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ORIGINAL RESEARCH Temporal Trends of Sex Disparity in Incidence and Survival of Colorectal Cancer: Variations by Anatomical Site and Age at Diagnosis

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Purpose: The incidence of colorectal cancer (CRC) varies by age, sex, and anatomical subsite. Few studies have examined the temporal trends of age-specific sex disparity in incidence and survival by age at diagnosis and anatomical site.

Patients and Methods: The study was performed on all incident cases of CRC, using data derived from the nationwide Swedish Cancer Register between 1960 and 2014, including right-sided colon cancer (RCC), left-sided colon cancer (LCC), and rectal cancer. Male-tofemale age-standardized incidence rate ratio (IRR) and male-to-female five-year survival rate ratio (SRR) were calculated as the main indicators. Furthermore, we performed joinpoint regression analyses to estimate average annual percentage change.

Results: The overall male-to-female IRR was 1.05 for RCC, 1.31 for LCC, and 1.66 for rectal cancer. Male-to-female IRR increased steadily for RCC by an average of 0.4% per year until the mid-1990s and then decreased gradually by an average of 1.0% per year. LCC patients showed an increase of 0.6% per year since the mid-1970s. For rectal cancer, a non-significant random fluctuation was noted during the study period. The temporal trends of male-to-female IRR varied by age at diagnosis. The male-to-female SRR was 0.87 for RCC, 0.88 for LCC, and 0.86 for rectal cancer, which remained relatively stable during the study period.

Conclusion: Sex disparity of CRC is age-, period-, and anatomical subsite-dependent. Further studies are needed to investigate the underlying contributing factors.

Keywords: colorectal cancer, sex disparity, incidence, survival, temporal trend

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy with more than 1.8 million new cases and the second leading cause of cancer death with more than 800,000 deaths worldwide in 2018.1 CRC shows sex differences in incidence and survival. Women are less likely to develop CRC than men,² and women with CRC have a longer survival time than men.³⁻⁵ CRC can be divided into three subsites according to the anatomical areas, including proximal or rightsided colon cancer (RCC), distal or left-sided colon cancer (LCC), and rectal cancer. RCC consists of cancers of the caecum, ascending and transverse colon, and splenic flexure, whereas LCC consists of cancers of the descending and sigmoid colon. A growing amount of data suggest that carcinomas of the right and left colon should be considered as different tumor entities. Meanwhile, sex disparity of CRC varied by anatomical subsite with females being more prone to develop RCC and males being more likely to develop LCC and rectal cancer.^{2,6}

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Although the underlying mechanisms for sex disparity of CRC are still unclear, some previous studies have suggested that the differences between males and females in environmental exposures, molecular pathways, and genetic and epigenetic alterations might contribute to the observed difference.^{7–10} As molecular pathways and genetic and epigenetic alterations are not associated with temporal changes, studies on the temporal trends of sex disparity in CRC and its subsites might provide additional evidence about environmental factors on the development of CRC, which is still largely unknown.

To better understand the sex-specific incidence and survival of CRC during recent decades, our study utilized data derived from the nationwide Swedish Cancer Register to describe the overall and age-specific temporal trends of maleto-female age-standardized incidence rate ratios (IRR) and male-to-female age-standardized five-year survival rate ratios (SRR) of RCC, LCC, and rectal cancer between 1960 and 2014. Furthermore, we performed joinpoint regression analyses to identify potential change points over the study period and to estimate the magnitude of the trends at each time segment.

Materials and Methods

Study Population

The cohort study used data from the Swedish Cancer Register, which was founded in 1958, and has almost complete nationwide coverage.¹¹ We identified all diagnoses of CRC according to the 7th Revision of International Classification of Diseases (ICD-7 code) as used in the Swedish Cancer Register. All subsite-, age, and sex-specific data were extracted from January 1, 1960 to December 31, 2014. Only the first diagnosis of CRC was counted as an incident case, and patients with multiple sites of CRC were not included. For RCC, the codes were 1530 (caecum and ascending colon) and 1531 (transverse colon and the splenic flexure). For LCC the codes were 1532 (descending colon) and 1533 (sigmoid colon). The codes were 1540 and 1548 for rectal cancer.

This study was approved on February 6, 2013 by the Ethics Committee at Lund University, Sweden (ref 2012/795). The project database is located at Center for Primary Health Care in Malmö, Sweden.

Statistical Analysis

Age-standardized sex-specific incidence rate (AIR) and male-to-female IRR were used as the main incidence

indicators. The AIR was calculated using the direct method and based on the standard age distribution of the Swedish population in the year 2000. Temporal trends of male-tofemale IRR were plotted according to the year at diagnosis and calculated separately using five-year time intervals: 1960–64, 1965–69, 1970–74, 1975–79, 1980–84, 1985–89, 1990–94, 1995–99, 2000–2004, 2005–2009, and 2010–2014.

Age-standardized sex-specific five-year survival rate (ASR) and male-to-female SRR were used as the main survival indicators. The overall survival analyses were restricted to the period 1960–2009 to ensure all patients with CRC could be followed for more than five years. Survival was counted from the date of diagnosis until the date of death (from any cause) or end of follow-up (December 31, 2014), whichever occurred first.

The trends of male-to-female IRR and male-to-female SRR were evaluated using the joinpoint regression analyses. Analyses were performed using the log-linear model and allowed for a maximum of four joinpoints. Permutation Test was used to select the final model. The annual percent change (APC) was calculated from the slope of the log-linear model. Empirical Quantile method was used to calculate the 95% confidence interval. We further stratified the analysis by age at onset of CRC: 0–49 years, and 50 years or older. Data analyses were performed using Joinpoint Regression Program version 4.7.0.0 and SAS version 9.4 (SAS Institute, Cary, NC, USA).

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

During the study period, a total of 66,229 patients were diagnosed with RCC (30,036 [45.4%] men and 36,193 [54.6%] women), 52,153 patients with LCC (27,026 [51.8%] men and 25,127 [48.2%] women), and 76,628 patients with rectal cancer (44,201 [57.7%] men and 32,427 [42.3%] women).

Table 1 presents the overall AIR and the temporal trends of male-to-female IRR of CRC by anatomical subsites. The AIR of RCC in males was consistently higher than in females until 2004 and then reversed. The lowest male-tofemale IRR of RCC was 0.96 between 2010 and 2014 and the highest male-to-female IRR was 1.11 between 1990 and 1994. The AIR of LCC and rectal cancer in males was consistently higher than females throughout the study period. For LCC, the lowest male-to-female IRR was 1.19

		Site	Period	All Ages	s				0-49 Years	ears				>49 Years	ars			
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1960-1964 1547 1499 11.24 882 127(1-19-1.36) 88 161 0.66 124 054(0.42-0.70) 1454 1328 31.56 2340 1950-1964 1957 1337 10.90 1.22(1.16-1.30) 127 159 0.79(0.55-1.00) 1870 1798 37.18 31.56 2340 1 1975-1973 2116 1.19(1.12-1.25) 133 160 1.08 1.33 0.81(0.64-1.00) 2030 2303 2303 2301 1 1980-1994 2523 1244 132 133 144 132 133 266 103 2164 234 244 1980-1994 2532 2188 11.5 881 1.22(1.14-1.27) 99 114 0.76(0.59-0.99) 2164 2241 239 2664 146 133 2164 234 247 8 1980-1964 2561 2242 126 137 126 137 1312 136 1314	1960-1964 1547 1495 11.24 882 127(1)9-130 869 154 056 124 0540,42-070 1454 1328 3156 2340 126 1950-1964 1957 1937 1937 1937 1937 1937 1937 1937 1937 1331 11.16 11.9(1,12-123) 95 119 073 114 2133 2931 2331 2331 2331 2331 1234 1390-1994 2313 2366 1204 132 160 108 133 06166-100 2003 3531 2331 1244 1390-1994 2313 2381 1234 1324 112 064 079 05665-610 2144 2244 124 144 1390-1994 2314 1234 116 117 027 0266 1244 124 144 2244 124 144 2244 124 144 2244 124 144 2244 124 144<		Overall	30,036	36,193	14.55	13.83	1.05(1.04–1.07)	1751	1614	1.12	1.07	1.05(0.98–1.12)	28,285	34,579	40.41	38.39	1.05(1.04–1.07)
1955-1969 197 13.37 10.90 12.3(1.6-1.30) 127 159 0.99 1.25 0.79(0.65-1.00) 1870 1798 37.18 30.10 1970-1974 2136 1290 12.31 11.16 1.19(1.12-125) 133 160 1.03 0.76(0.59-0.97) 2114 2193 35.03 35.03 35.03 35.01 1970-1974 2130 12.53 10.70 1.20(1.1-1.27) 99 114 0.78 1214 2193 35.03 23.31 35.17 28.33 30.10 1996-1999 2561 12.24 12.04 1.20(1.4-1.27) 99 141 0.78 0.79(0.61-1.00) 203 23.17 28.13 35.17 28.13 35.17 28.13 23.16 24.16	965-1969 1977 1976 10.00 1.2.20(1.14-1.2.12) 95 11.0 0.70 0.2017 12.01	U LC	1960–1964	1542	1489	11.24	8.82	1.27(1.19–1.36)	88	161	0.68	1.24	0.54(0.42-0.70)	1454	1328	31.56	23.40	1.35(1.26–1.45)
1970-1974 2136 2190 13.23 11.16 1.19(1.12-1.25) 133 160 1.03 10366-1.01) 2030 36.33 30.10 1997-1975 2210 2278 12.33 10.70 1.20(1.14-1.27) 94 114 0.78 1.04 0.56(0.59-0.97) 2114 2159 36.03 29.31 1995-1995 2230 21264 10.70 1.20(1.14-1.27) 94 112 0.64 0.78 0.80(0.61-1.06) 2189 2144 35.17 2830 24.16 1 1995-1995 2561 2242 12.61 1.32(1.14-1.27) 99 141 0.776(0.61-1.06) 2189 2846 2146 2416	1970-1974 2136 11.6 1.19(1.12-1.25) 133 160 1.08 1.33 081(0.66-1.01) 2033 26.36 36.01 1.23 1970-1974 2219 2238 12.34 1.030 1.201(1-1.21) 239 1.201 2331 1.201 2331 1.234 3.010 1.234 1990-1994 2264 1236 1234 1.201(1-1.21) 394 1.201 0.300(6-1.06) 2184 2337 26.46 1.201 1990-1994 2261 1201 9.27 1.261(1.9-1.33) 94 112 0.56 0.83 0.79(0.61-1.06) 2184 1.397 26.46 1.291 1990-1994 2541 1201 1231 124 1261 1231 124 1261 1241 1261 1241 <t< td=""><td></td><td>1965-1969</td><td>1997</td><td>1957</td><td>13.37</td><td>10.90</td><td>1.23(1.16–1.30)</td><td>127</td><td>159</td><td>0.99</td><td>1.25</td><td>0.79(0.63–1.00)</td><td>1870</td><td>1798</td><td>37.18</td><td>29.49</td><td>1.26(1.19–1.34)</td></t<>		1965-1969	1997	1957	13.37	10.90	1.23(1.16–1.30)	127	159	0.99	1.25	0.79(0.63–1.00)	1870	1798	37.18	29.49	1.26(1.19–1.34)
	1975-1979 2210 2278 12.83 10.70 12.0(1.3-1.27) 96 119 0.78 1.03 0.76(0.59-0.97) 2114 2159 36.03 2311 12.4 1980-1984 2263 12.64 0.47 1.20(1.1-1.27) 99 141 0.78 114 0.66(0.61-1.06) 2169 2194 3517 2830 1244 3517 2830 1246 1241 3517 2830 1246 1241 3517 2830 1246 1241 3517 2349 1471 1247 1246 1241 3517 2169 1246 2241 4490 1247 1246 1241 3517 1249 139 1246 1241 1247 1247 1247 1246 1246 1241 1247 1246 1241 1247 1246 1241 1247 1246 1247 1247 1247 1247 1247 1247 1247 1247 1247 1247 1247 1247 1247 <t< td=""><td></td><td>1970-1974</td><td>2136</td><td>2190</td><td>13.23</td><td>11.16</td><td>1.19(1.12–1.25)</td><td>133</td><td>160</td><td>1.08</td><td>1.33</td><td>0.81 (0.66–1.01)</td><td>2003</td><td>2030</td><td>36.63</td><td>30.10</td><td>1.22(1.15–1.29)</td></t<>		1970-1974	2136	2190	13.23	11.16	1.19(1.12–1.25)	133	160	1.08	1.33	0.81 (0.66–1.01)	2003	2030	36.63	30.10	1.22(1.15–1.29)
1980-1984 2382 12,4 0.42 1.20(1.14-1.27) 99 141 0.78 1.14 0.69(0.54-0.88) 2164 2351 2351 2351 2350 1980-1984 2336 12.06 1.20(1.14-1.27) 99 141 0.78 0.80(0.61-1.06) 2189 2194 3399 26.46 1 1990-1994 2270 2188 11.22(1.19-1.33) 057 126 0.80 0.91 0.79(0.61-1.06) 2189 2194 3399 26.46 1 1990-1994 2214 12.01 132(1.24-1.40) 105 135 0.66 0.83 0.79(0.61-1.06) 2184 2416 1 2000-2004 2734 1287 1.44(1.36-1.53) 105 133 0.77 0.99 2456 2107 35.58 24.46 1 2000-2004 2734 1440 1037 1.43(1.35-1.50) 153 177 0.99 0.76(0.61-1.06) 2187 23.61 24.16 1 24.18 24.18	1980-1984 2263 1234 10.42 1.20(1.14-1.27) 94 11.3 0.78 1.14 0.669(0.54-0.86) 2164 2311 33.17 2330 124(1.20) 1980-1994 2263 1206 1204 9.57 1.26(1.19-1.33) 94 112 0.64 0.79 0.89(0.61-1.06) 2189 2194 33.93 2564 1.36 1990-1994 2270 2188 11.38 8.81 1.32(1.24-1.40) 105 135 0.66 0.83 0.57(6.6-1.10) 2165 2062 32.84 149 137 2000-2004 2344 1490 10.39 1.44(1.36-1.33) 107 0.94 0.77 0.85 2065 32.86 147 33.93 2000-2004 3344 1490 10.39 1.44(1.36-1.34) 1307 1615 0.84 1.76 33.93 27416 1.47 2000-2004 2344 1490 10.39 1.44 107 0.84 0.77 0.84 2765 2		1975-1979	2210	2278	12.83	10.70	1.20(1.13–1.27)	96	611	0.78	1.03	0.76(0.59–0.97)	2114	2159	36.03	29.3 I	1.23(1.16–1.30)
1985-1989 2306 12.04 9.57 1.26(1.9-1.33) 94 112 0.64 0.79 0.80(0.61-1.06) 2189 2194 33.99 26.46 1990-1994 2270 2188 11.58 8.81 1.32(1.24-1.40) 105 126 0.66 0.83 0.79(0.61-1.04) 2165 2062 32.61 24.16 1990-1994 2770 2188 11.52 0.66 0.83 0.79(0.61-1.04) 2165 2062 32.61 24.16 1 1995-1999 2561 12.41 165 164 0.77 0.99 0.73(0.56-0.99) 24.56 21.73 35.58 23.84 1 2000-2004 2734 1430 1037 143(1.35-1.51) 116 131 0.77 0.98 0.666-1.10) 2168 24.66 12.66 24.16 12.66 24.16 12.66 24.16 12.66 12.66 12.66 12.66 12.66 12.66 12.66 12.66 12.67 32.68 36.33 <	1985-1989 22306 1204 9,57 1.26(.1.9-1.33) 94 112 0.64 0.79 0.80(0.61-1.06) 2189 2139 26.46 1.23 1990-1994 2270 2188 11.32(.1.24+1.40) 105 126 0.66 0.83 0.79(0.61-1.04) 2165 235.1 24.16 1.35 1990-1994 2270 2188 11.32(.1.24+1.40) 105 135 0.66 0.83 0.79(0.61-1.04) 2165 35.34 149 1995-1999 2561 2346 133(1.35-1.51) 116 131 0.77 0.99 085(0.66-1.10) 2618 241.4 2406 1.47 2005-2009 3346 2743 133(1.35-1.51) 116 131 0.77 0.94(0.77-1.16) 3493 25512 2619 134 2010-2014 3684 2715 123 137(1.29-1.34) 1307 1615 0.94 0.79(0.71-1.60) 2168 144 146 2010-2014 3684 2715 1316		1980–1984	2263	2382	12.54	10.42	1.20(1.14–1.27)	66	4	0.78	4	0.69(0.54–0.88)	2164	2241	35.17	28.30	1.24(1.17–1.32)
	1990-1994 2100 2188 11.58 881 1.32(1.24-1.40) 105 126 0.83 0.79(0.61-1.04) 2165 2062 32.61 24.16 1.35 1995-1999 2561 2242 12.61 8.75 1.44(1.36-1.53) 105 135 0.68 0.91 0.75(0.58-0.98) 2456 2107 3558 1.47 2000-2004 2734 2847 1430 1037 1.43(1.35-1.50) 153 177 0.99 1.17 0.84(067-1.05) 3193 2507 41.40 2808 1.47 2000-2004 2714 143 133-1.500 133 177 0.99 1.17 0.84(067-1.05) 3193 2730 41.44 2808 1.47 2010-2014 3848 2772 1.291 193 193 1661 1.17 0.94(067-1.05) 3193 2730 41.34 2801 1.46 2010-2014 3848 1617 1616 131 161 1617 0.78(068-1.10)		1985-1989	2283	2306	12.04	9.57	1.26(1.19–1.33)	94	112	0.64	0.79	0.80(0.61–1.06)	2189	2194	33.99	26.46	1.28(1.21–1.36)
1995-1999 2561 2242 1261 8.75 1.44(1.36-1.53) 105 135 0.6.8 0.91 0.75(0.58-0.98) 2456 2107 35.58 2334 1 2000-2004 2734 2387 1293 907 1.43(1.35-1.51) 116 131 0.77 0.90 085(0.66-1.10) 2618 2256 36.34 24.78 1 2000-2004 3346 2784 1480 10.37 1.43(1.35-1.50) 153 177 0.99 085(0.66-1.10) 2618 22.56 36.34 24.78 1 2005-2004 3346 2792 14.30 10.37 1.43(1.35-1.50) 153 177 0.94(0.77-1.16) 3493 2607 41.34 28.01 2010-2014 3684 27/026 2.154 1.307 1615 0.84 1.17 0.94(0.77-1.16) 23.512 36.18 26.69 1 26.69 1 26.69 1 26.69 1 26.69 1 26.69 1 26.13	1995-1999 2561 2242 1261 8.75 1.44(1.36-1.53) 105 135 0.68 0.91 0.75(0.58-0.98) 2456 2107 35.58 2334 1.49 2000-2004 2734 1287 12.93 907 1.43(1.35-1.51) 116 131 0.77 0.90 0.85(0.66-1.10) 2618 2256 36.34 2478 1.47 2000-2004 2734 1480 0.037 1.43(1.35-1.50) 153 177 0.90 0.85(0.66-1.10) 2618 24.78 147 2000-2004 3346 2730 1.43(1.35-1.50) 133 177 0.90 0.85(0.66-1.10) 2618 24.78 147 2000-2004 3346 1.470 0.39 1.34(1.36-1.30) 1307 1615 0.94 1.17 0.94(0.77-1.16) 3433 28.01 1.48 1760-1914 2701 12.91 12.41 165(1.54-1.70) 182 12.4 0.94(0.77-1.16) 3433 177 2801 1.46		1990–1994	2270	2188	11.58	8.8	1.32(1.24–1.40)	105	126	0.66	0.83	0.79(0.61–1.04)	2165	2062	32.61	24.16	1.35(1.27–1.44)
2000-2004 2734 2387 12.93 9.07 1.43(1.35-1.51) 116 131 0.77 0.90 0.85(0.66-1.10) 2618 2256 36.34 24.78 1 2005-2009 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 2808 2005-2004 3684 2924 1490 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 2808 2010-2014 3684 27,026 25,127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84 1.07 0.34(0.77-1.16) 3493 25.719 23.512 36.18 26.69 1 1960-1964 27,15 19.32 1.261 1.51 124 1.60 0.87(0.77-1.16) 34.93 24.69 1 23.64 34.61 24.78 36.69 1 26.67 31.61 28.61 <td>2000-2004 2734 2387 12.93 9.07 1.43(1.35-1.51) 116 131 0.77 0.90 0.85(0.66-1.10) 2618 2256 36.34 24.78 147 2000-2004 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2005-2004 3346 27.12 1.430 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2010-2014 3684 27.05 5.127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84(0.77-1.16) 3493 25.719 25.607 41.34 28.01 1.48 0verall 27.025 5.154 1.65(1.56-1.74) 182 1.60 0.87(0.71-1.06) 25.719 25.719 26.69 1.37 1960-197 3333 2478 1.66 1.88 1.51</td> <td></td> <td>1995–1999</td> <td>2561</td> <td>2242</td> <td>12.61</td> <td>8.75</td> <td>1.44(1.36–1.53)</td> <td>105</td> <td>135</td> <td>0.68</td> <td>0.91</td> <td>0.75(0.58-0.98)</td> <td>2456</td> <td>2107</td> <td>35.58</td> <td>23.84</td> <td>1.49(1.41–1.58)</td>	2000-2004 2734 2387 12.93 9.07 1.43(1.35-1.51) 116 131 0.77 0.90 0.85(0.66-1.10) 2618 2256 36.34 24.78 147 2000-2004 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2005-2004 3346 27.12 1.430 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2010-2014 3684 27.05 5.127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84(0.77-1.16) 3493 25.719 25.607 41.34 28.01 1.48 0verall 27.025 5.154 1.65(1.56-1.74) 182 1.60 0.87(0.71-1.06) 25.719 25.719 26.69 1.37 1960-197 3333 2478 1.66 1.88 1.51		1995–1999	2561	2242	12.61	8.75	1.44(1.36–1.53)	105	135	0.68	0.91	0.75(0.58-0.98)	2456	2107	35.58	23.84	1.49(1.41–1.58)
2005-2009 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 2010-2014 3684 2924 14.90 10.37 1.43(1.35-1.50) 153 177 0.94(0.77-1.16) 3493 2730 41.34 28.01 1 2010-2014 3684 2924 14.90 10.39 1.43(1.36-1.34) 1307 1615 0.84 1.07 0.78(0.77-0.84) 25.719 23.512 36.18 28.07 41.40 28.08 1 1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 16.07 23.512 36.18 28.69 1 1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 1.51 1.48 1.60 0.87(0.71-1.06) 23.512 36.18 26.69 1 1960-1964 2715 123 182 1.65 1.48 <td>2005-2009 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2010-2014 3684 2924 14.90 10.37 1.43(1.36-1.51) 191 194 1.17 124 0.94(0.77-1.16) 3493 2730 41.34 28.01 148 2010-2014 3684 2924 14.90 10.39 1.43(1.36-1.54) 1307 1615 0.84 1.07 0.78(0.71-1.16) 3493 2730 41.34 28.01 148 960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 166 173 136 173 136 13</td> <td></td> <td>2000–2004</td> <td>2734</td> <td>2387</td> <td>12.93</td> <td>9.07</td> <td>1.43(1.35–1.51)</td> <td>911</td> <td>131</td> <td>0.77</td> <td>0.90</td> <td>0.85(0.66–1.10)</td> <td>2618</td> <td>2256</td> <td>36.34</td> <td>24.78</td> <td>1.47(1.39–1.55)</td>	2005-2009 3346 2784 14.80 10.37 1.43(1.35-1.50) 153 177 0.98 1.17 0.84(0.67-1.05) 3193 2607 41.40 28.08 1.47 2010-2014 3684 2924 14.90 10.37 1.43(1.36-1.51) 191 194 1.17 124 0.94(0.77-1.16) 3493 2730 41.34 28.01 148 2010-2014 3684 2924 14.90 10.39 1.43(1.36-1.54) 1307 1615 0.84 1.07 0.78(0.71-1.16) 3493 2730 41.34 28.01 148 960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 166 173 136 173 136 13		2000–2004	2734	2387	12.93	9.07	1.43(1.35–1.51)	911	131	0.77	0.90	0.85(0.66–1.10)	2618	2256	36.34	24.78	1.47(1.39–1.55)
2010-2014 3684 2924 14,90 10.39 1.43(1.36-1.51) 191 194 1.17 124 0.94(0.77-1.16) 3493 2730 41.34 28.01 1 Overall 27,026 25,127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84 107 0.78(0.73-0.84) 25,719 23,512 36.18 26.69 1 1960-1964 2715 1933 19.02 11.54 1.61(1.54-1.70) 194 188 1.51 1.48 1.07(0.71-1.06) 2533 1728 57.45 34.53 1 1960-1964 2715 19.32 1.54 1.61(1.54-1.70) 194 188 1.51 1.48 1.07(0.71-1.06) 2533 1728 57.45 34.53 1 1970-1974 3303 2478 1.66(1.56-1.74) 182 1.32 1.32 0.97(0.71-1.06) 3141 27 35.53 34.53 1 1970-1974 3303 26.64 1.32 1.32 1.32	2010-2014 3684 2924 14.90 10.39 1.43(1.36-1.51) 191 194 1.17 1.24 0.94(0.77-1.16) 3493 2730 41.34 2801 1.46 Overall 27,026 25,127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84 1.07 0.78(0.73-0.84) 25,719 23,512 36.18 26.69 1.36 1960-1964 2715 1933 19.02 11.54 1.66(1.56-1.74) 182 205 1.39 160 0.87(0.71-1.06) 2533 1728 52.97 30.69 1.73 1960-1964 2715 1933 19.02 11.54 1.66(1.56-1.74) 182 205 1.35 1.36 1.37 1.66 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.37 1.66 1.36 1.36 1.36 1.66 1.36 1.66 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36		2005-2009	3346	2784	14.80	10.37	1.43(1.35–1.50)	153	177	0.98	1.17	0.84(0.67–1.05)	3193	2607	41.40	28.08	1.47(1.40–1.55)
Overall 27,026 25,127 12.92 9.82 1.31(1.29-1.34) 1307 1615 0.84 1.07 0.78(0.73-0.84) 25,719 23,512 36.18 26.69 1 1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 160 0.87(0.71-1.06) 2533 1728 52.97 30.69 1 1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 160 0.87(0.71-1.06) 2533 1728 57.38 34.41 1 1970-1974 3136 20.63 12.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1 1970-1974 303 2478 12.66 1.62(1.54-1.70) 162 163 1.32 0.97(0.79-1.19) 3141 2316 27.45 34.53 1 1970-1974 3130 2166 1.28 1.32 1.32	Overall 27,026 25,112 1.29.2 9.82 1.31(1.29-1.34) 1307 1615 0.84 1.07 0.78(0.73-0.84) 25,719 23,512 36.18 26.69 1.36(1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 1.60 0.87(0.71-1.06) 2533 1728 52.97 30.69 1.73(1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 1.60 0.87(0.71-1.06) 2533 1728 30.59 1.30(1970-1974 3136 2282 20.63 1.2.78 1.61(1.54-1.70) 182 1.37 1.09 1.21(19) 2141 2315 57.38 34.41 1.67 1970-1974 3733 2478 20.64 1.3.75 1.62(1.54-1.70) 162 163 1.37 1.97 30.59 27.38 34.41 1.67 1970-1974 3733 2478 1.30 1.66		2010-2014	3684	2924	14.90	10.39	1.43(1.36–1.51)	161	194	1.17	1.24	0.94(0.77–1.16)	3493	2730	41.34	28.01	1.48(1.40–1.55)
1960-1964 2715 1933 1902 11.54 1.65(1.56-1.74) 182 205 1.39 1.60 0.87(0.71-1.06) 2533 1728 52.97 30.69 1 1965-1966 3136 2282 20.63 1.278 1.65(1.54-1.70) 194 188 1.51 1.48 1.02(0.84-1.24) 2942 2094 57.45 34.53 1 1970-1974 3303 2478 12.66 1.62(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1 1970-1974 3303 2478 12.66 1.62(1.54-1.70) 162 163 1.32 0.97(0.79-1.19) 3141 2315 57.38 34.41 1 1970-1974 3303 2184 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 125(1.01-1.56) 337.37 214 2315 57.38 34.41 1 1980-1984 3150 21.31 1.57(1.50-1.65) 182	1960-1964 2715 1933 19.02 11.54 1.65(1.56-1.74) 182 205 1.39 1.60 087(0.71-1.06) 2533 1728 52.97 30.69 1.73 1965-1969 3136 2282 12.78 1.66(1.54-1.70) 194 188 1.51 1.48 1.002(084-1.24) 2942 2094 57.45 34.53 1.66 1970-1974 3303 2478 12.66 1.62(1.54-1.70) 162 163 1.35 0.97(0.79-1.19) 3141 2315 57.45 34.53 1.66 1970-1974 3303 2478 12.66 1.62(1.54-1.70) 162 163 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1.67 1970-1974 3303 2458 12.66 1.80(1.71-1.89) 166 128 1.37 1.183 1.62 1.67 1.83 1.66 1.83 1.25 1.314 2.315 2.471 61.24 33.47 1.83 1980-1984 3156 <td></td> <td>Overall</td> <td>27,026</td> <td>25,127</td> <td>12.92</td> <td>9.82</td> <td>1.31(1.29–1.34)</td> <td>1307</td> <td>1615</td> <td>0.84</td> <td>1.07</td> <td>0.78(0.73–0.84)</td> <td>25,719</td> <td>23,512</td> <td>36.18</td> <td>26.69</td> <td>1.36(1.33–1.38)</td>		Overall	27,026	25,127	12.92	9.82	1.31(1.29–1.34)	1307	1615	0.84	1.07	0.78(0.73–0.84)	25,719	23,512	36.18	26.69	1.36(1.33–1.38)
3136 2282 20.63 12.78 1.61(1.54-1.70) 194 188 1.51 1.48 1.02(0.84-1.24) 2942 2094 57.45 34.53 1 3303 2478 20.48 12.66 1.62(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1 3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1 3763 21.61 13.75 1.57(1.50-1.65) 162 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1 3950 3139 21.61 13.75 172 182 1.23 1.22 10.10(0.82-1.25) 37.37 60.63 37.37 1 4154 3196 22.06 13.31 1.66(1.59-1.74) 182 172 1.22 1.01(0.82-1.25) 3972 3024 </td <td>3136 2282 20.63 12.78 1.61(1.54-1.70) 194 188 1.51 1.48 1.02(0.84-1.24) 2942 2034 57.45 34.33 1.66(3103 2478 20.64 1.56(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1.67(3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1.83(3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.22 1.010 3778 2957 60.63 37.37 1.62(3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.22 1.24 1.80(1.62(1.58-1.74) 182 1.72 1.22 1.61(1.08-1.25) 37.37 1.62(1.62(1.54-1.20) 1.62(1.56-1.24) 31.61 1.62(1.56-1.24) 1.61(1.54-1.24) 1.62</td> <td>Rectum</td> <td>1960–1964</td> <td>2715</td> <td>1933</td> <td>19.02</td> <td>11.54</td> <td>I.65(I.56–I.74)</td> <td>182</td> <td>205</td> <td>1.39</td> <td>09.1</td> <td>0.87(0.71–1.06)</td> <td>2533</td> <td>1728</td> <td>52.97</td> <td>30.69</td> <td>1.73(1.63–1.83)</td>	3136 2282 20.63 12.78 1.61(1.54-1.70) 194 188 1.51 1.48 1.02(0.84-1.24) 2942 2034 57.45 34.33 1.66(3103 2478 20.64 1.56(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1.67(3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1.83(3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.22 1.010 3778 2957 60.63 37.37 1.62(3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.22 1.24 1.80(1.62(1.58-1.74) 182 1.72 1.22 1.61(1.08-1.25) 37.37 1.62(1.62(1.54-1.20) 1.62(1.56-1.24) 31.61 1.62(1.56-1.24) 1.61(1.54-1.24) 1.62	Rectum	1960–1964	2715	1933	19.02	11.54	I.65(I.56–I.74)	182	205	1.39	09.1	0.87(0.71–1.06)	2533	1728	52.97	30.69	1.73(1.63–1.83)
3303 2478 20.48 12.66 1.62(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 3.441 1 3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1 3763 2599 21.64 12.0(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1 3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.34 0.90(0.74-1.10) 3778 2957 60.63 37.37 1 4154 3196 22.05 13.31 1.66(1.59-1.74) 182 172 1.22 1.01(0.82-1.25) 3972 3024 62.12 36.58 1 4331 3336 21.66(1.59-1.74) 213 174 1.35 1.148(0.96-1.45) 4118 3162 61.88 <	3303 2478 20.48 1.26 1.62(1.54-1.70) 162 163 1.32 1.35 0.97(0.79-1.19) 3141 2315 57.38 34.41 1.67(3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1.83(3750 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.48 0.90(0.74-1.10) 3778 2957 60.63 37.37 1.62(4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.22 1.01(0.82-1.25) 3724 62.12 36.58 1.70(4131 3336 22.04 13.27 1.66(1.59-1.74) 182 172 1.22 1.01(0.82-1.25) 3724 62.12 36.58 1.70(4331 3336 22.04 13.27 1.66(1.59-1.74) 182 1.72 1.01(0.82-1.25) 3724 62.12 36.58 <		1965–1969	3136	2282	20.63	12.78	1.61(1.54–1.70)	194	88	1.51	1.48	1.02(0.84–1.24)	2942	2094	57.45	34.53	1.66(1.58–1.75)
3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1 3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.34 1.48 0.90(0.74-1.10) 3778 2957 60.63 37.37 1 4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.22 1.01(0.82-1.25) 3778 2957 60.63 37.37 1 4331 3336 22.04 13.27 1.66(1.59-1.74) 182 172 1.23 1.18(0.96-1.45) 3162 61.88 36.61 1 4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1	3763 2599 21.84 12.16 1.80(1.71-1.89) 166 128 1.37 1.09 1.25(1.01-1.56) 3597 2471 61.24 33.47 1.83(3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.34 1.48 0.90(0.74-1.10) 3778 2957 60.63 37.37 1.62(4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.23 1.22 1.01(0.82-1.25) 3972 3024 62.12 36.58 1.70(4313 3336 22.04 13.27 1.66(1.59-1.74) 182 172 1.23 1.21 1.01(0.82-1.25) 3972 3024 62.12 36.58 1.70(4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1.69(4408 3221 21.67 12.51 123 124 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1.77(44		1970-1974	3303	2478	20.48	12.66	1.62(1.54–1.70)	162	163	1.32	1.35	0.97(0.79–1.19)	3141	2315	57.38	34.41	1.67(1.58–1.76)
3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.34 1.48 0.90(0.74-1.10) 3778 2957 60.63 37.37 1 4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.22 1.01(0.82-1.25) 3972 3024 62.12 36.58 1 4331 3336 22.04 13.27 1.66(1.59-1.74) 2213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1 4408 3221 21.67 1.231 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1	3950 3139 21.61 13.75 1.57(1.50-1.65) 172 182 1.34 1.48 0.90(0.74-1.10) 3778 2957 60.63 37.37 1.62(4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.23 1.22 1.01(0.82-1.25) 3972 3024 62.12 35.58 1.70(4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1.69(4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4118 3162 61.88 36.61 1.69(4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3138 60.60 34.23 1.77(1975-1979	3763	2599	21.84	12.16	1.80(1.71–1.89)	166	128	1.37	60 [.] I	1.25(1.01–1.56)	3597	2471	61.24	33.47	1.83(1.74–1.92)
4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.22 1.01(0.82-1.25) 3972 3024 62.12 36.58 1 4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1 4301 3326 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1 4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1	4154 3196 22.05 13.31 1.66(1.58-1.74) 182 172 1.23 1.22 1.01(0.82-1.25) 3972 3024 62.12 36.58 1.70(4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 35.61 1.69(4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1.77(1980-1984	3950	3139	21.61	13.75	1.57(1.50–1.65)	172	182	I.34	I.48	0.90(0.74–1.10)	3778	2957	60.63	37.37	1.62(1.55–1.70)
4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1 4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1	4331 3336 22.04 13.27 1.66(1.59-1.74) 213 174 1.35 1.14 1.18(0.96-1.45) 4118 3162 61.88 36.61 1.69(4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1.77(1985-1989	4154	3196	22.05	13.31	I.66(I.58–I.74)	182	172	1.23	1.22	1.01(0.82–1.25)	3972	3024	62.12	36.58	1.70(1.62–1.78)
4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1	4408 3221 21.67 12.51 1.73(1.65-1.81) 222 183 1.44 1.23 1.17(0.96-1.43) 4186 3038 60.60 34.23 1.77(1990–1994	4331	3336	22.04	13.27	1.66(1.59–1.74)	213	174	I.35	41.1	1.18(0.96–1.45)	4118	3162	61.88	36.61	1.69(1.61–1.77)
	(Continued		1995–1999	4408	3221	21.67	12.51		222	183	<u>4</u> .	1.23	I.I7(0.96–I.43)	4186	3038	60.60	34.23	1.77(1.69–1.86)

Site	Period	All Ages	S				0-49 Years	ears				>49 Years	Irs			
		Cases		AIR ^a		e-to-Female	Cases		AIR^{a}		ıle	Cases		AIR^{a}		Male-to-Female
		Male	Female Male Female	Male	Female	IRR (95% CI)	Male	Female	Male	Female	IRR (95% CI)	Male	Female Male	Male	Female	IRR (95% CI)
	2000–2004 4604	4604	3392	21.72	12.82	1.69(1.62–1.77)	210	202	1.39	1.39	1.00(0.82–1.22)	4394	3190	60.87	34.82	I.75(I.67–I.83)
	2005-2009	4882	3453	21.36	12.74	1.68(1.60–1.75)	246	219	I.57	I.45	1.08(0.90–1.31)	4636	3234	59.45	34.48	I.72(I.65–I.80)
	2010-2014	4955	3398	20.03	12.07	l.66(l.58–l.74)	319	231	96.1	1.47	1.33(1.12–1.59)	4636	3167	54.83	32.49	1.69(1.61–1.77)
	Overall	44,201 32,427	32,427	21.02	12.65	I.66(I.64–I.69)	2268	2047	I.45	I.35	1.07(1.01–1.14)	41,933	30,380	58.70	34.39	1.71(1.68–1.73)
Notes: ^a R:	Notes: ^a Rates per 100,000 person-years) person-ye	ars]		1							

between 1970 and 1974 and the highest male-to-female IRR was 1.44 between 1995 and 1999. For rectal cancer, the lowest male-to-female IRR was 1.57 between 1980 and 1984 and the highest male-to-female IRR was 1.80 between 1975 and 1979. The male-to-female IRR of different subsites varied considerably according to the different age groups. In the younger group (0–49 years), the male-to-female IRR was 1.05 for RCC, 0.78 for LCC and 1.07 for rectal cancer. However, for CRC patients diagnosed at older ages (>49 years), the male-to-female IRR was 1.05 for RCC, 1.36 for LCC, and 1.71 for rectal cancer.

For all RCC patients, the male-to-female IRR increased steadily by an average of 0.4% per year until 1995 and decreased gradually ever since by an average of 1.0% per year (Table 2 and <u>Supplementary Figure 1</u>). However, male-to-female IRR of the younger group increased gradually by an average of 0.7% per year throughout the period of analysis. For LCC, the overall male-to-female IRR increased gradually since 1974 by an average of 0.6% per year. For rectal cancer, the overall male-to-female IRR showed random fluctuations.

Table 3 presents the overall ASR and the temporal trends of male-to-female SRR. The ASR of CRC in females was consistently higher than males throughout the period of analysis, irrespective of anatomical subsite. The lowest male-to-female SRR of RCC was 0.81 between 1975 and 1979 and the highest male-to-female SRR was 0.96 between 1960 and 1964. For LCC, the lowest male-to-female SRR was 0.83 between 1970 and 1974 and the highest male-to-female SRR was 0.91 between 2005 and 2009. For rectal cancer, the lowest male-to-female SRR was 0.79 between 1970 and 1974 and the highest male-to-female SRR was 0.93 between 2005 and 2009.

For RCC patients, the temporal trend of male-to-female SRR remained at a stable level during the whole study period (Table 4 and <u>Supplementary Figure 2</u>). For LCC patients aged younger than 50 years, male-to-female SRR increased steadily by an average of 0.6% per year. Male-to -female SRR among LCC patients aged 50 years and older remained stable during the study period. For all rectal cancer patients, male-to-female SRR increased slightly by an average of 0.2% per year, as well as patients aged 50 and older.

Discussion

Using data derived from the nationwide Swedish Cancer Registry, which covered a period of more than five decades, giving us the unique opportunity to analyze the

Table I (Continued)

Table 2	Annual Char	-ge of Male-	to-Female Age-S	tandardized	Table 2 Annual Change of Male-to-Female Age-Standardized Incidence Rate Ratio of Colorectal Cancer	atio of Colo	rectal Cancer					
Site	Age	Trend		Trend 2		Trend 3		Trend 4		Trend 5		AAPC ^b
	Group	Years	APC ^a (95% CI)	Years	APC ^a (95% CI)	Years	APC ^a (95% CI) Years	Years	APC ^a (95% CI)	Years	APC ^a (95% CI)	(95% CI)
RCC	0–49 years >49 years Overall	1960–2014 1960–1995 1960–1995	1960-2014 0.7 ^c (0.3, 1.1) 1960-1995 0.3 ^c (0.1, 0.5) 1960-1995 0.4 ^c (0.2, 0.5)	1995–2014 1995–2014	-1.1° (-1.6, -0.6) -1.0° (-1.5, -0.6)							0.7 ^c (0.3, 1.1) -0.2 (-0.4, 0.0) -0.1 (-0.3, 0.1)
ГСС	0–49 years >49 years Overall	1960–2014 1960–1973 1960–1974	1960-2014 0.6 ^c (0.1, 1.1) 1960-1973 -1.0 (-2.1, 0.0) 1960-1974 -0.7 (-1.6, 0.2)	1973–2014 1974–2014	0.6° (0.5, 0.8) 0.6° (0.4, 0.8)							0.6° (0.1, 1.1) 0.2 (-0.1, 0.5) 0.3° (0.0, 0.6)
Rectum	Rectum 0–49 years >49 years Overall	1960–1978 1960–1973 1960–1973	1960-1978 2.3 ^c (0.9, 3.7) 1978-1985 1960-1973 -0.8 (-1.6, 0.1) 1973-1976 1960-1973 -0.6 (-1.3, 0.2) 1973-1976	1978–1985 1973–1976 1973–1976	-7.3° (-13.7, -0.5) 7.8 (-8.1, 26.4) 7.6 (-7.3, 24.9)	1985–1988 1976–1979 1976–1979	1985-1988 19.8 (-21.2, 82.1) 1988-2007 -1.3 (-2.6, 0.1) 2007-2014 7.1 ^c (1.3, 13.3) 1.2 (-1.4, 3.9) 1976-1979 -6.3 (-20.1, 9.9) 1979-2014 0.1 (-0.0, 0.3) -0.0 (-1.3, 1.2) -0.0 (-1.3, 1.2) 1979-2014 0.1 (-0.0, 0.3) 1979-2014 0.0 (-1.1, 1.2)	1988–2007 1979–2014 1979–2014	1988-2007 -1.3 (-2.6, 0.1) 1979-2014 0.1 (-0.0, 0.3) 1979-2014 0.2 (-0.0, 0.3)	2007–2014	7.1° (1.3, 13.3)	1.2 (-1.4, 3.9) -0.0 (-1.3, 1.2) 0.0 (-1.1, 1.2)
Notes: ^a A _i	nnual percent ch	ange. ^b Average	annual percent chang	se. ^c APC or AA	Notes: ^a Annual percent change. ^b Average annual percent change. ^c APC or AAPC is significantly different from zero at $\alpha = 0.05$.	rent from zero	at $\alpha = 0.05$.					

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temporal trends of sex disparity in incidence and survival of CRC. Furthermore, we quantified the annual change by utilizing joinpoint regression analyses. Our results indicated that the temporal trends of sex ratio in incidence of different subtypes of CRC varied considerably during the study period and the observed sex bias varied according to the different age groups; this suggests that potential environmental factors that triggered the onset of CRC showed period-specific and age-specific patterns which may guide future studies exploring the underlying sex-specific mechanisms. In contrast, the temporal trends of sex ratio in survival of CRC remained stable during the study period.

CRC was described as an anatomical site-specific heterogeneous disease since the 1990s.¹² Subsequent research has described the distinct differences in pathogenesis, genetic and epigenetic alterations, molecular pathways, immunology, and gut microbiota depending on the anatomical site of tumor.^{7-9,13} Environmental factors that contribute to the development of site-specific CRC were also reported.^{10,14,15} The explanation of the observed sex differences concerning incidence of CRC can be divided into biological and environmental mechanisms. Biological hypotheses span over anatomy structure, genetic and epigenetic, and hormonal factors. It has been reported that certain genetic and epigenetic differences between sexes may determine colorectal cancer risk. The polymorphisms of ABCB1 differ significantly according to sex.¹⁶ A British study from 2003 observed a significantly increased risk of CRC in males with the $\epsilon 2/\epsilon 3$ ApoE genotype.¹⁷ CpG island methylator phenotype-high was associated with a higher incidence of female cecal tumors.¹⁸ A population-based case-control study revealed that estrogen exposure is a protective factor against microsatellite instability (MSI) cancer in women.¹⁹ This is reflected in that the lack of estrogen in older women increased the risk of MSI-high colon cancer. In the same study, hormone replacement therapy was associated with a reduced risk of unstable tumors.

Environmental factors include dietary, obesity, diabetes, et al. The variation of sex ratio of CRC with time period should mainly be due to sex-specific environmental exposures over time. A meta-analysis indicated that obesity was only associated with an increased risk of rectal cancer in men; this increase was not found in women.¹⁰ Meanwhile, increased body mass index (BMI) was more strongly associated with an increased risk of colon cancer than to rectal cancer. The BMI among the Swedish

Holi Althorization Althorization <th>Diagnosis</th> <th><u>_</u></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>	Diagnosis	<u>_</u>									
Free Years Survival Rate (y) Antion Rate Survival Rate (y) Antion Rate Survival Rate (y) Afree Free Years Survival Rate (y) Free Years Survival Rate (y) Antion Parts Free Years Survival Rate (y) Afree Free Years Survival Rate (y) Survival Rate (y) Antion Parts Free Years Survival Rate (y) 166-169 2.66 0.66(0.7-1-0) 2.69 100(0.61-1-0) 2.69 2.	Site	Period	All Ages			0-49 Years			>49 Years		
Mat France			Five-Year St	urvival Rate (%)	Male-to-Female SRR (95% CI)	Five-Year St	ırvival Rate (%)	Male-to-Female SRR (95% CI)	Five-Year S	urvival Rate (%)	Male-to-Female SRR (95% CI)
(96) (36) (36) (36) (36) (36) (36) (36) (3			Male	Female		Male	Female		Male	Female	
(96-196) 2.4.4 2.0.6 0.86(0.7-0.96) 5.5.6 6.1 0.20(0.7-1.2) 2.5.7 2.3.9 (17)-179 2.6.6 3.0.1 0.86(0.7-0.96) 5.6.6 3.0.1 3.6.7 3.2.9 (19)-179 3.6.5 3.0.1 0.86(0.7-0.96) 46.0 5.0.6 0.86(0.7-0.91) 3.1.8 2.7.3 2.3.9 (19)-199 3.2.5 0.86(0.7-0.91) 7.5.0 5.0.6 0.86(0.7-1.2) 3.1.8 2.7.3 (19)-199 4.1.5 0.81(0.7-1.20) 7.5.0 0.81(0.5-1.12) 3.8.9 1.7.0 4.6.3 (19)-199 4.1.5 0.81(0.7-1.20) 5.2.1 0.86(0.7-0.91) 3.1.9 4.7.7 (19)-199 4.1.5 0.81(0.7-1.01) 7.5.0 1.01(0.7-1.4) 4.6.7 4.6.3 1.1.7 4.6.8 1.1.7 4.6.8 4.6.7 4.6.0 4.6.6 4.6.8 4.6.7 4.6.8 4.6.7 4.6.8 4.6.7 4.6.8 4.6.7 4.6.8 4.6.7 4.6.8 4.6.7 4.6.8 4.6.7<	RCC	1960–1964	26.68	27.89	0.96(0.83–1.10)	59.33	55.90	1.06(0.81–1.40)	24.84	26.31	0.94(0.81–1.10)
(97)-197 36.1 0.88(79-0.9) 46.13 1.06(37-1.48) 3.5.3 3.3.3 (97)-197 23.51 0.88(77-0.9) 0.61 1.06(6.1.17) 2.5.3 2.3.3 (96)-198 34.55 41.55 0.88(77-0.9) 7.5 5.2.8 0.96(61.15) 2.3.8 7.3.3 (96)-199 34.55 41.55 0.88(079-02) 5.7.3 5.2.8 0.96(61.15) 2.3.8 (96)-199 41.75 4.5.3 0.88(019-02) 5.5.1 0.96(01-02) 3.3.6 0.97(05-1.4) 3.3.6 4.4.6 4.9.9 2000-2004 5.5.1 0.86(01-02) 5.5.3 0.86(015-04) 5.5.3 0.96(05-1.0) 3.3.6 2.1.6 <		1965–1969	26.24	30.66	0.86(0.76-0.96)	55.65	60.19	0.92(0.71–1.20)	24.57	28.99	0.85(0.75–0.96)
197-197 275 324 0310/7-0.90 400 4015 1.0008-1.7) 3267 3244 198-198 3455 088(075-0.94) 450 550 09006-1.15) 3181 770 198-198 3455 0130/7-0.94) 4750 5500 09006-1.15) 3181 770 198-198 4572 088(075-0.94) 570 570 09006-1.15) 3181 470 199-198 4517 520 089(03-0.95) 570 570 10707-1.43) 4146 515 2006-2009 770 451 550 943 700 446 516 2006-2009 770 4255 089(03-0.03) 550 9407 550 947 70 190-199 350 233 233 030 03102-1.13) 2325 2965 77 190-198 253 234 70 9407 70 940 77 190-198 253 2346 1000000-1.13) 0		1970–1974	26.62	30.21	0.88(0.79–0.98)	48.32	45.63	1.06(0.76–1.48)	25.39	29.33	0.87(0.77–0.97)
198 332 0.86(0.7-0.97) 7.10 7.20 7.20 1985-1989 3455 4156 0.88(0.7-0.97) 37.30 37.30 1995-1999 41.77 46.83 0.88(0.7-0.70) 37.30 40.70 40.30 1995-1999 41.77 46.83 0.88(0.7-0.70) 57.30 0.90(6.6-1.1) 38.91 40.70 1995-1999 41.77 46.83 0.88(0.7-0.70) 55.00 55.30 0.94(0.66-1.1) 38.91 40.70 2005-2009 47.10 2.2.52 0.88(0.7-0.10) 55.00 55.35 0.94(0.66-1.1) 35.89 41.77 2005-2019 2.2.52 0.36(0.7-0.30) 55.00 55.35 0.94(0.6-1.1) 35.89 41.77 1975-197 2.5.31 2.03 0.36(0.7-0.30) 55.00 55.35 2.966 41.77 1975-197 2.5.11 2.03 0.36(0.7-0.30) 34.76 0.39(0.6-1.1) 35.89 41.77 1975-198 2.5.11 2.5.11 2.5.16 0.36(0.7-0.10)		1975–1979	27.06	33.61	0.81 (0.73–0.89)	48.00	40.15	1.20(0.82–1.73)	25.87	33.24	0.78(0.70–0.86)
196:-196 4156 083(0.77-09) 7750 52.8 0.84(0.64.1.15) 38.0 40.72 1995-196 45.92 0.85(0.79-09) 67.7 70.0 0.89(0.64.1.15) 38.01 44.90 2000-2004 45.17 45.81 0.86(0.81-0.92) 55.10 59.10 59.11 10/0.77-1.47) 40.7 54.85 2000-2004 45.17 55.15 0.96(0.81-0.93) 55.00 53.35 0.94(0.64-1.03) 44.46 51.65 2005-2004 45.11 32.3 0.86(0.81-0.93) 55.00 53.35 0.94(0.64-1.12) 44.66 54.66 196-1961 53.11 52.32 0.86(0.81-0.93) 55.50 58.35 0.94(0.64-1.93) 54.66 10.77 196-1961 53.11 50.31 20.34 55.50 0.88(0.7-0.93) 54.67 0.94(0.64-1.93) 23.66 10.77 196-1961 53.14 45.17 20.3 20.66 10.66 23.77 23.67 20.66 1965-1961 53.14 45.61		1980–1984	32.83	38.25	0.86(0.79–0.94)	49.61	55.06	0.90(0.63–1.29)	31.88	37.30	0.85(0.78–0.93)
1996-1994 388 45.22 0.08(0.7-0.2) 5.7.7 0.04(0.61-1.1) 38.04 44.90 2000-2009 41.77 46.82 0.08(0.8-0.26) 56.07 57.03 0.94(0.51-1.27) 40.70 66.25 2000-2009 47.72 55.15 0.96(0.8-0.26) 55.50 0.94(0.71-1.23) 49.17 54.68 2000-2009 47.72 55.16 0.97(0.84-0.95) 55.00 53.55 0.94(0.71-1.23) 49.17 54.68 1965-1963 55.91 281.65 0.91(0.64-1.03) 57.10 51.18 0.81(77-1.91) 55.99 41.17 54.68 1970-1747 53.11 33.02 0.81(77-0.93) 54.16 0.81(0.57-1.19) 55.99 41.77 1975-197 53.11 33.02 0.81(77-0.93) 54.66 0.91(6.65-1.16) 32.17 23.26 1995-198 54.06 0.81(77-0.3) 54.74 0.91(6.65-1.16) 32.74 32.79 1995-198 54.66 0.81(75-1.2) 56.74 0.91(6.65-1.16) 32.66		1985–1989	34.55	41.56	0.83(0.77–0.90)	47.50	56.28	0.84(0.60–1.19)	33.81	40.72	0.83(0.76–0.90)
1975-1995 1/17 6.63 0.89(033-0.5) 6.74 57.03 1/07(07-1.47) 6.070 64.26 2000-2004 5.19 5.223 0.86(031-0.72) 55.00 58.35 0.91(0.65-1.30) 64.75 55.66 2000-2014 5.19 5.232 0.86(031-0.72) 55.00 58.35 0.91(0.65-1.30) 64.75 55.69 41.77 7000-2014 5.51 0.86(074-039) 55.00 58.35 0.91(0.65-1.31) 55.99 41.77 1970-1974 25.11 30.34 0.88(077-039) 37.70 45.61 0.81(055-1.19) 25.01 28.03 1970-1974 25.11 30.34 40.25 0.88(077-039) 37.70 45.61 0.81(055-1.19) 23.76 29.45 1970-1974 31.31 40.62 58.31 40.401 51.44 67.76 0.81(055-1.19) 23.76 29.45 1995-1996 34.46 41.77 23.86 0.91(055-1.19) 23.76 29.45 1995-1996 34.66 0.86(07-0.29)		1990–1994	38.88	45.92	0.85(0.78-0.92)	53.79	64.00	0.84(0.61–1.15)	38.04	44.90	0.85(0.78-0.92)
000-004 $4;19$ 52.22 $066(081-07)$ 58.20 64.22 $01(0.64-12)$ 44.46 51.65 $000-001$ 97.7 55.15 $00(085-0.6)$ 59.30 59.30 99.07 94.17 94.17 $000-001$ 55.15 $00(085-0.6)$ 59.30 59.30 59.32 $094(07-1-23)$ 94.17 94.17 $196-1961$ 25.93 29.46 $080(77-097)$ 72.07 97.07		1995–1999	41.77	46.83	0.89(0.83–0.96)	60.74	57.03	1.07(0.77–1.47)	40.70	46.26	0.88(0.82–0.95)
2005-2006 45.71 55.15 0.90(085-0.96) 55.50 53.30 0.40(77-1.23) 46.17 54.68 70erall 3.631 7.65 0.07(084-0.99) 55.00 58.35 0.94(0.86-1.04) 35.59 41.77 1956-1966 55.31 2.946 0.88(0.77-0.97) 55.10 58.33 0.94(0.86-1.04) 32.53 29.96 1956-1968 25.33 2.946 0.88(0.77-0.97) 45.61 0.93(0.55-1.19) 25.50 29.06 1950-1991 34.33 0.662 0.88(0.77-0.93) 44.01 51.46 0.99(0.56-1.41) 28.74 22.70 1950-1961 35.46 0.88(0.77-0.93) 44.01 51.44 0.99(0.56-1.41) 28.74 22.70 1950-1961 35.46 0.88(0.77-0.93) 44.01 51.44 0.310(56-1.44) 28.74 22.70 1950-1961 35.46 0.88(0.79-0.93) 6.61 107(077-1.49) 28.74 22.70 1950-1961 35.64 100(056-1.41) 38.66 17.70 25.26 <td< td=""><td></td><td>2000-2004</td><td>45.19</td><td>52.32</td><td>0.86(0.81-0.92)</td><td>58.20</td><td>64.22</td><td>0.91 (0.68–1.20)</td><td>44.46</td><td>51.65</td><td>0.86(0.80-0.92)</td></td<>		2000-2004	45.19	52.32	0.86(0.81-0.92)	58.20	64.22	0.91 (0.68–1.20)	44.46	51.65	0.86(0.80-0.92)
Overali 36.91 42.65 087(0.77-0.93) 55.00 58.35 0.94(0.86-1.04) 35.89 41.77 1960-1964 55.91 29.46 088(0.77-1.01) 47.19 51.18 0.82(0.55-1.21) 25.01 28.23 1955-1956 25.39 29.46 088(0.77-0.97) 37.70 45.61 0.83(0.57-1.19) 25.01 29.36 1955-1958 25.31 30.34 0.88(0.77-0.93) 34.56 0.98(0.57-1.39) 23.75 29.96 1950-1994 35.16 0.88(0.77-0.93) 34.51 46.07 0.91(0.56-1.41) 32.77 906 1950-1994 35.46 0.88(0.77-0.93) 44.01 51.46 0.88(0.55-1.25) 38.67 41.72 1950-1994 32.56 0.88(0.77-0.93) 44.01 51.46 0.88(0.55-1.25) 32.77 901 1950-1994 32.66 0.88(0.77-0.93) 64.67 0.91(0.56-1.44) 32.66 41.72 1950-1994 32.70 0.88(0.79-0.93) 64.67 0.90(0.67-1.49) 32.66 41.72 <td></td> <td>2005-2009</td> <td>49.72</td> <td>55.15</td> <td>0.90(0.85–0.96)</td> <td>59.50</td> <td>63.50</td> <td>0.94(0.71–1.23)</td> <td>49.17</td> <td>54.68</td> <td>0.90(0.85–0.96)</td>		2005-2009	49.72	55.15	0.90(0.85–0.96)	59.50	63.50	0.94(0.71–1.23)	49.17	54.68	0.90(0.85–0.96)
1960-1964 2934 088(0.77-10) 42.19 51.18 083(0.55-1.1) 25.2.6 2906 1970-1974 2511 3233 088(0.77-0.37) 37.70 45.61 083(0.57-1.19) 25.2.52 2906 1970-1974 2511 30.34 06.30 083(0.77-0.37) 45.61 083(0.57-1.19) 23.5.2 29.46 1970-1974 31.31 0.020 088(0.79-0.39) 45.61 088(0.59-1.36) 23.07 23.07 1980-1994 33.24 4.2.36 088(0.79-0.93) 44.01 41.72 23.70 23.70 1990-1994 35.46 0.38(0.79-0.31) 49.55 49.66 14.76 23.66.7 41.75 1990-1994 43.25 6.86(0.79-0.31) 47.66 093(0.59-1.46) 34.66 41.72 1990-1994 43.27 6.86.0 47.96 097(0.77-1.49) 46.65 41.25 1090-1914 37.70 42.56 088(0.79-0.31) 57.17 58.44 41.72 1000.5 212.7 58.47 <td></td> <td>Overall</td> <td>36.91</td> <td>42.65</td> <td>0.87(0.84–0.89)</td> <td>55.00</td> <td>58.35</td> <td>0.94(0.86–1.04)</td> <td>35.89</td> <td>41.77</td> <td>0.86(0.84–0.88)</td>		Overall	36.91	42.65	0.87(0.84–0.89)	55.00	58.35	0.94(0.86–1.04)	35.89	41.77	0.86(0.84–0.88)
1965-1969 2593 2097 037(0.77-0.97) 37.70 45.61 6.607 033(0.57-1.19) 25.2.6 29.06 1970-1974 32.11 30.34 033(0.77-0.93) 45.61 6.607 0.99(0.76-1.39) 23.35 29.45 1970-1974 32.11 30.34 038(0.77-0.93) 45.61 6.607 0.99(0.76-1.39) 23.35 29.46 1980-1994 33.23 4.62 088(0.79-0.94) 49.35 31.46 0.33(0.53-1.35) 33.79 4001 1985-1999 45.37 45.60 086(0.79-0.94) 49.35 55.40 100(69-1.44) 33.65 45.37 1990-1994 32.56 49.96 53.14 0.33(0.6.1.92) 31.76 45.37 1990-1994 32.67 97(0.77-1.49) 12.76 23.76 45.37 2000-2003 46.07 53.14 0.33(6.57-1.29) 38.66 45.37 2001-141 45.07 53.14 107(0.77-1.49) 12.56 45.37 20010-191 22.28 58.40	ГСС	1960–1964	25.93	29.46	0.88(0.77–1.01)	42.19	51.18	0.82(0.56–1.21)	25.01	28.23	0.89(0.77–1.02)
1970-197413:1130.340.83(0.74-0.93)45.6146.070.99(0.70-1.39)23.9529.451975-197923.0833.020.88(0.79-0.93)34.9938.650.91(0.55-1.41)23.7432.701980-198433.020.86(0.79-0.93)44.0151.460.86(0.59-1.25)33.7940011980-199433.250.86(0.79-0.93)44.0151.460.86(0.79-1.49)33.7940011980-199433.250.86(0.79-0.93)49.9553.370.96(0.79-1.49)33.7940011990-199433.250.86(0.79-0.93)60.3356.401.07(0.77-1.49)36.6541.721990-199452.879.99(0.85-0.90)67.1758.401.15(0.88-1.51)52.0653.042000-200446.0753.330.86(0.79-0.93)57.1752.740.97(0.77-1.29)52.0553.042000-200445.070.88(0.85-0.90)51.1752.740.97(0.77-1.29)52.0553.042000-200445.0723.3356.401.15(0.88-1.51)52.6553.042000-200445.0723.080.33(0.75-0.92)67.1752.740.97(0.7-1.29)52.6553.042001-201422.0723.080.33(0.75-0.92)63.1752.740.97(0.7-1.29)52.6653.042001-201422.0723.080.33(0.75-0.92)0.33(0.7-1.29)52.6653.041.95215823.7423.7723.7723.7723.7523.8724.95 <td></td> <td>1965–1969</td> <td>25.93</td> <td>29.95</td> <td>0.87(0.77-0.97)</td> <td>37.70</td> <td>45.61</td> <td>0.83(0.57–1.19)</td> <td>25.26</td> <td>29.06</td> <td>0.87(0.77–0.98)</td>		1965–1969	25.93	29.95	0.87(0.77-0.97)	37.70	45.61	0.83(0.57–1.19)	25.26	29.06	0.87(0.77–0.98)
1975-197529.0833.020.88(0.79-0.99)34.9936.650.9(10.58-1.41)28.7432.701960-194434.3340.620.88(0.77-0.33)44.0151.460.86(0.59-1.25)33.7740011980-194935.4642.560.88(0.77-0.92)49.9553.740.93(0.63-1.36)34.6641.721980-194935.4645.660.88(0.79-0.94)49.5349.6653.7433.7546.011980-194935.260.88(0.79-0.94)64.1467.780.95(0.07-1.29)34.6645.372000-200446.0753.830.88(0.79-0.97)67.1758.401.16(0.77-1.49)45.0558.212000-200446.7558.210.91(0.85-0.97)67.1758.401.16(0.77-1.49)45.0558.212000-200447.0653.740.95(0.77-1.29)67.1758.401.16(0.77-1.39)56.2558.212000-200442.560.88(0.79-0.92)67.1752.740.97(0.87-1.39)56.2523.662000-201422.0027.090.83(0.75-0.22)33.0749.130.67(0.49-0.93)24.132100-201422.0723.810.86(0.79-0.39)33.0749.1323.652.16211722.0723.810.97(0.77-1.39)2.1582.1682.168211722.0723.810.97(0.77-1.39)2.1582.1682.1682117214324.740.97(0.87-1.20)23.652.1682.1682117 <t< td=""><td></td><td>1970–1974</td><td>25.11</td><td>30.34</td><td>0.83(0.74-0.93)</td><td>45.61</td><td>46.07</td><td>0.99(0.70–1.39)</td><td>23.95</td><td>29.45</td><td>0.81(0.72-0.92)</td></t<>		1970–1974	25.11	30.34	0.83(0.74-0.93)	45.61	46.07	0.99(0.70–1.39)	23.95	29.45	0.81(0.72-0.92)
1980-198434.3340.620.85(0.77-0.93)44.0151.460.86(0.59-1.25)33.7940.011980-198435.464.2.360.84(0.76-0.92)49.9633.740.93(0.63-1.36)34.6641.721990-198439.2545.600.86(0.79-0.94)49.3345.641.00(0.69-1.44)38.6645.371990-198439.2545.600.86(0.79-0.93)6.0.235.6.401.07(0.77-1.49)38.6645.371991-199446.075.3.830.86(0.79-0.93)6.1.145.8.401.07(0.77-1.49)38.6649.652000-200446.075.3.830.96(0.79-0.93)6.1.175.8.401.07(0.77-1.49)45.6549.662001-20044.6075.3.830.91(0.80-0.95)6.1.175.8.401.07(0.77-1.49)52.0653.042002-20045.2870.91(0.80-0.95)6.1.175.8.401.17(0.87-1.19)52.6653.241960-19642.7.202.7.090.32(0.75-0.92)33.0749.1356.540.57(0.90-0.93)21.581960-19642.7.132.7.980.32(0.75-0.92)33.0743.0356.540.76(0.56-1.04)23.3323.891960-19642.7.202.7.443.1.330.77(0.72-0.89)14.3356.540.76(0.55-1.04)23.3323.891960-19642.7.472.7.483.1.275.5.336.7.755.530.90(6.5-1.10)23.3441.121960-19643.7.473.7.490.56(0.79-0.29)50.17 </td <td></td> <td>1975–1979</td> <td>29.08</td> <td>33.02</td> <td>0.88(0.79–0.98)</td> <td>34.99</td> <td>38.65</td> <td>0.91(0.58–1.41)</td> <td>28.74</td> <td>32.70</td> <td>0.88(0.79–0.98)</td>		1975–1979	29.08	33.02	0.88(0.79–0.98)	34.99	38.65	0.91(0.58–1.41)	28.74	32.70	0.88(0.79–0.98)
1985-198935.4 84.236 $0.84(0.76-0.92)$ 49.9653.740.39(0.63-1.44)34.6641.721990-199439.5 545.60 $0.86(0.79-0.94)$ 49.5349.5653.3045.371990-199439.5 545.60 $0.86(0.79-0.94)$ 49.5355.40 $1.07(0.77-1.49)$ 38.6645.371990-199445.0753.33 $0.86(0.79-0.93)$ 6.13 55.40 $1.07(0.77-1.49)$ 45.0553.302000-200446.0753.33 $0.86(0.79-0.93)$ 6.17 58.40 $1.07(0.77-1.49)$ 45.0553.302000-200445.07 $0.86(0.79-0.93)$ 6.17 5.440 $1.07(0.77-1.29)$ 45.0553.042000-200442.56 $0.86(0.79-0.93)$ 5.117 5.274 $0.97(0.89-1.61)$ 52.0653.04 $1960-1962$ 2.720 2.709 $0.86(0.73-0.93)$ 5.117 5.274 $0.97(0.49-0.33)$ 21.5824.79 $1960-1962$ 2.774 2.200 $0.83(0.75-0.93)$ 4.325 4.740 $0.76(0.6-1.04)$ 23.6223.87 $1970-1974$ 2.874 2.744 2.333 2.986 2.743 2.748		1980–1984	34.33	40.62	0.85(0.77–0.93)	44.01	51.46	0.86(0.59–1.25)	33.79	40.01	0.84(0.77–0.93)
1990-1994 39.2.5 45.60 0.86(0.79-0.94) 49.33 45.66 45.37 1990-1994 33.5.0 43.6 0.86(0.79-0.94) 49.5.8 1.00(0.69-1.4) 38.6.6 45.37 1990-1994 45.05 53.83 0.86(0.79-0.93) 64.14 67.78 0.95(0.70-1.29) 45.05 53.04 2000-2004 46.07 53.83 0.86(0.79-03) 64.14 67.78 0.95(0.70-1.29) 45.05 53.04 2005-2009 22.87 0.86(0.79-09) 51.17 58.40 1.15(0.88-1.51) 52.06 41.95 2005-2009 22.07 23.03 64.14 67.78 58.40 1.15(0.87-1.09) 35.62 41.98 1960-1964 22.00 27.00 0.97(0.47-0.93) 35.65 23.04 23.87 28.79 1960-1964 22.00 0.83(0.75-0.29) 33.07 49.13 0.97(0.47-0.93) 36.62 21.98 25.87 21.98 1960-1964 23.04 23.04 27.04 28.67 0.76(0.55-1.04)		1985–1989	35.48	42.36	0.84(0.76–0.92)	49.96	53.74	0.93(0.63–1.36)	34.66	41.72	0.83(0.75–0.91)
1995-199 43.50 49.98 0.87(0.80-0.95) 66.14 67.78 107(0.77-1.49) 42.56 49.62 2000-2004 46.07 53.83 0.86(0.79-03) 64.14 67.78 0.95(0.70-1.29) 45.05 58.01 2000-2004 46.07 58.82 0.86(0.79-03) 64.14 67.78 0.95(0.70-1.29) 45.05 58.21 2005-2009 52.87 58.22 0.91(0.85-0.90) 51.17 52.40 0.75(0.70-1.29) 45.05 58.21 1560-1964 27.20 27.09 0.88(0.85-0.90) 33.07 41.13 0.57(0.49-03) 36.62 58.21 1960-1964 27.20 27.99 0.88(0.75-0.92) 48.86 47.40 10.3(0.77-1.38) 23.62 23.79 1960-197 24.87 31.33 0.79(0.72-0.88) 33.07 48.86 0.74(0.90.3) 23.62 23.79 23.79 1960-1964 24.47 0.87(0.49-0.3) 0.86(0.67-1.00) 25.62 23.79 23.79 23.79 23.79 23.79 23.79 <td></td> <td>1990–1994</td> <td>39.25</td> <td>45.60</td> <td>0.86(0.79–0.94)</td> <td>49.53</td> <td>49.68</td> <td>1.00(0.69–1.44)</td> <td>38.66</td> <td>45.37</td> <td>0.85(0.78–0.94)</td>		1990–1994	39.25	45.60	0.86(0.79–0.94)	49.53	49.68	1.00(0.69–1.44)	38.66	45.37	0.85(0.78–0.94)
2000-2004 4607 53.83 0.86(079-0.93) 64.14 6.778 0.95(0.70-1.29) 45.05 53.04 2005-2009 52.87 58.22 0.91(0.85-0.97) 67.17 58.40 11.5(0.88-1.51) 52.06 58.21 2005-2009 52.87 58.22 0.91(0.85-0.97) 67.17 58.40 11.5(0.88-1.51) 52.06 58.21 1740 74.0 12.07 57.09 0.88(0.85-0.90) 33.07 49.13 0.97(0.87-1.09) 36.62 41.98 1960-1964 22.20 27.09 0.88(0.55-0.92) 48.66 47.40 10.30(77-1.39) 21.58 28.79 1975-1979 27.44 31.33 0.779(0.72-0.88) 43.47 0.86(0.65-1.04) 21.33 23.83 2887 1975-1979 27.44 31.33 0.770(0.72-0.88) 43.47 0.87(0.55-1.04) 21.33 23.83 2887 1980-1984 37.41 27.43 6.74 0.89(0.65-1.20) 33.41 34.65 1980-198 37.47 28.53		1995–1999	43.50	49.98	0.87(0.80-0.95)	60.23	56.40	1.07(0.77–1.49)	42.56	49.62	0.86(0.79–0.93)
2005-2009 5.8.12 0.91(0.85-0.97) 6.7.17 58.40 1.15(0.88-1.51) 5.2.06 58.21 Overall 37.40 4.2.56 0.88(0.85-0.90) 51.17 52.74 0.97(0.87-1.08) 36.62 41.98 1960-1964 2.2.20 27.09 0.82(073-0.92) 33.07 49.13 0.67(049-0.93) 36.62 41.98 1950-1974 2.473 2.980 0.82(073-0.89) 33.07 49.13 0.67(049-0.93) 21.58 25.82 1970-1974 2.473 2.980 0.82(075-0.92) 48.86 47.40 1.03(077-1.38) 23.33 29.89 1970-1974 2.473 2.920 0.82(075-0.88) 43.03 5.554 0.76(0.56-1.04) 23.33 29.89 1970-1974 2.473 32.47 33.06 0.77 5.553 6.079 0.91(6.69-1.20) 31.14 36.65 1980-1984 37.70 2.879 0.90(6.67-1.20) 33.41 26.66 41.12 1980-1984 37.74 2.879 0.91(6.69-1.20)		2000-2004	46.07	53.83	0.86(0.79–0.93)	64.14	67.78	0.95(0.70–1.29)	45.05	53.04	0.85(0.78-0.92)
Overali 37.40 42.56 0.88(0.85-0.90) 51.17 52.74 0.97(0.87-1.08) 36.62 41.98 1960-1964 22.20 27.09 0.82(0.73-0.92) 33.07 49.13 0.67(0.49-0.33) 36.62 41.98 1960-1964 22.20 27.09 0.83(0.75-0.92) 33.07 49.13 0.67(0.49-0.33) 21.58 25.82 1975-1979 27.44 31.33 0.79(0.72-0.89) 43.03 56.54 0.76(0.56-1.04) 23.83 29.89 1975-1979 27.44 34.28 0.80(0.73-0.89) 43.03 56.54 0.76(0.56-1.04) 23.83 29.89 1975-1979 27.44 34.28 0.80(0.73-0.89) 43.03 56.54 0.76(0.56-1.04) 23.83 29.89 1980-1984 32.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(6.6-1.20) 21.14 36.65 1980-1984 33.77 41.92 0.86(0.80-0.91) 0.86(0.66-1.10) 38.77 41.12 1980-1984 37.71 55.85 <td< td=""><td></td><td>2005-2009</td><td>52.87</td><td>58.22</td><td>0.91(0.85-0.97)</td><td>67.17</td><td>58.40</td><td>1.15(0.88–1.51)</td><td>52.06</td><td>58.21</td><td>0.89(0.83–0.96)</td></td<>		2005-2009	52.87	58.22	0.91(0.85-0.97)	67.17	58.40	1.15(0.88–1.51)	52.06	58.21	0.89(0.83–0.96)
1960-1964 27.00 27.09 0.82(0.73-0.92) 33.07 49.13 0.67(0.49-0.33) 21.58 25.82 1965-1969 24.73 29.80 0.83(0.75-0.92) 49.86 47.40 1.03(0.77-1.38) 23.35 28.79 1970-1974 24.87 31.33 0.79(0.72-0.88) 43.85 49.47 0.67(0.56-1.04) 23.33 29.89 1970-1974 24.47 34.28 0.30(0.73-0.88) 43.35 56.54 0.76(0.56-1.04) 23.33 29.89 1975-1979 27.44 34.28 0.30(0.73-0.88) 43.35 56.54 0.76(0.56-1.24) 23.33 29.89 1975-1979 27.44 34.28 0.30(0.73-0.88) 43.35 60.79 0.9(0.69-1.20) 21.33 29.89 1980-1984 34.7 55.55 60.79 0.9(0.67-1.20) 31.14 36.65 1985-1989 34.52 0.86(0.89-0.91) 55.45 0.90(0.67-1.20) 31.14 36.65 1990-1994 39.70 46.53 0.86(0.89-0.91) 0.86(0.65-1.10)		Overall	37.40	42.56	0.88(0.85–0.90)	51.17	52.74	0.97(0.87–1.08)	36.62	41.98	0.87(0.85–0.90)
66 24.73 29.80 0.83(0.75-0.92) 48.86 47.40 1.03(0.77-1.38) 23.35 28.79 77 24.87 31.33 0.79(0.72-0.88) 43.05 55.54 0.76(0.56-1.04) 23.33 29.89 79 27.44 34.28 0.80(0.73-0.88) 43.85 49.47 0.99(0.63-1.24) 26.50 33.41 86 32.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 33.65 33.41 87 34.52 41.92 0.86(0.79-0.93) 55.53 60.79 0.91(0.65-1.10) 33.65 41.12 89 34.52 41.92 0.86(0.81-0.92) 50.17 55.85 0.90(0.65-1.10) 33.65 41.12 91 34.55 0.86(0.81-0.91) 52.43 68.14 0.88(0.65-1.10) 33.65 41.12 91 45.55 0.86(0.81-0.92) 52.13 0.98(0.65-1.10) 33.65 41.12 91 45.55 0.86(0.81-0.92) 61.98 0.88(0.65-1.10) 33.65	Rectum	1960–1964	22.20	27.09	0.82(0.73–0.92)	33.07	49.13	0.67(0.49–0.93)	21.58	25.82	0.84(0.74–0.95)
774 24.87 31.33 0.79(0.72-0.88) 43.03 56.54 0.76(0.56-1.04) 23.83 29.89 779 27.44 34.28 0.80(0.73-0.88) 43.85 49.47 0.89(0.63-1.24) 26.50 33.41 864 32.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 31.14 36.55 893 34.52 41.92 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 31.14 36.55 944 37.70 44.53 0.82(0.80-0.91) 55.13 60.79 0.91(0.69-1.20) 33.62 41.12 954 33.70 44.53 0.85(0.80-0.91) 52.43 61.98 0.86(0.69-1.10) 38.97 45.65 964 45.55 50.26 68.14 0.88(0.69-1.10) 38.97 45.65 974 45.53 66.27 68.14 0.88(0.69-1.13) 33.62 41.12 976 45.55 0.86(0.80-0.91) 62.62 73.13 0.86(0.69-1.13) 42.38 49.2		1965–1969	24.73	29.80	0.83(0.75–0.92)	48.86	47.40	1.03(0.77–1.38)	23.35	28.79	0.81(0.73-0.90)
779 27.44 34.28 0.80(0.73-0.88) 43.85 49.47 0.89(0.63-1.24) 26.50 33.41 384 32.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 31.14 36.65 394 33.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 31.14 36.65 394 33.70 46.53 0.82(0.80-0.91) 55.43 61.98 0.85(0.65-1.10) 33.62 41.12 999 43.35 50.26 0.86(0.81-0.92) 52.43 61.98 0.88(0.69-1.10) 38.97 45.65 904 45.55 50.26 0.86(0.81-0.91) 52.43 61.98 0.88(0.69-1.10) 38.97 45.65 904 45.55 50.26 63.16 64.65 0.88(0.68-1.09) 38.97 45.65 905 51.33 55.28 0.98(0.68-1.09) 63.16 64.65 53.39 49.24 913 55.28 0.98(0.68-1.09) 63.16(0.69-1.20) 44.62 52.		1970–1974	24.87	31.33	0.79(0.72–0.88)	43.03	56.54	0.76(0.56–1.04)	23.83	29.89	0.80(0.72–0.88)
84 32.47 37.96 0.86(0.79-0.93) 55.53 60.79 0.91(0.69-1.20) 31.14 3.665 98 34.52 41.92 0.82(0.76-0.89) 50.17 55.85 0.90(0.67-1.20) 31.14 3.655 94 39.70 46.53 0.82(0.80-0.91) 52.43 61.98 0.85(0.65-1.10) 33.62 41.12 95 43.35 50.26 0.86(0.81-0.92) 60.27 68.14 0.88(0.69-1.13) 42.38 49.24 904 45.59 53.52 0.86(0.81-0.91) 62.62 73.13 0.86(0.68-1.09) 38.97 45.55 904 45.59 53.52 0.86(0.81-0.91) 62.62 73.13 0.86(0.68-1.03) 47.62 52.39 905 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.03) 50.65 54.75 913 42.24 93.08(0.78-1.03) 53.65 54.75 53.39 54.75 913 55.28 0.98(0.78-1.03) 53.06 0.98(0.78-1.03) <		1975–1979	27.44	34.28	0.80(0.73-0.88)	43.85	49.47	0.89(0.63–1.24)	26.50	33.41	0.79(0.72-0.87)
889 34.52 41.92 0.82(0.76-0.89) 50.17 55.85 0.90(0.67-1.20) 33.62 41.12 994 39.70 46.53 0.85(0.80-0.91) 52.43 61.98 0.85(0.65-1.10) 33.72 45.55 994 39.70 46.53 0.86(0.81-0.92) 52.43 61.98 0.85(0.65-1.10) 38.97 45.65 904 43.55 50.26 0.86(0.81-0.92) 60.27 68.14 0.88(0.69-1.13) 42.38 49.24 904 45.59 53.52 0.85(0.80-0.91) 62.62 73.13 0.86(0.68-1.09) 44.62 52.39 905 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.03) 50.65 54.75 905 51.33 55.28 0.98(0.84-0.88) 52.54 59.08 0.98(0.78-1.03) 50.65 54.75 91.33 55.28 0.86(0.84-0.88) 52.54 59.08 0.98(0.78-1.03) 50.65 54.75 92.4 59.08 0.89(0.82-0.07) 35.27		1980–1984	32.47	37.96	0.86(0.79–0.93)	55.53	60.79	0.91 (0.69–1.20)	31.14	36.65	0.85(0.78-0.92)
994 39.70 46.53 0.85(0.80-0.91) 52.43 61.98 0.85(0.65-1.10) 38.97 45.65 999 43.35 50.26 0.86(0.81-0.92) 60.27 68.14 0.88(0.69-1.13) 42.38 49.24 004 45.59 53.52 0.85(0.80-0.91) 62.62 73.13 0.86(0.68-1.08) 44.62 52.39 004 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.69-1.13) 42.62 52.39 005 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.23) 50.65 54.75 36.21 42.28 0.98(0.84-0.88) 52.54 59.08 0.99(0.82-0.97) 35.27 41.32		1985–1989	34.52	41.92	0.82(0.76–0.89)	50.17	55.85	0.90(0.67–1.20)	33.62	41.12	0.82(0.76–0.88)
999 43.35 50.26 0.86(0.81-0.92) 60.27 68.14 0.88(0.69-1.13) 42.38 49.24 004 45.59 53.52 0.85(0.80-0.91) 62.62 73.13 0.86(0.68-1.08) 44.62 52.39 009 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.23) 50.65 54.75 36.21 42.28 0.96(0.84-0.88) 52.54 59.08 0.99(0.82-0.97) 35.27 41.32		1990–1994	39.70	46.53	0.85(0.80-0.91)	52.43	61.98	0.85(0.65–1.10)	38.97	45.65	0.85(0.80-0.92)
004 45.59 53.52 0.86(0.80-0.91) 62.62 73.13 0.86(0.68-1.08) 44.62 52.39 009 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.23) 50.65 54.75 36.21 42.28 0.86(0.84-0.88) 52.54 59.08 0.89(0.82-0.97) 35.27 41.32		1995–1999	43.35	50.26	0.86(0.81–0.92)	60.27	68.14	0.88(0.69–1.13)	42.38	49.24	0.86(0.80-0.92)
009 51.33 55.28 0.93(0.87-0.99) 63.16 64.65 0.98(0.78-1.23) 50.65 54.75 36.21 42.28 0.86(0.84-0.88) 52.54 59.08 0.89(0.82-0.97) 35.27 41.32		2000-2004	45.59	53.52	0.85(0.80-0.91)	62.62	73.13	0.86(0.68–1.08)	44.62	52.39	0.85(0.80-0.91)
36.21 42.28 0.86(0.84-0.88) 52.54 59.08 0.89(0.82-0.97) 35.27 41.32		2005-2009	51.33	55.28	0.93(0.87–0.99)	63.16	64.65	0.98(0.78–1.23)	50.65	54.75	0.93(0.87–0.98)
		Overall	36.21	42.28	0.86(0.84–0.88)	52.54	59.08	0.89(0.82–0.97)	35.27	41.32	0.85(0.83–0.88)

Table 3 Age-Standardization Sex-Specific Five-Year Survival Rate and Male-to-Female Five-Year Survival Rate Ratio for Colorectal Cancer Stratified by Anatomical Site and Age at

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Site	Age Group	Trend I	
		Years	APC ^a (95% CI)
RCC	0–49 years	1960–2009	-0.1 (-0.8, 0.5)
	>49 years	1960–2009	-0.0 (-0.2, 0.2)
	Overall	1960–2009	-0.0 (-0.2, 0.1)
LCC	0–49 years	1960–2009	0.6 ^b (0.0, 1.2)
	>49 years	1960–2009	0.0 (-0.2, 0.2)
	Overall	1960–2009	0.0 (-0.1, 0.2)
Rectum	0–49 years	1960–2009	0.2 (-0.3, 0.8)
	>49 years	1960–2009	0.2 ^b (0.1, 0.4)
	Overall	1960–2009	0.2 ^b (0.1, 0.4)

Table 4 Annual Change in Male-to-Female Age-StandardizedFive-Year Survival Rate Ratio of Colorectal Cancer

Notes: ^aAnnual percent change. ^bAPC or AAPC is significantly different from zero at α = 0.05.

population has been steadily increasing since the 1970s, especially among men and adolescents.²⁰ Mean BMI between 1980/81 and 2004/05 increased from 24.1 to 25.5 for men and from 23.1 to 24.3 for women in Sweden.²¹ The association between dietary factors and CRC varied by the location of tumors and sex. High carbohydrate intake increased the risk of RCC in women, but not in men.²² Meat consumption, especially red meat, is associated with a higher risk of LCC and rectal cancer.²³ The Food and Agriculture Organization of the United Nations reported that the average amount of meat consumption in Sweden increased from 76.1 kg/person in 2002 to 80.2 kg/person in 2009, and the consumption of meat is usually higher in men than in women.

The difference in survival rates between males and females could be attributed to genetic, hormonal, and environmental factors. BRAF mutation - an independent prognostic factor for CRC - was more frequently occurring in females compared with males.²⁴ In addition, males with LCC and rectal cancer did not benefit from adjuvant chemotherapy while females with RCC did.²⁵ Cancer screening can reduce CRC mortality by finding cancer at an early and treatable stage.²⁶ The five-year survival rate of CRC can reach 90% when detected at an early stage. CRC screening tests include six types of examinations; these can be divided into stool-based tests and structural examinations.²⁶ Meanwhile, randomized clinical studies using sigmoidoscopy as the primary screening test have demonstrated both a reduced disease-specific mortality and a reduced incidence of CRC.^{27–29} One study showed that the prevalence of advanced LCC and rectal cancer was strongly reduced

within a 10-year period after a colonoscopy procedure, but not advanced RCC,³⁰ due to the fact that proximal colonic tumors are mostly flat, while distal colonic tumors are polypoid-type that are more distinguishable. In addition, a study demonstrated that colonoscopy appears to be a technically more difficult procedure in women than men.³¹ The rate of participating CRC screening tests is increasing for both men and women, although differences in screening use by sex have been documented.³² A study has found that men are more likely than women to receive a CRC screening test,² which was consistent with our data that the male-to-female SRR was increasing in rectal cancer patients; this suggests the possible contribution by screening.

One weakness of this study was the lack of information on known confounding factors such as alcohol consumption, dietary data as well as screening. Meanwhile, being an ecological study, it is not possible to investigate the causal relationships between the observed temporal trends and these relevant risk factors. Our study also has several strengths. We used 55 years of CRC incidence data from the Swedish Cancer Registry that has national coverage. Thus, our analyses had sufficient statistical power to assess temporal trends of sex bias by subsites and guarantee the accuracy of this study.

Conclusion

In conclusion, we found that the temporal trend of CRC showed a different pattern and the sex disparity of RCC, LCC, and rectal cancer varied by age at onset. The temporal variations of sex bias of CRC might be related to sex-specific exposures of environmental risk factors. Further understanding of the effect of modifiable environmental factors on CRC and sex-related exposure factors will be of vital importance. Although male sex is still associated with poorer survival, the gap of sex ratio of survival narrowed gradually, especially for rectal cancer.

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collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The researchers were independent of the funding agencies.

Disclosure

The authors report no conflicts of interest in this work.

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