Colorectal Cancer Incidence Trends in the United States and United Kingdom: Evidence of Right- to Left-Sided Biological Gradients with Implications for Screening

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Abstract

Several lines of evidence support the premise that screening colonoscopy reduces colorectal cancer (CRC) incidence, but there may be differential benefits for right- and left-sided tumors. To better understand the biological basis of this differential effect, we derived biomathematical models of CRC incidence trends in U.S. and U.K. populations, representing relatively high- and low-prevalence screening, respectively. Using the Surveillance Epidemiology and End Results (SEER) and the Office for National Statistics (ONS) registries (both 1973–2006), we derived stochastic multistage clonal expansion (MSCE) models for right-sided (proximal colon) and left-sided (distal colon and rectal) tumors. The MSCE concept is based on the initiation-promotion-paradigm of carcinogenesis and provides a quantitative description of natural tumor development from the initiation of an adenoma (via biallelic tumor suppressor gene inactivation) to the clinical detection of CRC. From 1,228,036 (SEER: 340,582; ONS: 887,454) cases, parameter estimates for models adjusted for calendar-year and birth-cohort effects showed that adenoma initiation rates were higher for right-sided tumors, whereas, paradoxically, adenoma growth rates were higher for left-sided tumors. The net effect was a higher cancer risk in the right colon only after age 70 years. Consistent with this finding, simulations of adenoma development predicted that the relative prevalence for right- versus left-sided tumors increases with increasing age, a differential effect most striking in women. Using a realistic biomathematical description of CRC development for two nationally representative registries, we show age- and sex-dependent biological gradients for right- and left-sided colorectal tumors. These findings argue for an age-, sex-, and site-directed approach to CRC screening.

Introduction

Colorectal cancer (CRC) is the second commonest cause of cancer deaths in the United States (1) and United Kingdom (2). Screening for cancer and its benign precursor (adenoma) offers the best opportunities to reduce cancer-related mortality. The American Cancer Society, the American College of Radiology, and the U.S. Multi-Society Task Force on Colorectal Cancer guidance on screening recommend a cancer “prevention,” rather than cancer “detection,” approach—the former including screening colonoscopy (1). Although untested by randomized trials, there are several lines of evidence supporting the effectiveness of screening colonoscopy, including (a) reductions in CRC mortality in trials of fecal occult blood (FOB) screening (3); (b) mathematical modeling (4); (c) case-control studies (5, 6); and (d) population-based studies following the initiation of large-scale colonoscopy programs (7). Accordingly, screening colonoscopy rates have increased 3- to 8-fold over the past two decades in the United States (8, 9). By contrast, in the United Kingdom, screening colonoscopy utilization rates are low and limited to high-risk patients, as FOB screening has been offered through a national-based program only since 2006 (10).

Studies of secular trends of CRC incidences in the United States consistently show declining incidence rates for left-sided cancers with barely any decreases for right-sided cancer incidences (11–13), changes which are generally attributed to the increasing utilization of endoscopic screening (11). Slower declines in left-sided cancer incidences in blacks (13) and Asia-Pacific populations (12) compared with whites that parallel the generally lower utilization of endoscopic screening among blacks support this hypothesis (1). It is tempting to posit that the relative decline of left-sided cancers is due mainly to flexible sigmoidoscopy, as historically its utilization rates were higher than those for colonoscopy. However, the choice of screening...
endoscopic modality has substantially reversed in the past decade—for example, among Medicare fee-for-service beneficiaries, flexible sigmoidoscopy rates halved from a period in the late 1990s to 2003, whereas colonoscopy rates increased almost 8-fold (8), yet the left-sided cancer incidence decline has remained the dominant effect. Furthermore, Baxter and colleagues (14), using a province-wide administrative database in Canada, recently reported that among CRC cases, previous exposure to complete colonoscopy was strongly associated with fewer deaths from left-sided CRC (odds ratio, 0.33) but not for right-sided CRC (odds ratio, 0.99). This apparent lack of effectiveness for right-sided lesions with screening colonoscopy may be due to higher miss rates for right-sided cancers, although the estimate for this misclassification is modest (2–6%; ref. 15). In the aggregate, these observations lead us and others (16) to hypothesize that the differential effects are, at least in part, due to biological differences between right- and left-sided disease.

In the absence of randomized trials to test this hypothesis, this study uses population-based CRC incidence data covering three decades to fit multistage clonal expansion (MSCE) models of CRC that were previously developed and published (17-19). The MSCE models capture the salient biological processes (including tumor initiation and promotion) involved in CRC and allow quantitative adjustments of the age-specific cancer incidence for calendar year and birth cohort effects. These effects capture indirectly the effect of screening and other environmental factors on CRC incidence. The direct comparison of two large cancer registries—the Surveillance Epidemiology and End Results (SEER) in the United States and the Office for National Statistics (ONS) in the United Kingdom, representing relatively high- and low-prevalence screening populations, respectively—strengthens our conclusions about the eminent role of tumor initiation and promotion in the apparent cancer risk differential between left-sided and right-sided colon.
Materials and Methods

Incidence data

U.S. incidence data for CRC were obtained from the SEER registry for the years 1973–2006. We extracted reported CRC cases by anatomic subsite, sex, race, age, and calendar year in the nine SEER geographic areas, which together represent an estimated 9.5% of the U.S. population. The subsites were categorized using the International Classification of Diseases for Oncology, 3rd Revision (ICD-O-3) codes as proximal colon: 180 through 184; distal colon: 185 through 187; and rectum: 199 and 209. Person-years by sex, race, age, and calendar year were obtained from the SEER registry (based on the U.S. Census Bureau). For comparability with the U.K. data, model fits were restricted to whites (including Hispanics) by sex.

Data for CRC cases in England and Wales were obtained from the ONS for the years 1973–2006 (for the purpose of this analysis, combined England and Wales was taken as synonymous with U.K.). In the absence of a recoding system as exists for SEER, subsites were categorized into proximal (equivocal to ICD-O-3 above) and equivalent subsite codes for ICD-8 and ICD-9 (Supplementary Data p4). As the proportion of colon cancers classified as "colon not otherwise specified (NOS)" in the U.K. data set was substantial (up to 18%), we randomly recoded NOS cases proportionate to the subsite distribution at the corresponding age and year of diagnosis. The population bases by age, sex, and calendar year were obtained from the ONS population census data. For the analysis period, we assumed that the great majority of the U.K. population was white.

For the trends in incidence baseline analyses, data were standardized to the U.S. 2000 total population. We used the terms “right-sided” as equivalent to proximal colon and “left-sided” as distal colon and rectum combined.

Biomathematical CRC model

Our analyses were based on a class of multistage carcinogenesis models that allow for the sequential random accumulation of a specific number of mutations (or epigenetic events) before the initiation of a premalignant lesion (here the adenoma). We previously showed that the most parsimonious model, consistent with the overall incidence of CRC in SEER and with the known pathogenesis of microsatellite-stable CRC, is a four-stage model (17, 19). This model posits two rare rate-limiting events and a high rate of asymmetrical stem cell divisions (reflecting transient amplification in a crypt) for the initiation of an adenomatous polyp (adenoma) and is consistent with molecular evidence showing that adenomas frequently show biallelic inactivation of the adenomatous polyposis coli (APC) gene (20, 21). Baseline exploratory analyses of CRC incidence data by subsite (proximal, distal, rectum) also revealed that a simpler three-stage model, which requires only two rare rate-limiting events for the initiation of an adenoma, is equally consistent with the CRC incidence in SEER. This model also agrees with the notion that tumor initiation requires biallelic inactivation of a tumor suppressor locus such as, but not exclusively, the APC gene (17). The three-stage model parameters are the number of susceptible stem cells, \( X \), the mutation rate of the first hit at the APC gene locus, \( \mu_0 \), the mutation rate of the second copy of the APC gene, \( \mu_1 \), the adenoma cell division rate, \( \alpha \), the adenoma cell death or differentiation rate, \( \beta \), and the malignant transformation rate, \( \mu_2 \) (Fig. 1A). The mathematical treatment of these models and the derivation of the corresponding hazard and survival functions are described elsewhere (17, 19).

We have previously shown that the hazard (or incidence) function of these models (as a function of age \( t \)) exhibits three distinct phases that reveal the carcinogenic process in reverse (17). In particular, for older ages, the hazard increases linearly, reflecting the incidence of adenomas in the tissue (Fig. 1B). The line approximating this (linear) phase has an intercept with the age axis that represents the mean sojourn time of an adenoma to become malignant \( (T_s) \), that is, the mean time between the initiation of an adenoma and its conversion into a clinical carcinoma. For mid-ages, the hazard increases exponentially, with a rate equal to the net growth rate of adenomas \( (\alpha - \beta) \). For younger ages, the hazard increases as a power of age. We have also shown previously that this behavior of the incidence function can be uniquely described by three parameter combinations (17), which are identified in the next section.

Reported outcomes

We estimated the following biological parameters within the models: the slope of the adenoma incidence \( (\mu_0 x \mu_1 \mu_2) \), as a proxy of adenoma initiation, where \( p_\alpha \), denotes the adenoma survival probability (i.e., the asymptotic probability that a polyp does not become extinct); the growth rate of adenomas \( (\alpha - \beta) \); the mean sojourn time of an adenoma \( (T_s) \); and the adenoma conversion rate \( (\mu_2 / p_\alpha) \).

Adjustments for secular trends

In the model, the effect of age is modeled parametrically; whereas secular trends (i.e., birth cohort and calendar year effects) are modeled nonparametrically. The effect of screening on CRC incidence is captured indirectly by the calendar year effects. For a given age \( t \), birth cohort \( b \), and calendar year (period) \( c \), the age-specific incidence is estimated by

\[
I_c(t) = \theta_a \theta_b h_{\text{mult}}(t),
\]

where \( \theta_a \) and \( \theta_b \) are coefficients that modify the incidence function predicted by the multistage process \( h_{\text{mult}}(t) \) allowing for nonspecific calendar and birth cohort trends. Conforming with the format in which the SEER and U.K. data are distributed, we stratified the data in age groups \( (0–4, 5–9, ..., 80–84, 85+ \text{ y}) \) and into 34 calendar years (1973–2006). Age group 85+ was excluded for men due to rapidly declining person-years after age 85. We then fitted three-stage clonal expansion models to the number of observed proximal and distal colon cancers and rectal cancers stratified by age group and calendar year. We obtained parameter estimates by maximizing the likelihood across all age-calendar strata assuming that the number of cases in each stratum was Poisson distributed with mean \( I_c(t) PY_{ip} \) where
\(PY_{ij}\) denotes the number of person-years in age group \(i\) and calendar year \(j\). All analyses were done by sex, country, and subsite. The Markov Chain Monte Carlo method was used to compute the 95\% confidence intervals of all parameter estimates.

### Adenoma prevalence simulations

We used the methods developed by Jeon and colleagues (18) to derive estimates of the prevalence of proximal, distal, and rectum adenomas in asymptomatic individuals of ages 40, 45, 50, 55, ..., 80 years simulating 100,000 asymptomatic individuals for each age band and computing the fraction of these individuals with adenomas larger than 1 mm in size. The model expressed sizes in terms of the number of tumor (forming) stem cells, and to transform these into diameter units, we assumed that a 1-mm adenoma contains about 500,000 cells (22). Of these cells, for the main model, we assumed that 1\% (23) are tumorigenic (i.e., 5,000 cells in a 1-mm adenoma).

### Sensitivity analyses

We tested a number of critical modeling assumptions using sensitivity analyses. First, recognizing that the assumption of the molecular pathway of biallelic inactivation of a tumor suppressor gene may prevail in only 60\% of CRCs, we repeated the model analyses, dropping histologic types (i.e., mucinous adenocarcinomas; ICD-O-3 codes 8480 and 8481) that seem to develop by molecular pathways that may not be captured adequately by our choice of model [i.e., pathways characterized by high levels of microsatellite instability (MSI-H) and/or a CpG island methylator phenotype (CIMP-high); ref. 24]. Second, to test if the patterns found in the biological parameter estimates were robust against the choice of period, we repeated the analyses, restricting the model fits to the periods 1973–1984, 1985–1994, and 1995–2006, which broadly correspond in the United States to periods of low screening, mainly flexible sigmoidoscopy screening, and mainly colonoscopy screening, respectively (8). Although we do not model the effect of screening and intervention (i.e., polypectomy) explicitly here, the effect of screening on CRC incidence is captured effectively by adjusting the common (i.e., unperturbed) incidence function for secular trends as described in Eq. A. Our previous work (18) showed how interventions can be modeled as a stochastic process within the multistage model framework. Third, for the U.K. data, where there was a high proportion of cancers defined as colon NOS, we repeated the model fitting, either excluding the NOS cases or recoding them in equal proportions for proximal and distal colon subsites. Finally, for the adenoma prevalence simulations, we repeated the model fitting assuming that 6.5\% of cells in an adenoma are tumorigenic stem cells (25).

### Results

#### Baseline characteristics

Table 1 shows the baseline characteristics for both registries. For the study period (1973–2006), there were 340,582 (men: 170,754; females: 169,828) cancers among whites from the SEER database and 887,454 (men: 451,030; females: 436,424) cancers from the ONS database. Proportionally, cancers arising in the rectum were higher in the U.K. population, especially for men. For both registries, the mean ages of cancer detections were older for right-sided cancers in both sexes.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>United States (SEER whites 1973–2006)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of cancers (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>59,409 (34)</td>
<td>74,369 (44)</td>
<td>133,778 (39)</td>
</tr>
<tr>
<td>Distal colon</td>
<td>55,575 (33)</td>
<td>51,168 (30)</td>
<td>106,743 (32)</td>
</tr>
<tr>
<td>Rectum</td>
<td>55,770 (33)</td>
<td>44,291 (26)</td>
<td>100,061 (29)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>70.23 (12.15)</td>
<td>73.36 (11.76)</td>
<td></td>
</tr>
<tr>
<td>Distal colon</td>
<td>68.43 (11.53)</td>
<td>69.75 (12.44)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>67.01 (11.89)</td>
<td>69.17 (12.91)</td>
<td></td>
</tr>
<tr>
<td><strong>United Kingdom (ONS 1973–2006)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cancers (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>125,198 (28)</td>
<td>161,719 (37)</td>
<td>286,917 (32)</td>
</tr>
<tr>
<td>Distal colon</td>
<td>134,652 (30)</td>
<td>133,590 (31)</td>
<td>268,242 (30)</td>
</tr>
<tr>
<td>Rectum</td>
<td>191,180 (42)</td>
<td>141,115 (32)</td>
<td>332,295 (38)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>69.67 (11.59)</td>
<td>72.80 (11.47)</td>
<td></td>
</tr>
<tr>
<td>Distal colon</td>
<td>69.31 (10.74)</td>
<td>70.22 (11.68)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>68.61 (10.91)</td>
<td>71.24 (11.81)</td>
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</tbody>
</table>
Model fit

We fitted three-stage models to sex-specific CRC incidences among whites in the SEER registry and separately for all cases in the U.K. registry. Each model was fitted independently for each anatomic subsite (Supplementary Data p5–p10). We assumed identical calendar effects for distal colon and rectum, but independent calendar effects for proximal colon, and as screening practices have mainly changed with calendar year rather than birth cohort, we assumed identical birth cohort effects across all CRC subsites.

Calendar and birth cohort effects for the United States and United Kingdom

For the SEER data, the standardized incidences (per 100,000 populations) for white men were 67.1 in 1973, peaking in 1985 at 79.0 and declining to 49.9 in 2006. For white women in the United States, the respective incidences were 51.2 in 1973, peaking in 1985 at 57.5 and declining to 39.1 in 2006 (Fig. 2A). For the ONS data, the standardized incidences for men were 49.1 in 1973, increasing steadily to 58.6 in 2006, and for women were 36.9 in 1973, remaining almost unchanged at 37.6 in 2006 (Fig. 2C).

The U.S. calendar effects show a strong decreasing trend in the incidence of left-sided (distal colon and rectum) cancers since the mid-1980s, but no such trend was observed for right-sided (proximal colon) cancers for the age-calendar cohort–adjusted model (Fig. 2B). No important sex differences were seen in the calendar effects. For the United Kingdom, no considerable differences in calendar effects were found between the subsites, although the model-based analysis suggested an increasing trend among men but not women (Fig. 2D).

No clear birth cohort trends are discernible in either data set for births before 1945 (Supplementary Data p11). After
## Table 2. Parameter estimates for CRC incidences for the United States and United Kingdom

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal colon</td>
<td>Distal colon</td>
</tr>
<tr>
<td>United States (SEER)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma initiation rate (\mu_0 X_{\mu_1 p_0})</td>
<td>10.42e-05</td>
<td>6.37e-05</td>
</tr>
<tr>
<td>Adenoma growth rate (\alpha - \beta)</td>
<td>0.1438</td>
<td>0.1862</td>
</tr>
<tr>
<td></td>
<td>(0.1415–0.1463)</td>
<td>(0.1821–0.1898)</td>
</tr>
<tr>
<td>Mean sojourn time* (T_s)</td>
<td>63.7 (63.1–64.3)</td>
<td>54.2 (53.8–54.6)</td>
</tr>
<tr>
<td>Adenoma conversion rate (\mu_2 \bar{p}_\infty)</td>
<td>1.52e-05</td>
<td>0.77e-05</td>
</tr>
<tr>
<td></td>
<td>(1.41e-05–1.63e-05)</td>
<td>(0.68e-05–0.88e-05)</td>
</tr>
<tr>
<td>United Kingdom (ONS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma initiation rate (\mu_0 X_{\mu_1 p_0})</td>
<td>7.34e-05</td>
<td>5.38e-05</td>
</tr>
<tr>
<td>Adenoma growth rate (\alpha - \beta)</td>
<td>0.1218</td>
<td>0.1502</td>
</tr>
<tr>
<td></td>
<td>(0.1200–0.1235)</td>
<td>(0.1479–0.1527)</td>
</tr>
<tr>
<td>Mean sojourn time* (T_s)</td>
<td>66.6 (65.9–67.3)</td>
<td>59.3 (58.8–59.7)</td>
</tr>
<tr>
<td>Adenoma conversion rate (\mu_2 \bar{p}_\infty)</td>
<td>3.66e-05</td>
<td>2.03e-05</td>
</tr>
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</table>

NOTE: Unless otherwise stated, values in parentheses are 95% confidence intervals.

*Mean sojourn time: time in years from the appearance of the first cell in an adenoma to the clinical detection of a carcinoma.
1945 (post-WWII), there seems to be a slight (10–20%) increase in CRC risk in the United States and a decrease of similar magnitude in the United Kingdom. However, the number of CRC cases for these recent birth cohorts is relatively small in both data sets, and with a limited number of post-WWII cohorts, the significance of these nascent trends remains unclear.

Parameter estimates
The model parameter estimates by sex showed consistent patterns across subsites for U.S. and U.K. data (Table 2). Specifically, the mean adenoma initiation rates (measured by the slope parameter) were higher for the proximal colon, decreasing in the main through distal colon to rectum. The mean initiation rates for the distal colon and rectum, both in the United States and United Kingdom, were significantly higher in men than in women. By contrast, the estimated mean adenoma growth (net cell proliferation) rates were lower in the proximal colon with a trend to higher values through the distal colon to the rectum, especially among men. As with mean initiation rates, the mean adenoma growth rates were generally higher in men compared with women.

The adenoma mean sojourn times (the time it takes from an adenoma origin to its transition into a clinical carcino-
women in both registries, and was higher for proximal colon versus distal colon and rectum for both sexes in the United States and for women in the United Kingdom. In contrast to the cancer incidence data, there was no “cross-over” at the age of 70 years, with the exception of men in the United Kingdom.

**Sensitivity analyses**
Histologic subtypes were recorded in the SEER database, but not in the ONS. There were 32,504 (men: 15,072; women: 17,432) individuals or 9.5% with a histologic diagnosis of mucinous adenocarcinoma; in turn, this histologic subtype was most prevalent in the proximal colon. When these were excluded and the models repeated, there were no material changes in the patterns of parameter estimates (Supplementary Data p12). We also recalculated the parameter estimates for the U.S. and U.K. data separately for the periods 1973–1984, 1985–1994, and 1995–2006, and found similar patterns as the main analysis (Supplementary Data p13–p15). We repeated the model fitting of the U.K. data, reallocating colon NOS cases either by exclusion or in equal amounts to proximal and distal colon subsites, and found consistent results (Supplementary Data p16–p17). Finally, we repeated the adenoma prevalence simulations assuming that 6.5%, rather than 1%, of cells are tumorigenic stem cells (25), and obtained similar results as with the baseline assumption (Supplementary Data p18).

**Discussion**

**Main findings**
This study derived estimates of tumor initiation rates and tumor growth rates for right- and left-sided CRCs using data on more than 1 million cancers from two nationally representative populations and previously developed mathematical models for CRC development. Despite considerable differences in background screening practices between the two countries, the patterns of parameter estimates were very similar, namely, tumor initiation rates were highest for right-sided whereas tumor growth rates were highest for left-sided tumors. In almost all scenarios, these rates are greater in men than in women. The net effect of these two fundamental processes in carcinogenesis (expressed by the hazard function) is consistent with a model in which the incidences of left-sided CRCs dominate over right-sided CRCs before the age of 70 years, with a reversal in the respective incidences thereafter, independent of screening prevalence. A notable unexplained exception occurred
for men in the United Kingdom, who are at a higher risk for developing left-sided cancers throughout life.

**Study limitations and strengths**

The study has a number of limitations. First, in common with any mathematical model, our modeling framework is a simplification of the biological complexity of carcinogenesis and neglects the influence of various endogenous and exogenous modifiers of CRC risk—for example, obesity (26), physical inactivity (27), alcohol (28), smoking (29), and decreased risk from hormonal replacement therapy in women (30)—covariate information that was not available for this study. Second, implicit in the three-stage clonal expansion model is the assumption of two rate-limiting events representing the biallelic inactivation of a tumor suppressor gene (APC gene and/or others) for tumor initiation, which account for 60% to 80% of sporadic CRC cases (24). Tumors that exhibit MSI-H and/or CIMP-high may require more than two rate-limiting events for the initiation of neoplastic growth. We addressed this by excluding mucinous adenocarcinomas, where MSI-H and/or CIMP-high are prevalent, and found no material differences in the parameter estimates. Third, the high proportion of colon NOS cancers registered in the U.K. database may lead to misclassification biases. To address this, we randomly recoded the colon NOS cases proportionate to the subsite distributions at the corresponding age and year of diagnosis and performed additional sensitivity analyses; we found that these did not alter our conclusions. Fourth, although our integrated biological approach of modeling incidence implicitly predicts the age-specific adenoma prevalence (18), these estimates cannot be compared directly with empirical data on observed adenoma prevalence. The model expresses sizes in terms of the number of tumor-forming stem cells, which currently cannot be identified due to a lack of appropriate markers. We dealt with these uncertainties using estimate tumor stem cell percentages of 1% (23) and 6.5% (25), the latter estimate consistent with that inferred from DNA methylation patterns in CRC assuming 50% asymmetrical divisions (31). Our model predicts lower age-specific adenoma prevalence rates than are typically observed in colonoscopy studies of asymptomatic subjects (32-36): 12.5% for age 40 to 49 years; 19.1% to 28.0% for 50 to 59 years; 32.0% to 44.7% for 60 to 69 years; and 33.3% to 57.9% for 70+ years, although the cited series were either exclusively (33, 34) or predominantly from male subjects (32, 35, 36). However, our model correctly predicted a greater adenoma prevalence in men than in women (37, 38) and predicted differential changes with increasing age (38).

The use of a biologically based multistage model for CRC has several strengths. First, the mathematical model has previously been developed (17, 19, 39) and validated in clinical scenarios, including the evaluation of CRC screening strategies (18). Additionally, the model has been used to explore the potential benefits and risks for CRC resulting from folic acid supplementation (40) and used to describe the age-specific incidence of pancreatic cancer (17). Second, having previously validated this model against U.S. CRC incidence data (17, 19, 39), we extended this validation to U.K. CRC incidence data and arrived at similar patterns for the parameter estimates, suggesting common physiologic gradients in colon and rectum for these two populations. Third, this study used two large established registries with three decades of data and from comparable westernized populations, allowing us to focus on the subsite-specific biological parameters that determine tumor development. Despite differences in screening practices between the two countries, after adjustment for calendar year effects to capture the impact of screening, we obtained consistent estimates for the biological parameters (by subsite) for the two populations, suggesting that the differential age- and sex-related adenoma prevalences and CRC incidences between proximal and distal colon and rectum are real and not caused by screening.

**Comparison with other literature**

In common with previous epidemiologic studies (11-13), we have shown that, in the United States, there has been a decline in CRC incidences since the mid-1980s and that this decline is limited to left-sided cancers. The derived model parameters suggest higher adenoma initiation rates in the proximal colon compared with distal colon and rectum, gradients that might arise from site-specific differences in the number of susceptible tissue stem cells. In turn, the numbers of intestinal crypts per individual are related to colon lengths and surface areas. Consistent with the relative estimates of the adenoma initiation rates in our study, using measurements from barium enema radiographs, Sadahiro and colleagues (41, 42) reported larger surface areas in the proximal colon relative to the distal colon, although their estimated proximal colon surface area was 1.6 times that of the distal colon in women, whereas our estimate of the adenoma initiation rate in the proximal colon in women was 2.6 times that of the distal colon. In general, adenoma initiation rates are higher in men than in women, especially in the distal colon and rectum. This finding is consistent with measurements from magnetic imaging colonoscopy that show greater left-sided colonic lengths in men compared with women (43). The lower initiation rates in the rectum are consistent with cell proliferation studies showing significantly lower labeling indices in the rectum (44), although other studies have reported no differences in the mutational load between proximal and distal colon (45). Tumor growth rates of premalignant lesions increase from right to left colon, a finding that is consistent with a similar gradient noted by labeling index measurements of cell proliferation in chemically induced rat colon tumors (46).

The adenoma mean sojourn times (time from the appearance of the first cell in an adenoma to the clinical detection of a carcinoma) that we report (>50 years) are estimations, not assumptions, obtained independently for the U.S. and U.K. data. These durations may seem long, but are not inconsistent with estimations from lesion sequencing studies (47). These should be contrasted with the mean dwell time of observable adenomas progressing toward clinical cancer and the presymptomatic duration of CRC [about 20 and
6.7 y, respectively, as estimated by Landsdorp-Vogelaar and colleagues (48). However, these estimates are for colon and rectal tumors combined and thus do not differentiate right versus left colon. Our estimates of the adenoma sojourn time differ between right (slower) and left (faster) colon by about 10 to 15 years.

**Clinical implications and future research**

Our findings support the hypothesis that there is a differential preventive effect on right- and left-sided cancers from screening endoscopy. They lend support to the study by Baxter and colleagues (14) who found that colonoscopy significantly reduces left-sided CRC mortality (by 70%) but does not seem to have a significant effect on right-sided CRC mortality. Whereas external factors such as missed proximal colonic lesions and/or incomplete coverage of the whole colon during colonoscopy may be relevant, this study argues that differences in the biological characteristics of right- and left-sided tumors are equally relevant. It is often cited that right-sided grow faster than left-sided adenomas, implying that there might be a smaller window of opportunity to detect polyps in the proximal colon by screening—but this is mainly based on MSI-H tumors associated with hereditary nonpolyposis CRC (49). In fact, our analyses show the opposite: Proximal colon polyps grow slower than polyps in distal colon and rectum in a sex-specific manner, which is consistent with the delayed onset of right-sided CRC relative to left-sided CRC. Whether or not right-sided malignancies grow faster (and therefore escape detection) requires further study and preferably a model-based analysis that includes additional data on screen-detected colorectal neoplasia. For general population CRC screening, our findings point to the importance of designing screening schedules that recognize the differences between women and men (37, 38, 50) and to the potential benefits from targeting screening strategies differentially to the right- and left-sided lesions at different ages.

Our study provides additional rationale to reconsider screening paradigms of colonoscopy versus FOB versus flexible sigmoidoscopy. From a pragmatic point of view, the CRC model described here may assist the design of future clinical studies that integrate optimal modalities and target strategies. For example, in an aging population with limited resources, flexible sigmoidoscopy may be more cost-effective under the age of 70 years, but thereafter screening colonoscopy may be more appropriate, assuming it has adequate efficacy in the proximal colon.

In view of these findings, future colonoscopy trials should appropriately power recruitment to allow a priori stratified analyses for right- and left-sided neoplastic end points. Moreover, there is a need for translational research to better characterize the effect of risk factors such as obesity and smoking on relevant biological end points (e.g., cell proliferation, differentiation, and apoptosis) during adenoma initiation and progression. Finally, there is an opportunity to "piggyback" the CRC risk models used in the cancer control field onto cancer stem cell research recognizing the recent identification of key tumor stem cell markers in CRC, for example, Lgr5 (25) and CD133 (51). Promising are studies of DNA methylation patterns to "fingerprint" the age of adenomas (31), which is a key parameter of virtually all CRC models in the field. Such improvements in modeling will undoubtedly lead to more reliable risk predictions and thereby better inform policymakers on cost-effective screening and intervention strategies to prevent CRC more effectively at the population level.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Grant Support**

NIH grants R01 CA107028 and R01 CA119224. A.G. Renehan is supported by a Higher Education Funding Council for England “new blood” senior lectureship. R. Meza acknowledges the support of the Division of Mathematical Modeling at the UBC Centre for Disease Control.

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Received 12/07/2009; revised 04/21/2010; accepted 04/23/2010; published OnlineFirst 06/08/2010.

**References**

Colorectal Cancer Incidence Trends in the United States and United Kingdom: Evidence of Right- to Left-Sided Biological Gradients with Implications for Screening

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Cancer Res  Published OnlineFirst June 8, 2010.

Updated version  Access the most recent version of this article at: doi:10.1158/0008-5472.CAN-09-4417

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