

Supplementary Materials

Model Calibration

We simultaneously calibrated our model to multiple types of studies. We matched data on adenoma and cancer outcomes from (1) persons followed after a colonoscopic polypectomy with intermittent colonoscopies performed and (2) persons followed after resected CRC with regular colonoscopies performed. Hence, we assumed that the disease risks associated with post-resected CRC patients was similar to those with resected adenomas. One challenge in these calibrations is to accurately capture the colonoscopy use. The more often that colonoscopies are performed the more likely adenomas will be found but the less likely that CRC will be found in the long run. We censored deaths from other causes during our calibration runs and did not allow any metastatic recurrences (i.e., we only considered intraluminal disease for these calibrations).

Martinez et al. conducted a meta-analysis of eight prospective studies of persons following colonoscopic polypectomy.¹ For a median follow-up time of 47.2 months with a median number of two colonoscopies over the follow-up interval, Martinez et al. reported that 46.7% of persons were diagnosed with any adenoma, 7.8% persons were diagnosed with adenomas 10 mm or larger, and 0.6% were diagnosed with CRC. We used our model to project the 4-year incidence of colorectal outcomes assuming that persons had a colonoscopy at years 1 and 4. Model projections were close to observed values (Appendix Table 1) but were lower in order to match the other studies (described below).

Appendix Table 1. Model Calibration to Meta-Analysis of Eight Prospective Studies of Post Colonoscopic Polypectomy

Outcome	Martinez et al.	Model projection
Any adenoma or cancer diagnosis	46.7%	41.0%
Adenoma 10 mm or larger, or cancer	7.8%	6.9%
Cancer diagnosis	0.6%	0.5%

Several longer-term studies have followed individuals following the diagnosis and removal of *high-risk* adenomas, or deemed at higher risk than average persons. Atkin et al. reported a 10-year risk of cancer incidence of 3.3% [95%CI, 2.6% to 4.2%] without surveillance in a group identified to be at higher risk.² Assuming that resected cancer patients have a prognosis similar to these higher-risk persons we projected the risk of cancer over 10 years and were able to match this estimate in a modeled population *without* surveillance colonoscopy (model-projected estimate = 3.2%). We were also able to match the reported 10-year incidence for persons with 1 surveillance colonoscopy (2.8%, assuming the surveillance occurred between 6 and 7 years post resection) and the 10-year incidence for persons with 2 surveillance colonoscopies (2.2%, assuming the surveillance colonoscopies occurred at 5 and 10 years post resection).

Using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer randomized clinical trial, Click et al. reported a 15-year cumulative CRC incidence of 2.9% [95%CI, 2.3% to 3.7%] among persons diagnosed with advanced adenoma.³ We used a study reporting on colonoscopy usage for a subset of the PLCO screening trial participants with advanced adenomas to project the 15-year cumulative incidence considering the distribution of surveillance colonoscopies reported⁴ and were able to match the estimated cumulative risk (2.9%).

In a long-term follow-up study conducted in Norway, Loberg and colleagues reported a 13-year cumulative risk of CRC-related death of 1.9% following the diagnosis of a high-risk adenoma (Figure 2 of

paper).⁵ We assumed a surveillance schedule of 10-yearly colonoscopy (i.e., the Norwegian recommendation for surveillance colonoscopy for patients with high-risk adenomas). If we assumed that all persons received a surveillance colonoscopy our model projects a 13-year CRC death of 1.3%, which is lower than found in the study. However, Loberg et al. do not report on colonoscopy use and it's likely adherence is not 100%. Colonoscopy adherence affected our projection minimally; increasing cancer-specific mortality rates by 50% (following diagnosis of CRC) increase our projection to 1.6%, which is still lower than the Loberg study.

Kronborg et al. conducted a study where they performed interval colonoscopy on post-resected CRC patients every 6 months and reported only on those patients who had colonoscopy each year.⁶ We used our model to project the incidence of any adenoma or CRC at each 6-month interval over 2.5 years and compared our findings with those reported by Kronborg et al. The model predicted more high-risk adenomas compared to that reported by Kronborg et al. (Appendix Table 2) and projected a 2.5-year risk of CRC of 0.5%.

Appendix Table 2. Model Calibration to Post-Resected CRC Patient Study

Time since resection (month)	Kronborg Any adenoma	Model Any adenoma	Kronborg HR adenoma	Model HR adenoma
6	0.086	0.105	0.016	0.02
12	0.084	0.062	0.007	0.003
18	0.027	0.05	0	0.0016
24	0.037	0.047	0	0.0013
30	0.051	0.046	0	0.0013

HR, high-risk.

Appendix Table 3 shows the values of the model parameters derived through the calibrations described above and Appendix Table 4 shows the values for cancer-specific mortality rates by stage.

Appendix Table 3. Natural History Model Parameters

Disease Progression Parameters	Estimate
No disease to adenoma 1-5 mm	0.045+(Age-60)*0.0024
1-5 mm to 6-9 mm adenoma	0.02
6-9mm to adenoma 10 mm or larger	0.12
Adenoma 10 mm or larger to localized PCC	0.06
Localized to regional PCC	0.28
Regional to distant PCC	0.63
Localized PCC to localized CRC	0.25
Regional PCC to regional CRC	0.55
Distant PCC to distant CRC	0.99
Probability of metastasis recurrence diagnosis	Time dependent

Appendix Table 4. Annual Cancer-Specific Mortality Rates Derived from Surveillance, Epidemiology, and End Results (SEER) Program

Cancer stage	Estimate [Range]	Distribution
Localized cancer	0.021 [0.018-0.025]	Normal(0.021, 0.002)
Regional cancer	0.068 [0.063-0.074]	Normal(0.068, 0.003)
Distant cancer	0.395 [0.337-0.455]	Normal(0.395, 0.030)

References

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3. Click B, Pinsky PF, Hickey T, et al. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. *JAMA.* 2018;319:2021-31.
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