



## Screening

# Effects of screening and universal healthcare on long-term colorectal cancer mortality

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## Abstract

**Background:** To evaluate the time trends of colorectal cancer (CRC) affected by a Nationwide Colorectal Cancer Screening (NCCS) programme with biennial faecal immunochemical testing (FIT) and Nationwide Healthcare Insurance (NHI).

**Methods:** Data from the national registries on cancer and death in Taiwan were separated into years 1984–1993, 1994–2003 and 2004–2013 based on the implementations of NHI (starting 1995) and NCCS (starting 2004). The adult population was divided into three age groups (young, 30–49; middle-aged, 50–69; and old, 70–84 years); only the middle-aged were eligible for NCCS. Crude and adjusted effects of NCCS and NHI were quantified by percentage change and 95% confidence interval (CI) with respect to CRC mortality, according to the attributions from incidence and survival.

**Results:** Within 335 million person-years of follow-up, 204 362 incident CRCs and 80 771 CRC-related deaths were identified. Increasing mortality trends were noted for 1994–2003 (post-NHI) vs 1984–1993 due to remarkable increasing incidence trends that could not be offset by improved survival as a result of NHI. During 2004–13 (post-NCCS), mortality continued to increase by 15% (95% CI: 10–21%) in young adults (30–49 years) and

8% (95% CI: 6–11%) in older adults (70–84 years), whereas middle-aged adults (50–69 years) had a reduction of 7% (95% CI: 5–9%) due to a remarkable stage shift and subsequent improvement in survival. In the middle-aged adults, increased incidence was less but survival improvement was more compared with other age groups.

**Conclusions:** Whereas universal healthcare insurance led to improvement in CRC survival, FIT-based screening has made an even greater contribution to reducing CRC mortality.

**Key words:** cancer prevention, screening, colorectal cancer, colonoscopy

#### Key Messages

- We used an age-period-cohort analysis to investigate the impacts of secondary prevention with faecal immunochemical testing (FIT) and tertiary prevention with universal healthcare on the time trends of colorectal cancer (CRC) mortality.
- We also separated the attributions of CRC incidence and survival on the observed mortality changes.
- A significant reduction in CRC mortality occurred only 10 years after the implementation of a FIT-based screening programme in the eligible subpopulation, even though the equal access to the best healthcare through universal insurance coverage has continuously improved the survival of CRC patients.
- By considering the common global phenomenon of increased CRC incidence but improved survival over time, the present study particularly proves that active screening with FIT as a healthcare policy can lead to a substantial shift in CRC stages at diagnosis and efficiently reduce the number of deaths from CRC on a nationwide scale.

## Introduction

Colorectal cancer (CRC) is a global health threat; among the new cases and deaths from CRC, 42.6 and 45.6%, respectively, occurred in Asia in parallel with economic growth, changes in lifestyle and increased life expectancy.<sup>1</sup> To reduce the burden of CRC, global populations require an effective strategy by which to control modifiable risk factors (primary prevention), implementation of a screening programme for early detection (secondary prevention) and provision of universal healthcare and better access to the best healthcare available (tertiary prevention).

Compared with the long time before the benefits of new behaviours become observable and high cost and limited survival after aggressive therapy for advanced diseases, screening is the most effective method to modify risk.<sup>2</sup> Colonoscopy is the main tool used to reduce the incidence and mortality of CRC via the removal of colon polyps and early detection of cancer;<sup>3–8</sup> nonetheless, low population adherence and limited availability of endoscopists have hindered the widespread use of colonoscopy as the primary tool for population-based screening programmes. The use of faecal occult blood testing is an alternative approach to identifying patients with the highest risk so endoscopic resources can be allocated efficiently.<sup>9</sup> This is especially

true because the traditional guaiac-based test has been replaced increasingly by the faecal immunochemical test (FIT),<sup>10–12</sup> which has higher specificity and a more patient-friendly sampling design.<sup>13</sup>

Research evidence is needed to support the effectiveness of interventions so that adjustments can be made to maximize these benefits. Reduction of CRC mortality is the uppermost goal, whereas mortality is the final sequelae of the counterbalance between incidence and survival,<sup>14</sup> which, in turn, is associated with a complex causal interaction between risk-factor exposure, screening and treatment. In the absence of data from a large cohort with chronological changes in the disease burden after different interventions, it remains challenging to clarify the benefits generated from an ongoing screening programme (secondary prevention) and universal healthcare (tertiary prevention).

In Taiwan, cancer epidemiology has gradually shifted towards the Western pattern.<sup>15</sup> The Nationwide Colorectal Cancer Screening (NCCS) programme was launched in 2004 to control the soaring burden of CRC.<sup>16</sup> In addition, universal healthcare insurance, starting in 1995, has given all residents of Taiwan equal access to medical care.<sup>17</sup> Given data collected one decade before and after each intervention, our primary objective was to

answer whether or not a FIT-based screening programme and universal healthcare could reduce CRC mortality, and to do this by evaluating the common temporal trends of an increased incidence of CRC along with improved survival over time. Our secondary objective was to explore the cohort effect, which may serve as a measure of risk-factor exposure and provide a basis for primary prevention.

## Methods

### Study population

Data on the burden of CRC in Taiwan were retrieved from the National Cancer Registry, with indication of high coverage (99%; each hospital mandated to report all cases of CRC) and high accuracy (percentage of death-certificate-only cases of less than 1% for CRC).<sup>18</sup> Patient data included gender, number of patients with a specific type of cancer, age at cancer diagnosis and age at cancer-related death for each calendar year since 1979.<sup>19</sup> Incidence and mortality rates were calculated by dividing the numbers of incident cases of CRC and deaths from CRC by the number of persons at risk. The definition of CRC was based on the International Statistical Classification of Diseases (ICD) and Related Health Problems, 10<sup>th</sup> revision, in which CRCs were coded as C18–21.<sup>20</sup> Cancer staging was based on the American Joint Committee on Cancer (AJCC) system, which has been available since 2004.<sup>21</sup>

### NCCS programme

In 2004, a nationwide screening programme for CRC was launched in Taiwan; details regarding the accuracy of FIT,<sup>11</sup> colonoscopic referral<sup>22</sup> and preliminary effectiveness<sup>16</sup> have been reported elsewhere. In brief, residents aged 50–69 years were invited to have biennial FIT screening. The cut-off concentration for a positive test was 20 µg haemoglobin per gram of faeces (using kits from Eiken Chemical Co, Tokyo, Japan or Kyowa Medex Co Ltd, Tokyo, Japan). Colonoscopy was recommended within 3 months of a positive faecal test.<sup>23</sup> The histopathology of colonic lesions was classified according to the World Health Organization criteria.<sup>24</sup>

In the inaugural period between 2004 and 2009, the delivery of FIT was based on a community-based outreach to community residents who did not use or who underused medical services, encouraging them to participate in the free screening service at public health centres. The annual number of persons screened was about 250 000 and, with a target population of about 5 million, the coverage rate reached 21.4% in 2009.

To increase the accessibility of screening, starting in 2010, the previous approach was combined with an in-reach,

hospital-based programme that invited subjects who were already engaged in the healthcare system for treatment unrelated to CRC.<sup>25</sup> During this full-implementation period, the annual number of persons screened increased substantially to about 1 million, and the coverage rate reached 44.6% in 2011 and 63.8% in 2013.

### Nationwide Healthcare Insurance (NHI)

Before the implementation of NHI, public healthcare insurance in Taiwan included only certain subpopulations such as government employees, labourers, farmers, fishermen and low-income households. To expand the coverage, starting in 1995, NHI consolidated all small insurance plans into a universal insurance system that aimed to provide equal access and standard quality of healthcare for all citizens at affordable costs.<sup>17</sup> A family of four typically paid a premium equivalent to about US \$100 per month, which accounted for about 2% of the average household income in Taiwan. In 1995, about 92% of the whole population was covered by NHI and the coverage rate increased to 96% in 2000 and reached 99.9% in 2016.

In addition to achieving good accessibility to treatment, comprehensive population coverage and relatively low costs, NHI quality control was ensured by providing a nationwide databank to generate studies to monitor and evaluate healthcare services with the purpose of narrowing healthcare disparities.<sup>26,27</sup>

### Study design

This study followed the principle of age-period-cohort analysis to evaluate the effects of NCCS and NHI on chronological changes in the CRC burden in Taiwan. To allow sufficient follow-up time for evaluation, data from 1984 to 2013 were retrieved and separated into three 10-year periods, including Period 1, 1984–1993; Period 2, 1994–2003 (post-NHI); and Period 3, 2004–2013 (post-NCCS), according to the implementation dates of NHI and NCCS. Because CRC is rare in patients aged <30 years and the average lifespan of a Taiwanese is about 80 years (83.2 years for women and 76.7 years for men), analyses were limited to the population aged 30–84 years.

### Statistical analysis

For descriptive analyses, data were first stratified into 11 5-year age bands: 35–39, 40–44 ... to 80–84. Next, participants were divided into six time periods: 1984–1988, 1989–1993 ... to 2009–2013 for every 5 years. Together, these stratifications generated 16 successive birth cohorts: 1902–1906, 1907–1911 ... to 1977–1981 with equal

lengths of time. An age-and-period cross-table was generated that allowed evaluation of the changes in CRC. Different outcomes were also evaluated according to gender because of its important role in policymaking.

Second, time-trend analyses were performed by presenting CRC incidence, survival (case-fatality rates: the mortality/incidence ratio, an indicator for cancer survival; a lower case-fatality rate indicates better survival) and mortality in graphs, giving special attention to the changes before and after the implementation of NCCS and NHI. Because only subjects aged 50–69 years were eligible for NCCS, the population was divided into three age groups (young adults, 30–49; middle-aged, 50–69; and older adults, 70–84 years) in order to identify differences between them.

Third, to quantify the effects of interventions, the Poisson regression model was applied, with Periods 1–3 as the explanatory indicators, after adjusting for age and sex. Periods 1 and 2 were compared with assess the effect of NHI and between Periods 2 and 3 to assess the effect of NCCS. The main objective was to evaluate the changes in the middle-aged subgroup during Period 3 because they had been exposed to NCCS; hence, within this period, other age groups could also serve as comparators. The results are presented with the relative risk or the percentage of change expressed by  $(\text{relative risk} - 1) \times 100\%$  and the corresponding 95% confidence interval (CI). Interactions of period-by-age and period-by-sex were also evaluated.

To verify the benefit of early detection of CRC by the NCCS programme, cancer-stage data of the middle-aged subgroup and the other age groups were compared by hypothesizing that, in the middle-aged group, early detection would lead to a lower incidence rate of advanced-stage CRC. The results are presented with the proportion of advanced-stage (defined as stage II–IV) to overall CRCs over time.

Since cancer mortality is determined by incidence and survival, we estimated the attributable proportion of CRC mortality related to these two determinants (detailed in [Supplementary Material](#), available as [Supplementary Data](#) at *IJE* online), assuming that a substantial increase in screening volume for the middle-aged group would lead to widespread early detection of CRC and improvement in CRC survival may outweigh the increase in new incident cases.

Finally, knowing that patients in the same birth cohort may share exposure to similar socio-environmental factors, a cohort analysis was conducted to quantify the effect of risk-factor exposures. Most subjects in the 16 birth cohorts had been exposed to both NHI and NCCS, so this analysis does not address the effects of these two interventions. A Bayesian approach was applied to deal with the potential confounding effects and linear dependencies of age, period and cohort ([Supplementary Figure 1](#), available as

[Supplementary Data](#) at *IJE* online).<sup>28,29</sup> The results are presented as the annual percentage change of CRC incidence.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge, UK).

## Results

### Descriptive analysis

Data for the present study were derived from approximately 11 million persons per year, a follow-up time of three decades and approximately 335 million person-years of follow-up. Overall, there were 204 362 incident CRCs and 80 771 CRC-related deaths. As shown in [Tables 1](#) and [2](#), the incidence and mortality rates of CRC increased with both age and period. When data were stratified by sex ([Supplementary Tables 1 and 2](#), available as [Supplementary Data](#) at *IJE* online), the increasing trends were similar but their magnitudes were different. For the younger-age subgroup, the incidence and mortality rates were similar between sexes; during middle age, the increasing trends became more substantial in men. Until the period of 2009–13, women and men reached parity in CRC incidence and mortality rates only when the women were about 10 and 5 years older than men, respectively.

The numbers on the diagonal indicate the mortality rates with age for a specific birth cohort; e.g. the cells in shadow indicate the mortality rates of the population bore during the period of 1947–51 ([Table 2](#)).

### Time-trend analysis

As shown in [Figure 1](#), the overall CRC incidence rate increased with time. Men had a more dramatic increase in CRC incidence than women. During Period 3, although it had a similar increasing trend in mortality, the slope decreased slightly. Using Period 1 as the reference group, 1.83- and 2.78-fold increases were observed in incidence, and 1.45- and 1.70-fold increases in mortality, respectively, during Periods 2 and 3.

### Age-specific findings

Results were then stratified according to age. In the middle-aged group ([Figure 2](#)), the trends for incidence and mortality rates were different from those of the two other age groups. The incidence rate reached a peak in 2010, the time of full implementation of NCCS, and gradually declined thereafter. Mortality reached a plateau during Period 2 and also was followed by a decreasing trend during Period 3. In contrast, results were similar in the other age groups to those of the overall group; the trends for incidence and mortality were increasing continuously ([Supplementary Figures 2A and 2B](#), available as [Supplementary Data](#) at *IJE* online).

**Table 1.** Age-specific incidence rates of CRC cross-tabulated by period in Taiwan from 1984 to 2013 to derive the birth-cohort-specific rates in the diagonal matrix

	Period					
	1984–1988	1989–1993	1994–1998	1999–2003	2004–2008	2009–2013
Age						
30–34	3.7	4.5	5.2	6.0	6.9	7.9
35–49	6.0	7.5	8.1	9.7	11.5	14.6
40–44	9.1	12.0	14.8	16.9	19.1	23.2
45–49	16.4	19.9	23.9	29.8	33.6	40.8
50–54	25.8	33.3	41.9	47.8	59.1	72.2
55–59	39.2	50.9	67.1	77.0	91.9	111.5
60–64	55.9	76.6	101.2	120.5	138.8	161.5
65–69	72.1	99.4	141.2	174.1	194.7	224.1
70–74	88.9	135.6	178.0	226.7	255.9	274.5
75–79	77.6	152.0	216.8	276.0	318.4	357.6
80–84	74.8	111.6	224.1	299.0	358.3	406.4

Per 100 000 person-years, crude rate.

The numbers on the diagonal indicate the incidence rates with age for a specific birth cohort; e.g. the cells in shadow indicate the incidence rates of the population bore during the period of 1947–51.

**Table 2.** Age-specific mortality rates of CRC cross-tabulated by period in Taiwan from 1984 to 2013 to derive the birth-cohort-specific rates in the diagonal matrix

	Period					
	1984–1988	1989–1993	1994–1998	1999–2003	2004–2008	2009–2013
Age						
30–34	1.9	2.0	2.1	2.2	2.3	2.1
35–49	3.0	3.1	3.2	3.3	3.4	3.9
40–44	4.4	4.9	5.3	5.7	5.5	6.0
45–49	7.3	7.6	8.4	9.2	10.0	9.7
50–54	11.7	13.2	13.3	15.6	16.3	16.4
55–59	19.2	20.6	24.3	25.7	25.4	27.5
60–64	30.2	32.2	41.5	40.8	41.6	39.8
65–69	45.6	49.6	62.0	65.3	62.6	61.7
70–74	68.4	73.1	89.3	100.9	101.2	90.2
75–79	98.2	102.6	135.2	153.0	149.3	145.9
80–84	120.3	112.8	173.2	207.7	216.7	213.9

Per 100 000 person-years, crude rate.

### Sex differences

Similarly to differences shown in the age-and-period cross-tables, sex differences started at middle age and increased gradually over time. Similarly, improvements in survival rates were observed between the different age groups and between sexes.

### Multivariable regression analysis

The results of multivariable regression analysis are shown in Table 3. The age-by-period interactions were significant but the sex-by-period interactions were not, so the results were stratified by age and were adjusted for sex.

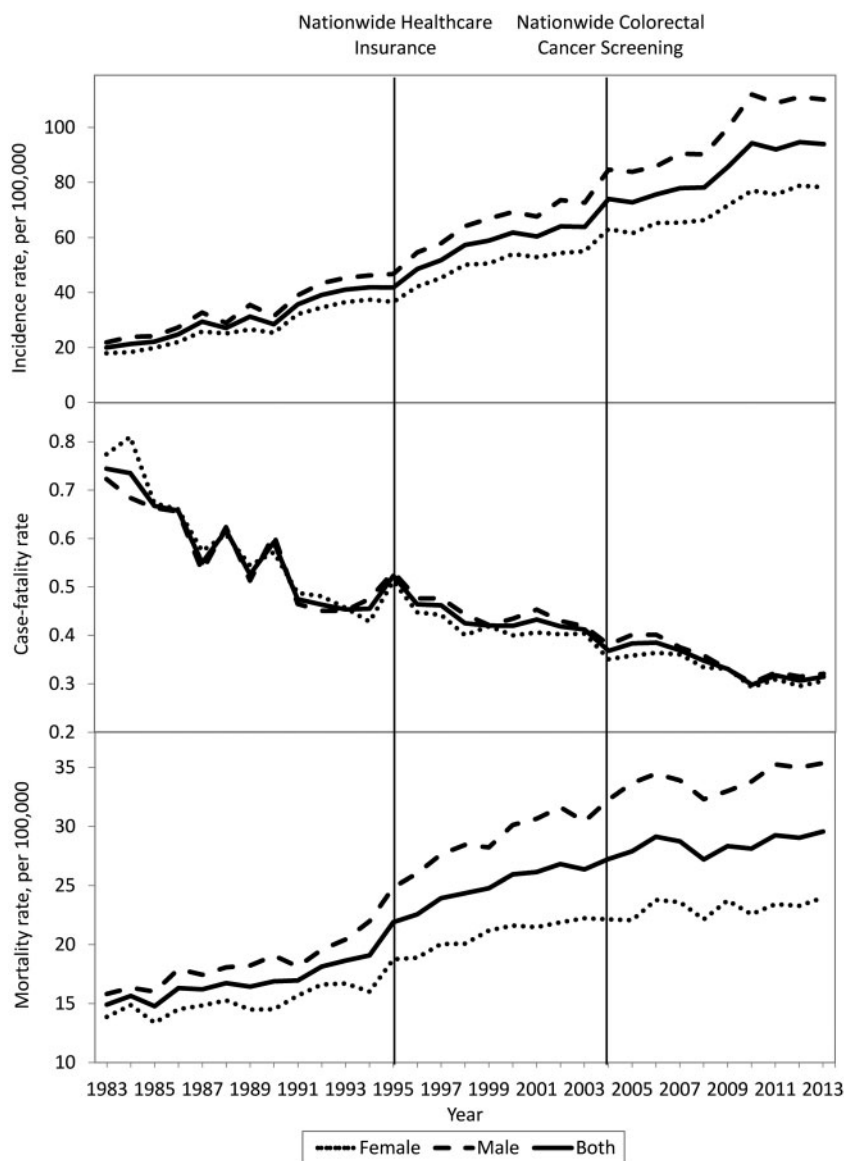
### Effects of healthcare policies on CRC incidence

Using Period 1 as the baseline comparator, the incremental percentages (95% CIs) of CRC incidence during Period 2

were 56% (51–62%), 71% (68–74%) and 101% (95–106%), respectively, for the young-, middle- and older-age subgroups, and results for all subgroups indicated an increasing trend in incidence. Using Period 2 as the reference group, the incremental percentages during Period 3 were 46% (42–49%), 29% (28–31%) and 40% (38–42%) for the young-, middle- and older-age subgroups, respectively. Although the increasing trend was seen in the middle-aged subgroup, the increase was attenuated compared with that in the other age subgroups that were not eligible for the NCCS programme.

### Effects of healthcare policies on CRC survival

Using the baseline comparator of Period 1, improvements in the survival rate during Period 2 were 21% (18–25%), 24%



**Figure 1.** Chronological trends regarding CRC incidence (upper), survival (case-fatality, middle) and mortality rates (lower) in Taiwan during 1983–2013 for the overall population, stratified by sex.

(22–26%) and 29% (27–31%), respectively, for the young-, middle- and old-age subgroups. Using Period 2 as the baseline, the improvements during Period 3 were 21% (18–24%), 28% (26–29%) and 21% (19–23%), respectively, for the young-, middle- and older-age subgroups; the middle-aged subgroup had greater improvement in CRC survival.

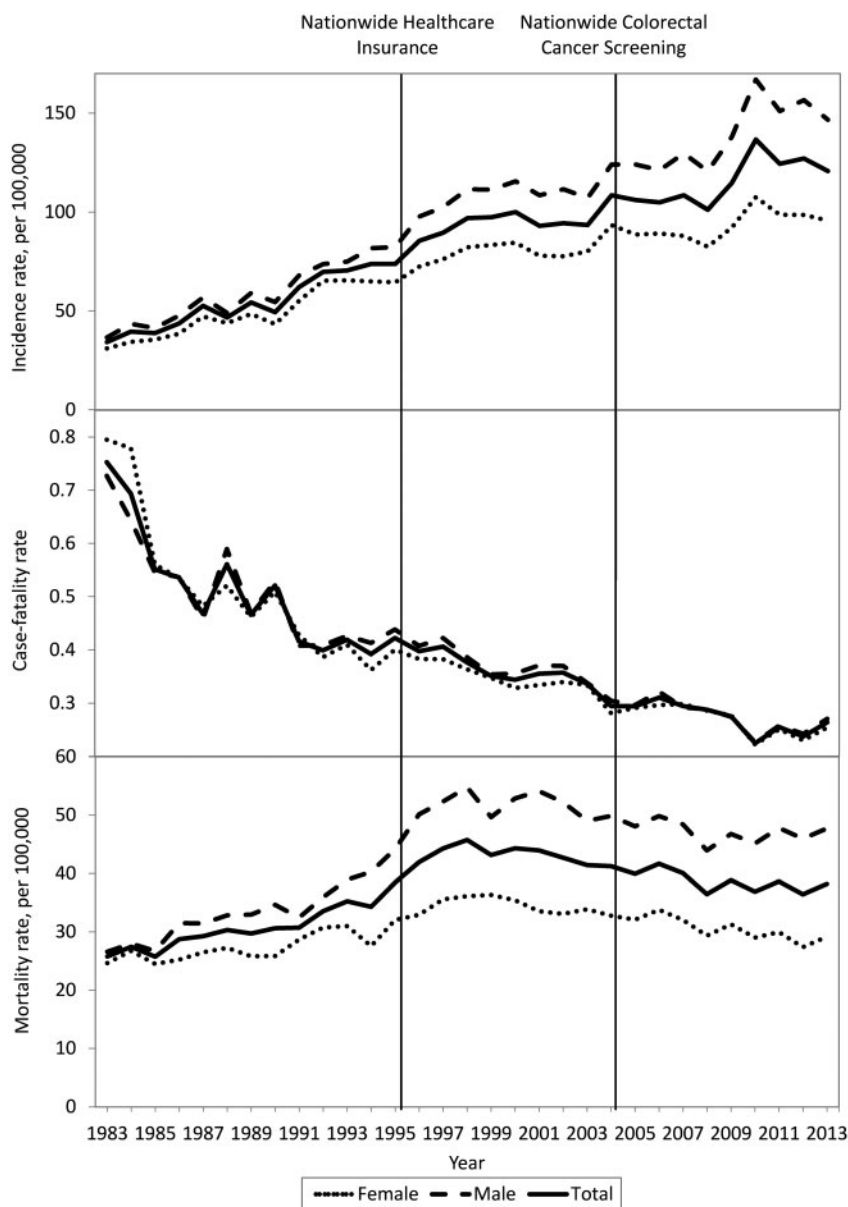
#### Effects of healthcare policies on CRC mortality

As compared with Period 1, the incremental percentages for the young-, middle- and older-age subgroups were 24% (18–32%), 41% (37–44%) and 51% (45–57%), respectively, during Period 2. Using Period 2 as the baseline, the incremental percentages during Period 3 were 15% (10–21%) and 8% (6–11%) for the young- and older-age subgroups, respectively. In contrast with the increased mortality

rate in the other age subgroups that were not eligible for NCCS, the mortality rate of the middle-aged subgroup decreased by 7% (5–9%), with reductions of 5% (3–8%) and 9% (6–13%), respectively, for men and women.

#### Distribution of CRC stages at diagnosis

The cancer staging at diagnosis during Period 3 is shown in Figure 3. The proportions of advanced-stage to overall CRCs decreased with time in all three age subgroups (Supplementary Table 3, available as Supplementary Data at *IJE* online). However, the decrease in the middle-aged subgroup (declined from 77 to 56%, difference: 21%, 95% CI: 19–22%) was greater than those in both the younger-age subgroup (declined from 84 to 70%,



**Figure 2.** Chronological trends regarding CRC incidence (upper), survival (case-fatality, middle) and mortality rates (lower) in Taiwan during 1983–2013 for the population aged 50–69 years, stratified by sex.

difference: 14%, 11–18%) and older-age subgroup (declined from 81 to 68%, difference: 13%, 11–15%), indicating that NCCS had remarkable effects on the stage shift towards earlier diagnosis. If stages 0–II were defined as the early stage, the results were similar.

#### Attributable proportion of CRC mortality

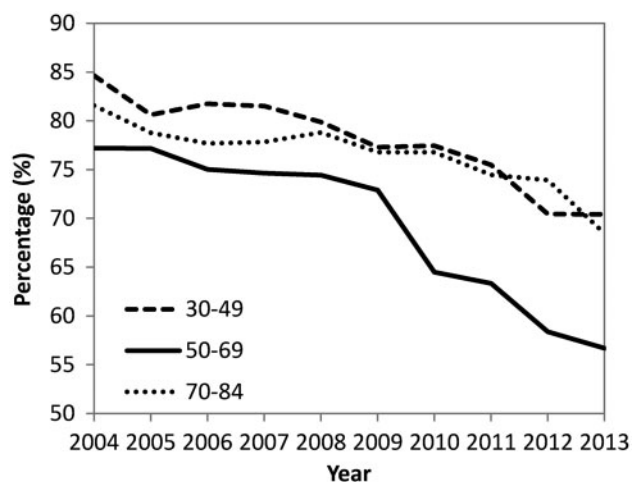
The overall attributable proportion of mortality between Periods 2 and 3 was  $-6.9\%$  (95% CI:  $-9.2$  to  $-4.4\%$ ) in the middle-aged subgroup whereas those in the younger- and older-age subgroups were  $+11.8\%$  (7.1–16.3%) and  $+5.4\%$  (2.8–8.0%), respectively (Supplementary Table 4,

available as [Supplementary Data](#) at *IJE* online). When the mortality change was separated according to the impact of incidence and survival, the results showed an increase of  $+23.0\%$  (95% CI: 21.7–24.2%) in CRC-related deaths in the middle-aged subgroup after NCCS implementation was related to the emergence of new cases; however, that was outweighed by a reduction in case fatality ( $-28.3\%$ , 95% CI:  $-30.4$  to  $-26.1\%$ ), resulting in a net decrease in the mortality rate. Both figures were lower than those in the younger-age ( $+31.0$  and  $-21.7\%$ ) and older-age subgroups ( $+26.4$  and  $-22.1\%$ ), in which the survival improvement was apparently outweighed by the emergence of new cases, leading to a continuous increase in the mortality rate.

**Table 3.** The relative risk for colorectal cancer incidence, survival and mortality rates by age and period, adjusted for sex

Age	Period	Incidence rate		Survival rate		Mortality rate	
		aRR (95% CI)		aRR (95% CI)		aRR (95% CI)	
30–49	1984–1993	1	–	1	–	1	–
	1994–2003	1.56 (1.51–1.62)	1	0.79 (0.75–0.82)	1	1.24 (1.18–1.32)	1
	2004–2013	2.27 (2.20–2.35)	1.46 (1.42–1.49)	0.62 (0.60–0.65)	0.79 (0.76–0.82)	1.43 (1.36–1.51)	1.15 (1.10–1.21)
50–69	1984–1993	1	–	1	–	1	–
	1994–2003	1.71 (1.68–1.74)	1	0.76 (0.74–0.78)	1	1.41 (1.37–1.44)	1
	2004–2013	2.21 (2.17–2.25)	1.29 (1.28–1.31)	0.55 (0.54–0.57)	0.72 (0.71–0.74)	1.30 (1.27–1.33)	0.93 (0.91–0.95)
70–84	1984–1993	1	–	1	–	1	–
	1994–2003	2.01 (1.95–2.06)	1	0.71 (0.69–0.73)	1	1.51 (1.45–1.57)	1
	2004–2013	2.81 (2.74–2.88)	1.40 (1.38–1.42)	0.56 (0.55–0.58)	0.79 (0.77–0.81)	1.64 (1.57–1.70)	1.08 (1.06–1.11)

aRR, adjusted relative risk; CI, confidence interval.



**Figure 3.** Proportions of advanced-stage (stage II–IV) to overall CRCs during 2004–13 in Taiwan.

### Cohort analysis

As shown in [Supplementary Figure 3](#), available as [Supplementary Data](#) at *IJE* online, the incidence rates of CRC increased in the same age range in successive birth cohorts. The incidence in the younger-age subgroup increased by 4.10–4.51% per year of birth cohort ([Supplementary Table 5](#), available as [Supplementary Data](#) at *IJE* online). When the cohorts entered middle age and old age, the increases in CRC incidence were 4.55–4.82 and 5.40–8.79%, respectively. Consistently with findings from age-and-period cross-tables, sex differences in outcomes began to increase starting in middle age.

### Discussion

In addition to the contribution of universal healthcare that is conducive to improving CRC survival, results of the present study demonstrate a significant reduction in CRC mortality occurring only 10 years after the implementation

of a FIT-based screening programme in the eligible sub-population. This reduction offers a striking contrast with the trend towards increasing mortality among ineligible subjects. This finding offers solid evidence to support the nationwide use of this screening strategy and can likely be generalized to most populations in developed and developing regions, in which similar dynamic changes in the CRC burden and healthcare use are taking place.

The prominent effects of FIT screening seen in the present study are related to its high accuracy in detecting CRC.<sup>13</sup> FIT-based screening programmes have additional merits, including a convenient design that helps to enhance patients' acceptance;<sup>10</sup> results that are specific to lower gastrointestinal lesions;<sup>30</sup> quantitative outcomes that can be used either for risk stratification of screening candidates<sup>31</sup> or for setting priorities among colonoscopy candidates;<sup>22</sup> a cut-off point that can be adjusted according to the limited number of colonoscopists available;<sup>32</sup> and a favourable cost–benefit ratio.<sup>33,34</sup> Nonetheless, a FIT-based screening programme, in comparison with the approach of one-off colonoscopy screening, entails additional programmatic considerations.<sup>11,35–39</sup> Research evidence to support the effectiveness about results remains limited.<sup>12,16</sup>

In the FIT screening programme in Taiwan, which has a current annual volume of about 1 million participants, the FIT positivity rate is about 8% and, in nearly 50 000 confirmatory colonoscopies performed per year, the number of screening-detected CRC cases is >2000 per year, of which about half were at stage 0–I.<sup>25</sup> This results in two major benefits that contribute to decreasing the mortality rate. First, early detection leads to a substantial shift in CRC stages at diagnosis, which is associated with improvements in patients' survival. Second, a peak in CRC incidence was seen after full implementation of NCCS, which was then followed by a reducing trend, which was likely due to the detection and removal of colon polyps.<sup>40</sup>



Results of the present cohort analysis indicate a strong driving force on CRC incidence over decades; that seems to continuously purge the number of new CRC cases without active intervention. The finding that men have the more rapid increase of CRC after 50 years of age indicates extensive exposure to risk factors before cancer onset. This interpretation is supported by two important findings. First, in a nationwide survey in Taiwan, the prevalence of cigarette smoking reached a peak of about 40% at 41–45 years among men whereas, in contrast, the corresponding rate was only 5.5% for women.<sup>41</sup> Additional compelling evidence is available from a colonoscopy-based study in which the prevalence of advanced polyps (2.1%) in men aged 40–49 years was similar to that of women aged 50–59 years.<sup>42</sup>

Strengths of the present study include the large sample size, long follow-up time, execution of different interventions on a nationwide scale and the availability of a registry of cancer incidence and mortality so the unique independent effects of NCCS and NHI could be distinguished and statistically estimated in association with age and time periods. However, the present study has certain limitations. First, some of the programme indicators regarding NCCS still have room for improvement, such as the suboptimal referral rate after a positive FIT<sup>22</sup> and the colonoscopy quality issue associated with the occurrence of post-colonoscopy CRC,<sup>43</sup> both of which may decrease the programme's effectiveness. Nevertheless, the magnitude of benefit will likely become larger when the coverage rate is increased. Second, regarding primary prevention, ongoing interventions are already in place. However, because development of CRC that follows the adenoma–carcinoma sequence may require decades to occur, the observation time in the present study may be insufficient to evaluate the benefits of primary prevention that have great potential impact on CRC incidence.

Taking into consideration the common global phenomenon of increased CRC incidence but with improved survival over time as demonstrated by the effectiveness of universal healthcare in Taiwan, results of the present study suggest, in particular, that active screening with FIT can efficiently reduce the number of deaths from CRC on a nationwide scale. Results of the present study add important implications for informing healthcare policy towards efficient resource allocation in the campaign to reduce the enormous burden of CRC.

## Supplementary Data

Supplementary data are available at *IJE* online.

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**Conflict of interest:** The authors report no conflicts of interest.

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