, when cohorts now experiencing highest rates, were young. Screening and improvement of diagnostic techniques may increase colorectal cancer incidence over a short period. On the longer term, however, screening and routine check ups followed by preventive removal of large bowel polyps, may reduce colorectal cancer incidence.

In this study, we used age-period-cohort (APC) analysis to explain the trends of colorectal cancer in Singapore. Modelling of period and cohort effects can help unravel the potential contribution of changes in exposure to carcinogenic risk factors and the increased or improved diagnostic activity on the increasing colorectal cancer incidence.

MATERIAL AND METHODS

The Singapore Cancer Register is a well-documented nationwide registry. It started in 1968 and since then receives notifications of incident cancers from all medical practitioners and pathology laboratories as well as reviews of all hospital discharges and death certificates. The completeness of reporting was 97.8% for the period 1968-1977 and 99% for 1993-1997.(2, 13) In the present study, we focused on patients with colorectal cancer (ICD-9 codes 153 and 154; ICD-O2 codes C18-21). We described trends in colorectal cancer incidence using age-specific rates and number of incident cancer cases published by the Singapore Cancer Register.(2) As there were too few cases below the age of 30, analyses were restricted to those above 30 years old.

Statistical analysis

We used APC-modelling to explore the trends in colorectal cancer in Singapore. Multivariate APC models included seven 5-year periods between 1968 and 2002, eleven 5-year age categories (30-80+ years) and seventeen 5-year birth cohorts (starting in 1886-1990 and ending in 1971- 1975).

The APC model is a Poisson regression model, where the number of events in age group i, period j and birth cohort k (Y_{ijk}) is modelled as a Poisson random variable with mean θ_{ijk} as follows: Y_{ijk} = number of events in age group i, period j and cohort k; N_{ijk} = number of person-years in age group i, period j and cohort k; rate $R_{ijk} = Y_{ijk} / N_{ijk}$.

$$E [\ln R_{ijk}] = E [\ln \theta_{ijk} / N_{ijk}] = \mu + \alpha_i + \beta_j + \gamma_k$$

where μ denotes the baseline rate in the chosen reference stratum, α_i denotes the effect of the *i*th interval, β_j denotes the effect of the *j*th calendar period and γ_k is the effect of the *k*th birth cohort (derived from period minus age).

Thus, there is an exact linear dependency between these age, period and cohort effects since the birth cohort k = j – i + m, where m is the total number of age classes. As a result of this collinearity, we cannot estimate all the effects from the full model; so we limit our analysis to fitting age-cohort (AC) and age-period (AP) models to the data.

For both males and females, we performed APC analysis with all age groups together and for those <65 years and ≥65 years separately. The reference groups were as follows: i) age 30-34, period 1968–1972, and birth cohort 1921–1925 for models with all ages; ii) age 30-34, period 1968-1972, and birth cohort 1921-1925 for both males and females < 65 years of age, and iii) age 65-69, period 1968-1972 and birth cohort 1921-1925 for both males and females ≥65 years of age.

The deviance statistics and Z-test were used to determine the goodness of fit of the models and significance of the effects, respectively.(14) The Akaike Information Criterion (AIC) was also calculated as it enables the comparison of non-hierarchical models, with smaller values indicating better fit.(15) Incidence rate ratios (IRRs) were used to summarize the effects of birth cohort and calendar period. IRRs obtained from the models with significant results were plotted. For statistical analyses, we used STATA version 9.

RESULTS

Between 1968 and 2002, 11 859 men and 10 750 women, were diagnosed with colorectal cancer in Singapore. In men, the age-standardized (world standard population) incidence rate of colorectal cancer doubled from 19.6 in 1968-1972 to 40.1 per 100 000 person years in 1998-2002 (Figure 1). In women, colorectal cancer rates increased from 15.6 in 1968-1972 to 28.7 per 100 000 person years in 1988-1992, and remained fairly stable afterwards (29.4 per 100 000 person years in 1998-2002) (Figure 1).

For both sexes, the incidence rate of colorectal cancer increased with age and highest colorectal cancer rates were observed in the oldest age groups (Figure 2). In terms of changes within each age group, every succeeding birth cohort of men experienced a higher risk of colorectal cancer (Figure 2 panel A). For example, within the group of 75-79 year old men, those born between 1891-1895 had a colorectal cancer incidence of 163.4 per 100 000 person years, while those born between 1921-1925 had a risk of 416.2 per 100 000 person years.

In women, we observed increasing colorectal cancer rates in succeeding birth cohorts within the oldest age groups only (75-79 and 80+ year olds) (Figure 2, panel B). Below the age of 75 years, there was an increase in incidence rates in the earliest succeeding birth cohorts, followed by a stabilization of incidence rates in the most recent birth cohorts.

When all age-groups were analysed together, none of the models (age only, age-period and age-cohort) provided a good fit, neither for men nor women (Table 1). After stratification into younger (<65 years) and older (≥65 years) age groups, a model including age and birth cohort provided a good fit for men of 65 years and older (i.e. non

significant deviance test and lowest value of the AIC). For women under 65 years of age, the model including age and period provided the best fit (nonsignificant deviance test and lowest AIC). For 'younger' males and 'older' females none of the models provided a convincing fit.

The cohort effect in men ≥65 years is displayed in more detail in Figure 3. After adjustment for age, there was a constant increase in relative risk for colorectal cancer in subsequent birth cohorts. Taking men born between 1921 and 1925 as a reference, those born at the end of the 19th century had a 60 to 70% lower risk of developing colorectal cancer, while men born between 1936-1940 had a 30% higher risk of developing colorectal cancer.

The period effect observed in women between 30 and 65 years is presented in Figure 4. The risk of being diagnosed with colorectal cancer for women between 30 and 65 years increased by more than 40% between 1973-1977 and 1978-1982. From 1983 onwards, the risk of developing colorectal cancer remained stable for women between 30 and 65 years.

DISCUSSION

This study showed marked gender differences in incidence trends of colorectal cancer in Singapore. Up until 1992, colorectal cancer rates were increasing for both sexes. Between 1993 and 2002, rates continued to increase in men, but remained stable for women.

The incidence increase in men older than 65 years was dominated by cohort-based changes, while for women between 30 and 65 years of age, the increase in incidence was explained by a period effect. For younger men and older women, no significant cohort or period changes could be observed.

In general, cohort effects implicate increasing exposure to risk factors in successive birth cohorts. The risk of developing colorectal cancer is closely related with dietary and lifestyle factors.(6) There is a strong positive association with high intake of saturated fat and animal protein (especially red meat), and a negative association with consumption of fruit and vegetables and physical activity.(16)

Over the past decades, dietary and lifestyle habits of the Singaporean population have undergone major changes. Singapore became independent in 1965 and has undergone rapid economic growth and industrialization since. Per capita Gross Domestic Product has leaped from US$ 427 in 1960 to US$ 26,833 in 2005.(17) This rapid economic growth was followed by changes towards a ‘westernized’ lifestyle, i.e. increased consumption of meat and saturated fat and a reduced intake of fruit and vegetables.(12) A case-control study conducted among Singaporean Chinese has shown that high levels of meat intake and low fruit and vegetable consumption was strongly associated with an increased colorectal cancer risk.(18)

With the increasing affluence, fewer Singaporeans are employed in physically demanding jobs and sedentary lifestyles are prevalent in the Singaporean population.(19) Singapore has also experienced increasing rates of chronic diseases, such as obesity and diabetes mellitus, which are in itself risk factors for colorectal cancer.(6) The impact of these accumulated risk factors may have translated to a strong cohort effect on colorectal cancer incidence in males aged 65 and older.

Although the lifestyle of the younger Singaporeans has also changed significantly over the past decades, there was no cohort effect on colorectal cancer incidence in younger men. Changes in lifestyle and diet in the younger generations will probably only translate in higher colorectal cancer rates when these young people grow older.

The changes in female colorectal incidence are more challenging to interpret. Overall female incidence rates increased rapidly up until 1992 and have been stabilizing since 1993. Also within age groups, colorectal cancer rates stabilized in the most recent birth cohorts. Only for women of 75 years and older, colorectal cancer rates continued to increase in subsequent birth cohorts.

We observed a significant period effect among women aged 30-65 years. In this age group, the colorectal cancer rates increased by more than 40% between 1978 and 1982. After 1983, colorectal cancer rates remained stable for women under 65 years. It is difficult to offer a good explanation for this sudden increase. There may be indirect evidence for an increase in access to healthcare in younger women during the seventies. In Singapore, employers provide medical benefits for their employees (20) and the number of women participating in labour force increased sharply, from 29.5% in 1970 and 44.3% in 1980 to 55.5% in 2000. This implies that more women aged 30-65 years

gained access to health checks, which could possibly explain the significant period effect. This increased case finding in younger age groups, set off by better access to medical care and increased diagnostic surveillance which subsequently could lead to an increase in prophylactic removal of precancerous lesions, may account in part for the stabilization of incidence rates in the older women.

An alternative explanation for the stabilization of colorectal cancer rates in females may be less exposure to changes in lifestyle risk factors than Singaporean men. Women in general are known to have healthier habits related to nutrition (21-23) and in Singapore women may have adopted the westernised lifestyle to a lower extent than their male counterparts.

Today, Singaporean colorectal cancer rates are comparable to those in Asians/Pacific Islanders in the United States, who have been exposed to a Westernised lifestyle for a longer time. In 2000-2003, colorectal cancer incidence rates (standardized to world population) for Asians and Pacific Islanders living in the USA were 31 and 22 per 100,000 person years for men and women respectively, compared to 40 and 29 per 100,000 person years, respectively, between 1998-2002 in Singapore.(24)

Colorectal cancer is a major health problem in Singapore, so it is important to implement prevention strategies for this disease. The results of this APC analysis suggest that prevention of colorectal cancer, for example promotion of a healthier lifestyle, is especially important among older men is Singapore. Thereby, it is known that older people are less likely to go for FOBT screening and that increasing knowledge about colorectal cancer may improve screening uptake (25). So, healthcare professionals may

promote colorectal cancer screening among older men in Singapore to make them more aware of this health problem, and the attendance rate will increase.

In conclusion, colorectal cancer incidence is still increasing among men, but seems to have reached a plateau in women. The increase in men is mainly attributable to an incidence increase among the oldest age groups, probably due to rapid changes in exposure to dietary and lifestyle risk factors earlier in life. The pattern in women could represent a real stabilization in female colorectal cancer risk, probably due to lower exposure to life style risk factors and/or prophylactic removal of precancerous lesions.

Table 1. Age-Period-Cohort modelling results, Colorectal Cancer Singapore 1968-2002

Model	Group [a]	Deviance	df	p	AIC [b]
Age	Males	557.38	66	<.001	1077.5
Age + period	Males	136.18	60	<.001	668.4
Age + cohort	Males	76.56	50	.009	628.7
Age	Females	458.63	66	<.001	973.4
Age + period	Females	171.10	60	<.001	697.9
Age + cohort	Females	90.75	50	<.001	637.6
Age	M < 65	251.84	42	.000	571,5
Age + period	M < 65	82.46	36	.000	414,2
Age + cohort	M < 65	43.84	30	.049	387,5
Age	M > 65	305.54	24	.000	506,0
Age + period	M > 65	39.50	18	.002	252,0
Age + cohort	M > 65	20.46	15	.155	238,9
Age	F < 65	105.16	42	.000	418,0
Age + period	F < 65	44.09	36	.167	368,9
Age + cohort	F < 65	53.41	30	.005	390,3
Age	F > 65	353.46	24	.000	555,4
Age + period	F > 65	50.16	18	.000	264,1
Age + cohort	F > 65	30.71	15	.010	250,7

[a] M < 65 = Males under 65 years of age, M > 65 = Males over 65 years of age, F < 65 = Females under 65 years of age, F > 65 = Females over 65 years of age.
[b] AIC = Akaike Information Criterion

Figure 1. Age standardized incidence rates (ASR) per 100’000 per year, standardised to World Standard Population of colorectal cancer in males and females in Singapore, 1968-2002

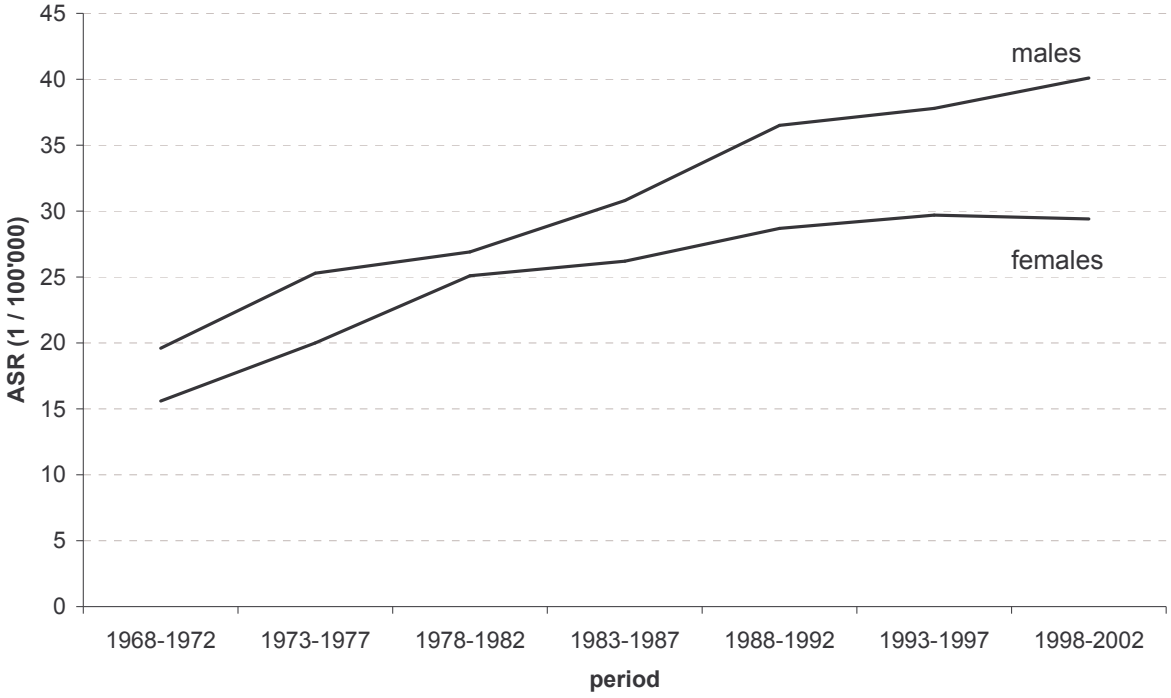
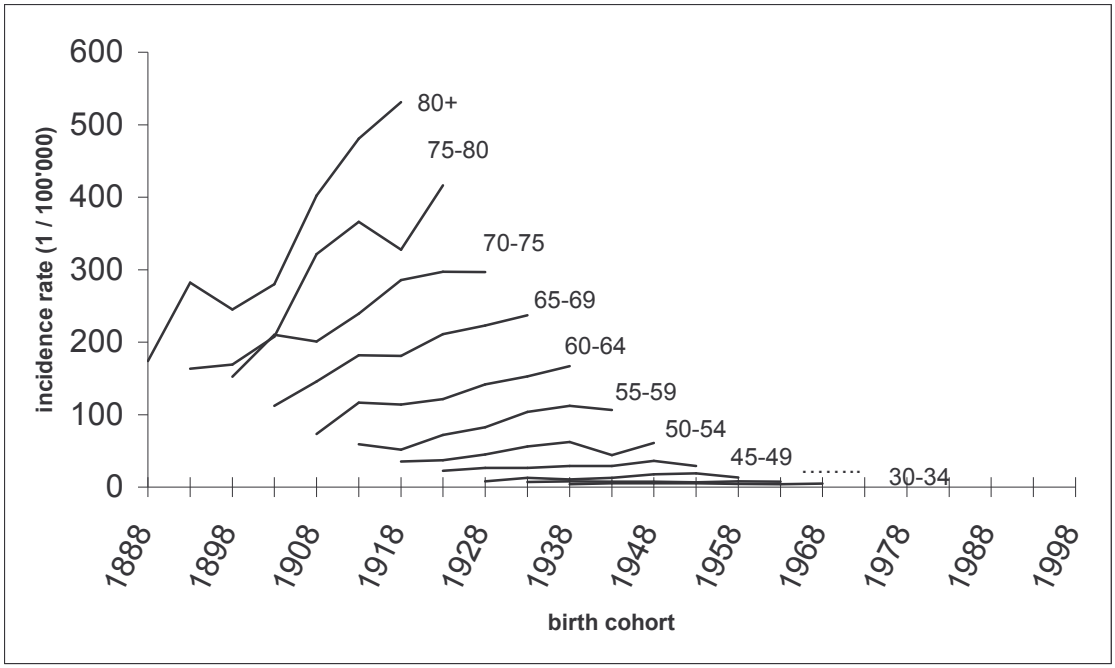


Figure 2. Age specific incidence rates of colorectal cancer by 5-year interval and birth cohorts for men (panel A) and women (panel B) 1968-2002.

A



B

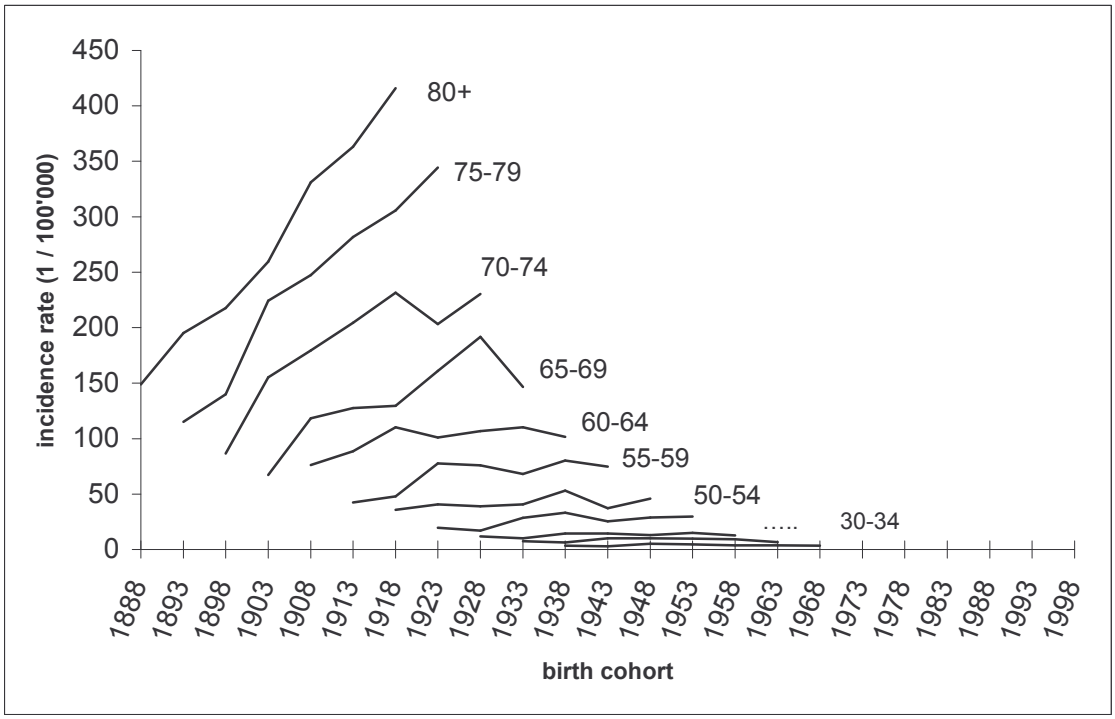


Figure 3. Relative risks (95% CI) of colorectal cancer according to birth cohort for men 65 years and older, with cohort 1921-1925 as a reference category. Estimates derived from age-cohort model, 1968 and 2002

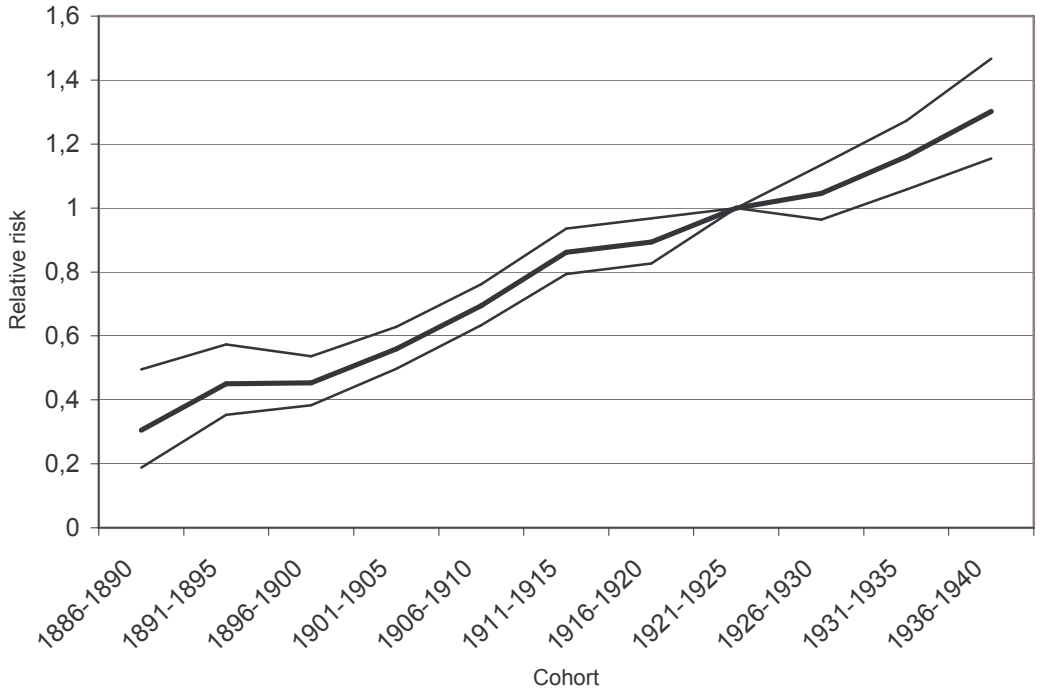
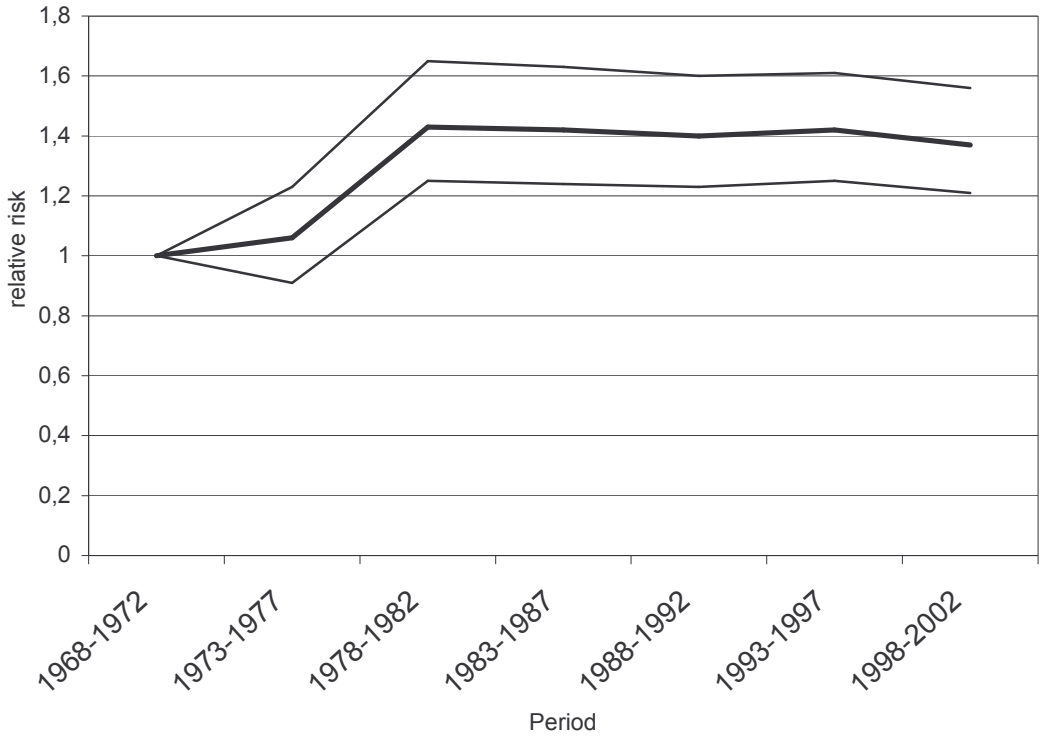


Figure 4. Relative risks (95% CI) of colorectal cancer according to period for women 30-65 years, with period 1968-1972 as a reference category. Estimates derived from age-period model, 1968-2002



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