Colorectal cancer incidence trends in the US and UK: evidence of right- to left-sided biological gradients with implications for screening
Supplementary information

R. Meza, J. Jeon, A. G. Renehan & E.G. Luebeck

March 11, 2010

1 Data fits

Figures S1-S3 show the US (SEER-Whites) CRC age-specific incidence stratified in 5-year periods and the corresponding model fits after adjusting for secular trends . Figures S4-S6 show the UK CRC age-specific incidence stratified in 5-year periods and the corresponding model fits after adjusting for secular trends. The figures show the excellent fit of the model to the CRC incidence in both datasets.

2 Birth-cohort effects

Figure S7 shows the estimated birth-cohort effects for CRC incidence in the US (SEER-Whites) and UK. No clear birth-cohort trends are discernible in either dataset for births before 1945. After 1945 (post WWII) there appears to be a slight (10-20%) increase in CRC risk in the US and a decrease of similar magnitude in the UK. However, the number of CRC cases for these recent birth cohorts is relatively small in both datasets and, with a limited number of post WWII cohorts, the significance of these nascent trends remains unclear.

3 Sensitivity analyses

3.1 Histological analyses

We repeated model analyses dropping histological types (namely mucinous adenocarcinomas: ICD-O-3 codes, 8480 and 8481), which tend to dominate other molecular pathways such as those defined by high levels of microsatellite instability (MSI-H) and/or the CpG island methylator phenotype (CIMP-high). Table S2 shows the number of mucinous adenocacinomas in the US (SEER-Whites) by sex and subsite and the parameter estimates when excluding those from the analysis. There were no material changes in the patterns of parameter estimates in comparison with the baseline results.

3.2 Adenoma prevalence

Figure S8 shows predicted prevalence of adenomas of at least 1 mm in size for men and women in the US (top) and the UK (bottom). In this prediction we assume that 6.5% of the cells in an adenoma are tumorigenic stem cells consistent with recent reports on the low fraction of tumor stem cell in adenoma and CRC (Barker et al., Nature 2009). These results suggest that the relative prevalence of right-sided versus left-sided adenomas increases with age (consistent with the cancer incidence data). In terms of sex, we find a significantly higher prevalence of left-sided adenomas in men. Similar results are obtained if we assume that 1% of cells in an adenoma are tumorigenic stem cells (see main text).

3.3 Fits for different time periods

To investigate if the general patterns found in the biological parameters are independent of the period covered in the analysis, we performed a sensitivity analysis by restricting the model fits to three independent time periods; 1973-1984, 1985-1994 and 1995-2006. For comparability, for each time period we kept one calendar-year coefficient equal to the corresponding baseline value so that the estimated trends are consistent with the baseline results. We also kept the birth cohort coefficients fixed to the baseline estimates, since the ages covered for each birth cohort vary significantly by time period. Tables S3, S4 and S5 show the corresponding biological parameter estimates. Although there were some changes in the absolute values of some of the parameters when

restricting the period of analysis, the ranking of the estimated adenoma initiation rates, growth rates, and mean sojourn times by site and sex remains consistent with the ranking of the baseline estimates.

3.4 Colon NOS cases in the UK

There was a substantial proportion of colon cancers registered in the UK database as NOS (15% of men cases and 18% of women cases). So we randomly recoded the UK NOS cases proportional to the subsite distribution (proximal vs distal) at the corresponding age and year of diagnosis. As alternatives, we also either excluded the UK NOS cases from the analysis or recoded them in equal propotion as proximal or distal. Table S6 shows the UK biological parameter estimates when we exclude the NOS cases from the analysis. Table S7 shows the UK biological parameter estimates when we recode the UK NOS cases in equal proportion as proximal or distal. The tables show that the general patterns observed in the biological parameters are robust to the assumptions made about the UK NOS cases.

Table S1: Equivalent codes for proximal and distal colon sites and rectum according to ICD classification system over the study period 1973 to 2006 for ONS data (UK)

	Period	Proximal colon	Distal colon	Rectum	Colon, NOS
ICD-8	1973 to 1978	153.0,153.1	153.2,153.3	154.0,154.1	153.8,153.9
ICD-9	1979 to 1994	153.0,153.1,153.4	153.2,153.3,153.7	154.0,154.1	153.8,153.9
		153.5,153.6			
ICD-10	1995 to 2006	18.0,18.1,18.2	18.5,18.6,18.7	19.0,20.0	18.8,18.9
		18.3,18.4			

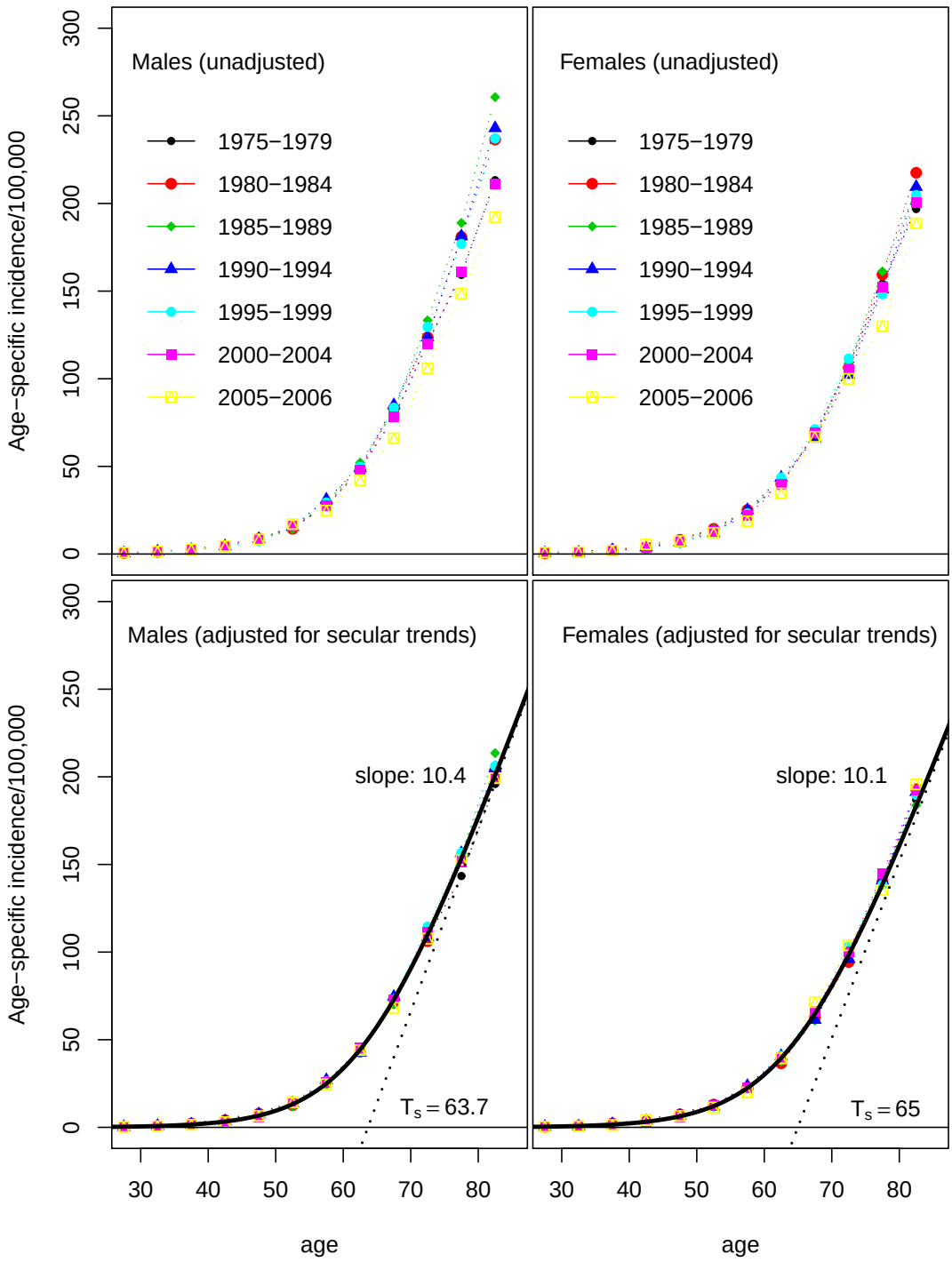

Figure S1: Proximal CRC incidence - SEER. (Upper) SEER proximal CRC incidence. (Lower) proximal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard. The slope of the linear phase of the hazard and the mean sojourn time of premalignant lesions can be determined directly from the adjusted incidence data.

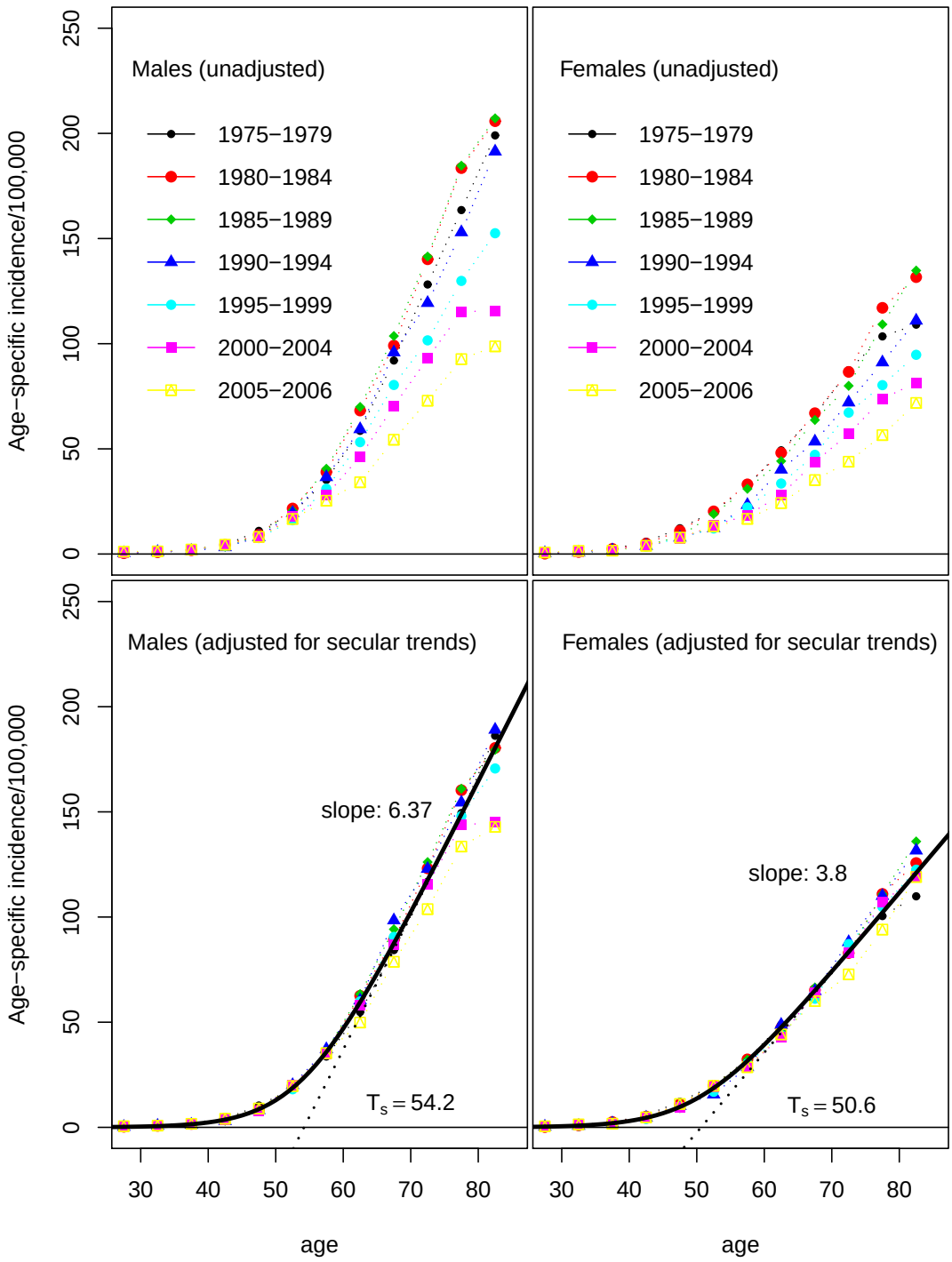

Figure S2: Distal CRC incidence - SEER. (Upper) SEER distal CRC incidence. (Lower) distal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard.

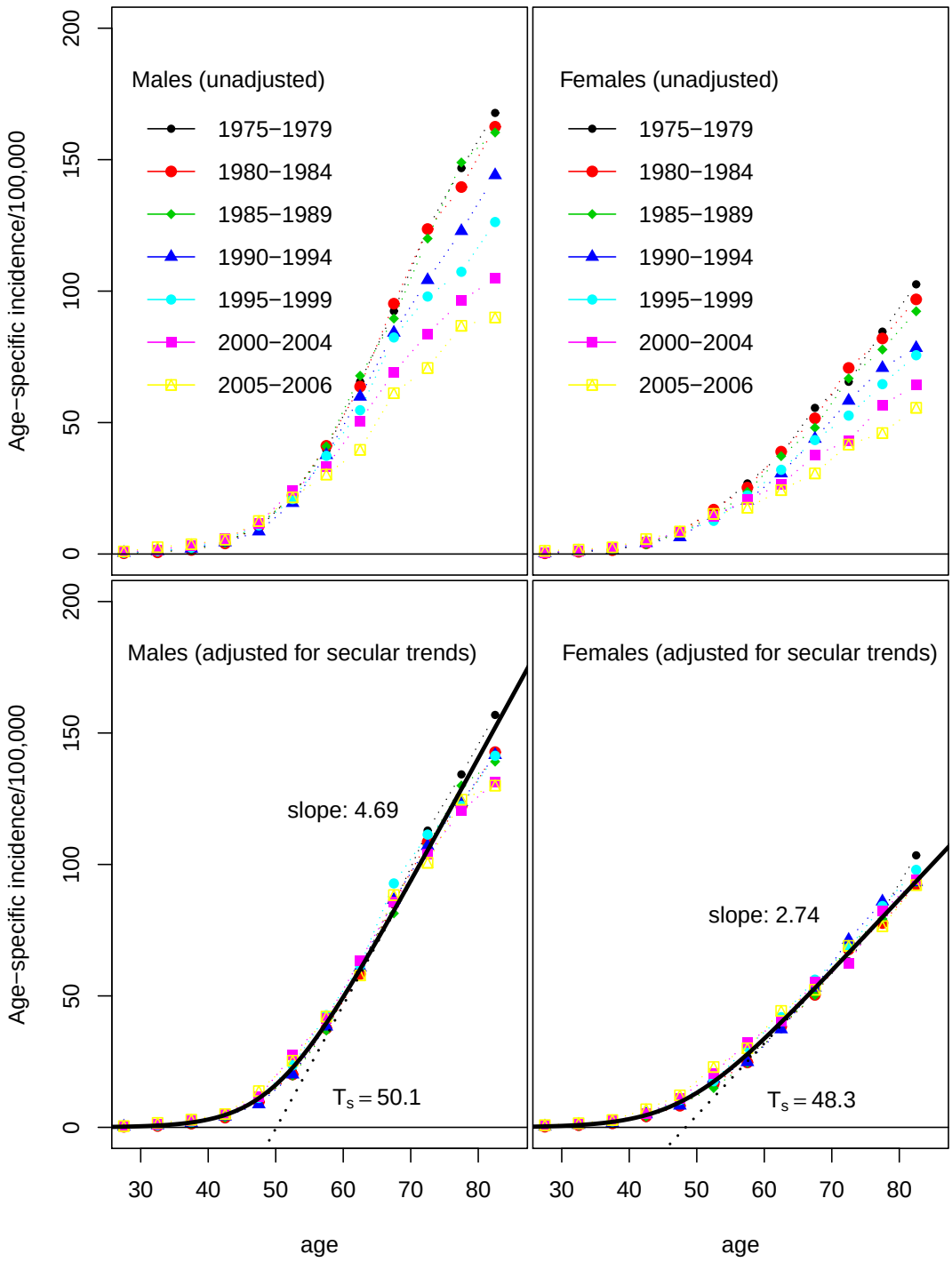

Figure S3: Rectal CRC incidence - SEER. (Upper) SEER rectal CRC incidence. (Lower) rectal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard.

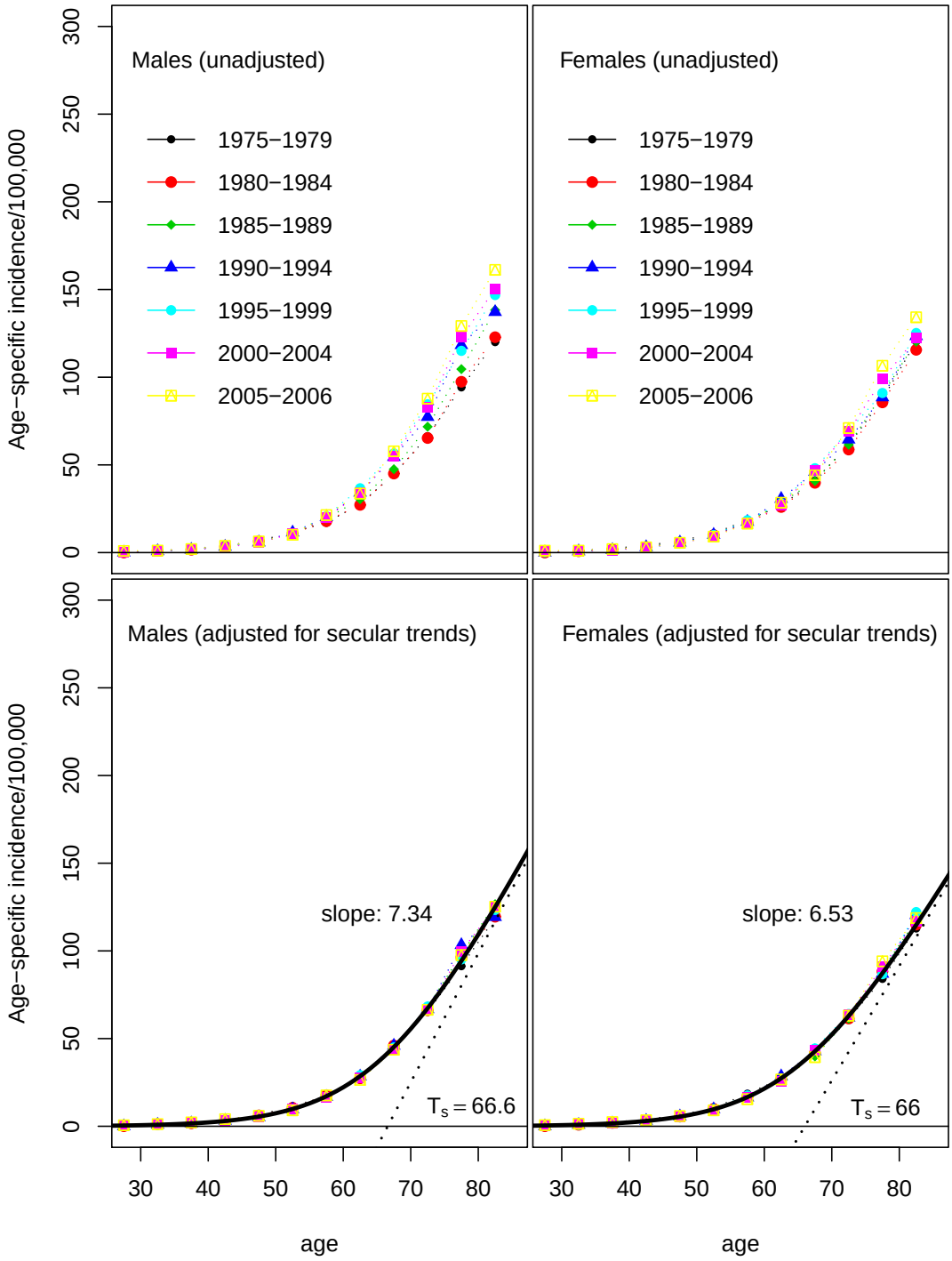

Figure S4: Proximal CRC incidence - UK. (Upper) UK proximal CRC incidence. (Lower) proximal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard.

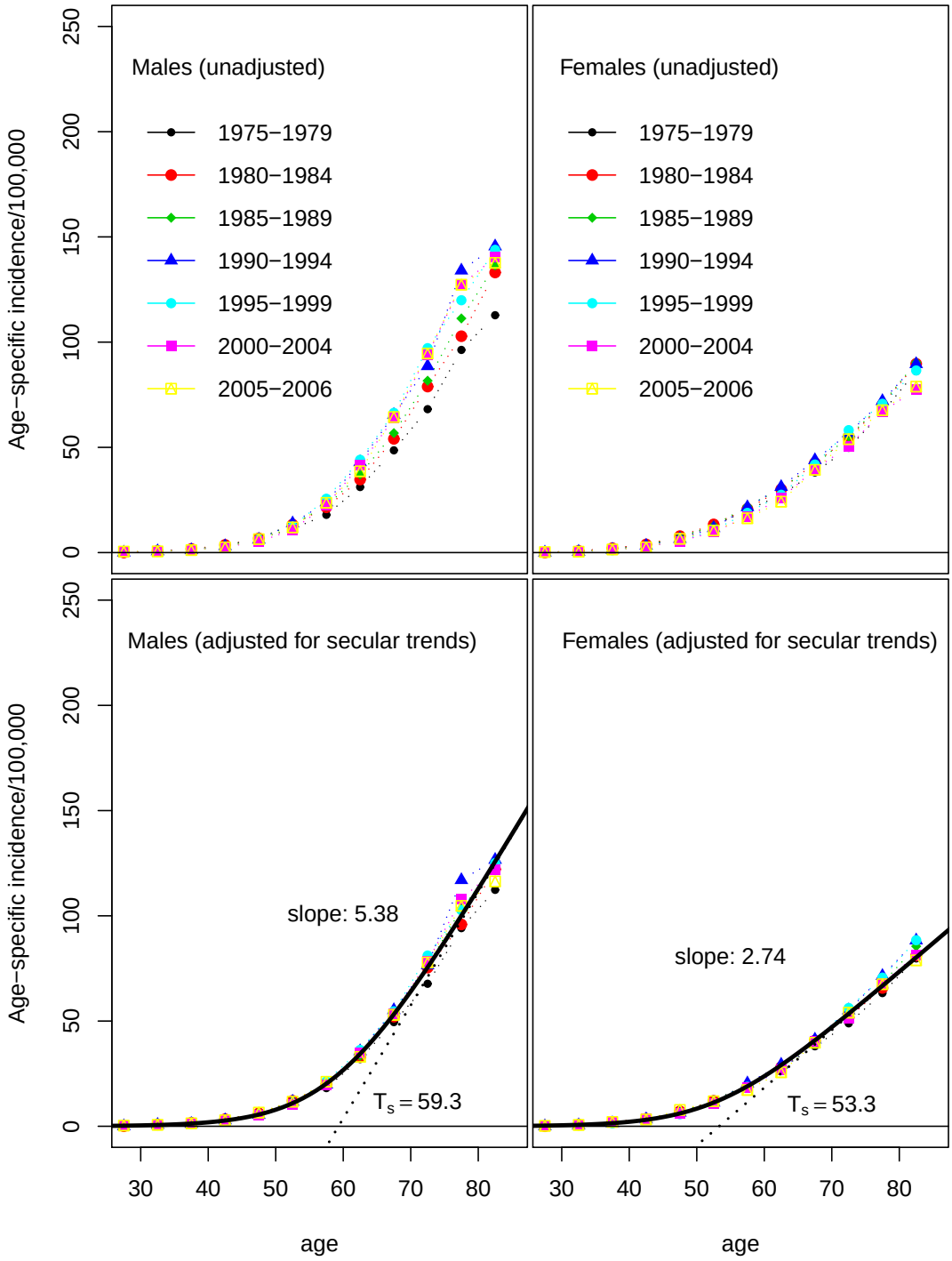

Figure S5: Distal CRC incidence - UK. (Upper) UK distal CRC incidence. (Lower) distal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard.

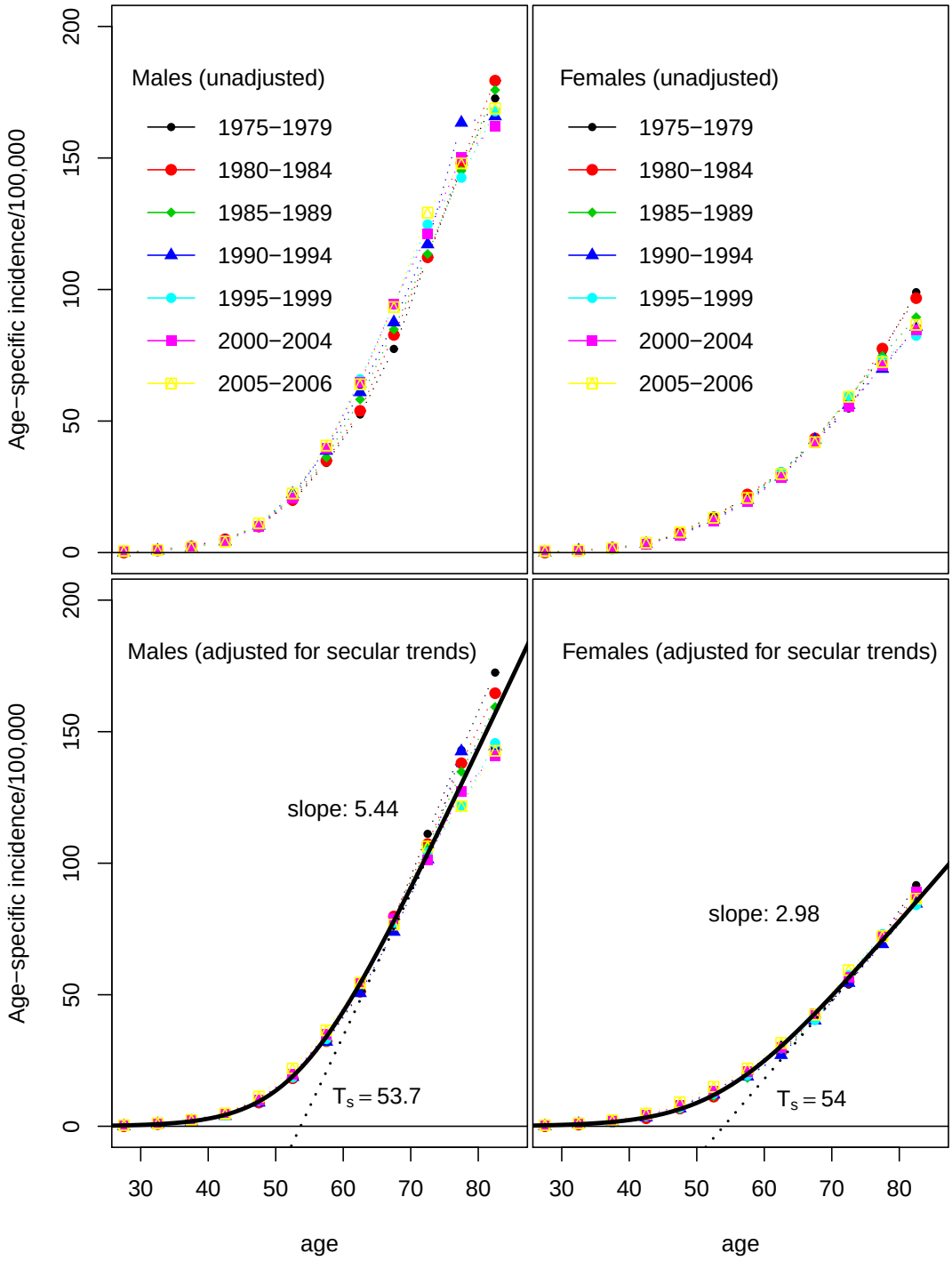

Figure S6: Rectal CRC incidence - UK. (Upper) UK rectal CRC incidence. (Lower) rectal CRC incidence adjusted for secular trends (using estimated calendar year and birth cohort effects from the three-stage model fit). Solid line: three-stage model hazard.

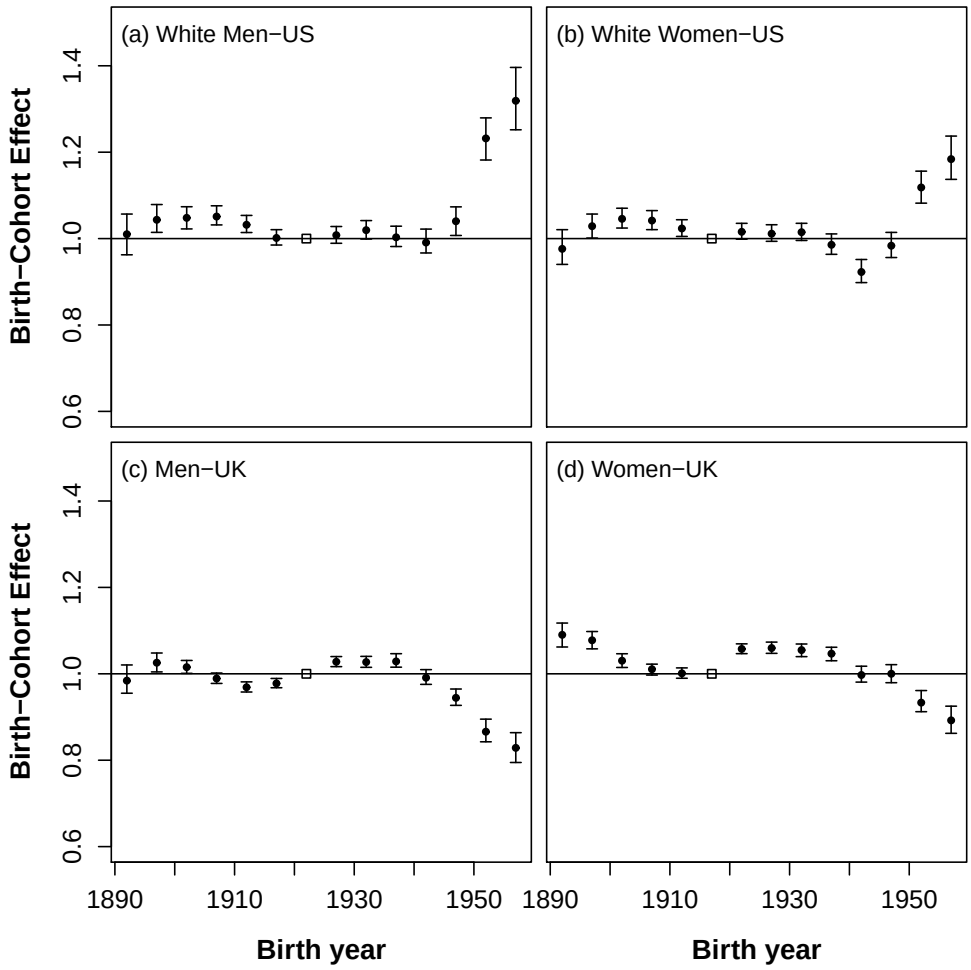

Figure S7: Estimated birth-cohort effects.

Table S2: Parameter estimates for CRC incidences for the US, excluding mucinous cases

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
US (SEER Whites)						
CRC cases	59409	55575	55770	74369	51168	44291
Mucinous cases	8030	3749	3293	11060	3770	2602
Percentage mucinous (%)	13.5	6.7	5.9	14.9	7.4	5.9
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	8.44e-05	5.46e-05	4.32e-05	7.76e-05	3.08e-05	2.55e-05
Adenoma growth rate $(\alpha - \beta)$	0.1476	0.1927	0.2025	0.1393	0.1890	0.1804
Mean Sojourn Time (T_s)	63.2	53.7	49.9	64.3	49.1	48.2
Adenoma conversion rate (μ_2/p_∞)	1.30e-05	0.62e-05	0.83e-05	1.79e-05	1.76e-05	3.02e-05

Table S3: Parameter estimates for CRC incidences for the US and UK: MLEs (1973-1984).

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
US (SEER Whites)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	10.81e-05	6.88e-05	5.03e-05	11.72e-05	3.63e-05	2.99e-05
Adenoma growth rate $(\alpha - \beta)$	0.1334	0.1689	0.1969	0.1217	0.1783	0.1753
Mean Sojourn Time (T_s)	64.9	55.7	51.2	68.0	49.5	50.1
Adenoma conversion rate (μ_2/p_∞)	2.31e-05	1.38e-05	0.83e-05	3.07e-05	2.62e-05	2.70e-05
UK (ONS)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	6.28e-05	4.96e-05	6.13e-05	5.95e-05	2.50e-05	2.97e-05
Adenoma growth rate $(\alpha - \beta)$	0.1237	0.1448	0.1646	0.1207	0.1558	0.1548
Mean Sojourn Time (T_s)	64.5	59.2	55.1	64.8	52.1	53.6
Adenoma conversion rate (μ_2/p_∞)	4.22e-05	2.74e-05	1.88e-05	4.85e-05	4.65e-05	3.84e-05

Table S4: Parameter estimates for CRC incidences for the US and UK: MLEs (1985-1994).

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
US (SEER Whites)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	10.83e-05	6.63e-05	4.79e-05	10.08e-05	4.05e-05	2.75e-05
Adenoma growth rate $(\alpha - \beta)$	0.1437	0.1981	0.2042	0.1393	0.1819	0.1818
Mean Sojourn Time (T_s)	64.1	53.9	50.7	64.9	51.4	48.9
Adenoma conversion rate (μ_2/p_∞)	1.44e-05	0.45e-05	0.65e-05	1.64e-05	1.59e-05	2.50e-05
UK (ONS)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	6.89e-05	5.55e-05	5.57e-05	6.70e-05	2.84e-05	3.05e-05
Adenoma growth rate $(\alpha - \beta)$	0.1298	0.1540	0.1735	0.1235	0.1600	0.1472
Mean Sojourn Time (T_s)	65.0	59.2	54.2	66.1	53.2	54.9
Adenoma conversion rate (μ_2/p_∞)	2.80e-05	1.69e-05	1.44e-05	3.52e-05	3.20e-05	4.56e-05

Table S5: Parameter estimates for CRC incidences for the US and UK: MLEs (1995-2006).

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
US (SEER Whites)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	10.04e-05	5.87e-05	4.47e-05	9.29e-05	3.77e-05	2.57e-05
Adenoma growth rate $(\alpha - \beta)$	0.1504	0.1909	0.1989	0.1486	0.1702	0.1805
Mean Sojourn Time (T_s)	62.7	53.2	48.8	63.2	51.2	46.4
Adenoma conversion rate (μ_2/p_∞)	1.21e-05	0.73e-05	1.22e-05	1.24e-05	2.80e-05	4.17e-05
UK (ONS)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	8.48e-05	5.41e-05	4.95e-05	6.74e-05	2.83e-05	2.91e-05
Adenoma growth rate $(\alpha - \beta)$	0.1160	0.1535	0.1736	0.1180	0.1489	0.1423
Mean Sojourn Time (T_s)	69.0	59.0	52.4	66.5	54.2	53.5
Adenoma conversion rate (μ_2/p_∞)	3.85e-05	1.78e-05	1.93e-05	4.57e-05	4.65e-05	7.02e-05

Table S6: Parameter estimates for CRC incidences for the UK: MLEs (1973-2006). **Colon NOS cases not included in the analysis.**

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
UK (ONS)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	5.55e-05	3.73e-05	5.48e-05	4.31e-05	1.65e-05	3.02e-05
Adenoma growth rate $(\alpha - \beta)$	0.1194	0.1577	0.1723	0.1262	0.1813	0.1498
Mean Sojourn Time (T_s)	66.7	57.7	53.6	63.4	48.7	53.9
Adenoma conversion rate (μ_2/p_∞)	4.11e-05	1.77e-05	1.68e-05	4.19e-05	2.64e-05	4.68e-05

Table S7: Parameter estimates for CRC incidences for the UK: MLEs (1973-2006). **Colon NOS cases redistributed half to distal and half to proximal colon cancer.**

	Men			**Women**		
	Proximal colon	Distal colon	Rectum	Proximal colon	Distal colon	Rectum
UK (ONS)						
Adenoma initiation rate $(\mu_0 X \mu_1 p_\infty)$	7.40e-05	5.34e-05	5.46e-05	6.35e-05	2.88e-05	2.97e-05
Adenoma growth rate $(\alpha - \beta)$	0.1214	0.1501	0.1715	0.1202	0.1507	0.1478
Mean Sojourn Time (T_s)	66.7	59.3	53.7	65.8	53.8	53.9
Adenoma conversion rate (μ_2/p_∞)	3.69e-05	2.04e-05	1.73e-05	4.38e-05	4.53e-05	5.08e-05

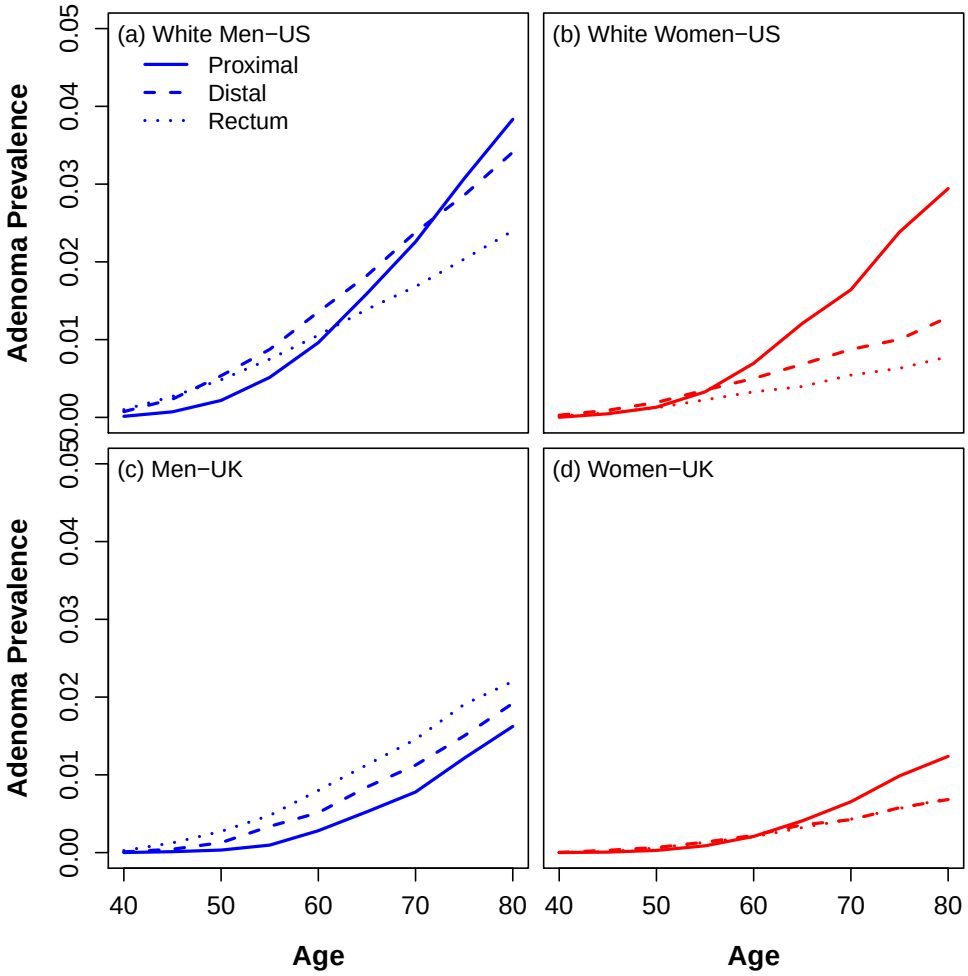

Figure S8: Simulated adenoma (≥1mm) prevalence in asymptomatic individuals by country, sex and subsite. We assume that there are about 500,000 cells in a 1mm adenoma (Pinsky, JTB 2000) and that about 6.5% of those are stem cells (Barker et al., Nature 2009).