Model of estimated rates of colorectal cancer from polyp growth by year of surveillance

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Abstract

***Objective*—Most studies show protective effects of non-steroidal anti-inflamatory drugs (NSAIDs) against polyps and colorectal cancers (CRCs) of up to 50%. Current models are unable to directly estimate changes in effects of chemoprevention on CRCs. The purpose is to develop a model to examine effects of changes in growth rates of polyps on surveillance intervals and risk of CRC .**

***Methods*—The growth model simulates 500 people after polypectomy, estimating number and size of polyps annually over 10 years. Each polyp is assigned a random growth rate consistent with distributions of empirically observed growth assumed to follow a log linear model. Rates of CRC were calculated from largest polyps distributed to people.**

***Results*—Simulated distributions of polyps and CRCs closely match empirical estimates which confirms the usefulness of the model. If polyp growth is 25% of normal, the number of cancers by year 10 after index colonoscopy decrease from 146 to only 57/100 000 for those in risk group 0 (no polyps at index colonoscopy) and from 840 to 124/100 000 for those of risk group 3 (4 or more polyps).**

***Conclusions*—This is the first model based on polyp growth rates. The CRC rates suggest that for those with no polyps on index colonoscopy, surveillance may be as for people of average risk (7–10 years), whereas those with one polyp or more need more surveillance (2–5 years). The use of the model is the indication that surveillance intervals could be increased by as much as 2–10 years if the growth rates of polyps are slowed.**

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Colorectal cancer is the second leading cause of death among all cancers in the United States and the lifetime risk of death from colorectal cancer (CRC) is currently about 2.5%.[1] Most evidence indicates that a progression exists from adenomatous polyps to the development of CRC and is termed the "adenoma-carcinoma sequence".[2] This has led to an interest in the screening and surveillance of polyps as the main preventative measure for CRC. However, although 70%–90% of CRCs arise from polyps,[3–5] only 0.25% of polyps/year become CRCs.[6] Because most polyps do not develop into CRCs and the estimates of malignant transformation from polyps to CRCs are variable, the setting of screening and surveillance guidelines becomes more difficult and the cost effectiveness of different types and frequencies of screening have dominated assessments of CRC prevention measures.

GROWTH MODEL APPROACH TO MODELLING CHEMOPREVENTION OF COLORECTAL CANCER

There is increasing attention being paid to screening and chemoprevention as an important method for primary prevention. This is due in part to the poor compliance with recommended guidelines for preventive screening and surveillance so that only 35% of CRCs are currently diagnosed at an early stage.[7] Most studies show a protective effect of NSAIDs against CRC. A study by Rosenberg *et al*, showed in a case-control study that regular use of NSAIDs reduced the risk of cancer by 50%,[8] and two other studies found a 50% reduction in CRC with the use of aspirin.[9 10] The effects of sulindac on the regression of polyps themselves have also been shown in patients with familial polyposis, although this is expressed as reductions in number and diameter of polyps rather than growth rate.[11–15] Although chemoprevention with NSAIDs has shown important reductions in CRC, it also has considerable gastrointestinal side effects (30%–40%) making their recommendation for widespread use in the population too risky.[16–19] Newer, more selective NSAIDs for chemoprevention, however are under development; cyclooxygenase-2 (cox-2) inhibitors. They inhibit only cox-2 expression, which is increased in inflammatory cells and intestinal tumours rather than cox-1, which is responsible for most of the side effects from NSAIDs.[20] Now there is much evidence that cox may play a part in the genesis of CRC, which provides an explanation for the protective effects shown by NSAIDs in prevention of human CRC.[20] Although the exact change in growth rate with the use of NSAIDs in people of average risk is not known, it will be important to examine the potential cost effectiveness of this and other chemoprevention efforts with models sensitive to these effects on tumour growth.

MODELS OF CURRENT TECHNOLOGY FOR PREVENTION SCREENING AND SURVEILLANCE

Efforts to prevent CRC and therefore models for estimating cost effectiveness of screening have primarily been directed towards the use of different technologies (screening tests) or different schedules of screening and surveillance for polyps. Therefore they have used empirical evidence of populations screened with these technologies to estimate variables in

their models. There are four main influential models that have been used in establishing the cost effectiveness of most relevant screening strategies.[21–26] However, these existing models cannot be used to make direct estimates of the observable effects of new chemoprevention efforts on polyps, CRC, or survival. Chemoprevention affects rates of apoptosis and thus the size and number of observable polyps. The effects of a slowed growth rate of polyps is not a variable that can be changed directly in these existing models because they depend on estimates of use of current screening technology given polyp initiation and growth rates without chemotherapy. Because the introduction of chemoprevention changes many variables surrounding the behaviour of polyps and eventually CRC, data from existing models will not accurately describe the effects of chemoprevention. Therefore a new model is necessary to include variables which are affected by these agents.

The purpose of this study was to develop such a model to examine the effects of different intervals of surveillance on the risk of CRC, using for the first time, primarily the growth rate of polyps derived from studies of polyps in humans. This model is unique in the use of growth rates as a basic variable, a key observable variable affected by chemopreventive agents.

PREDICTORS OF MALIGNANT POTENTIAL

Size, histology, and degree of dysplasia have been shown to be important predictors of malignant potential with such strong correlations between these factors that it makes it difficult to specify any one predictor of malignant potential with certainty. However, many think that size is the most important predictor of CRC and it is widely used in both studies and in clinical recommendations for screening and surveillance.[3 27 28] There is a close relation between the size of the adenoma and the risk of cancer. As size increases, so does degree of dysplasia. Morson[29] showed that 50% of adenomas over 2 cm in diameter had invasive cancer, whereas only 1.3% less than 1 cm had invasive cancer. Another study showed that invasive cancer occurred in almost 10% of adenomas 1.5 cm or greater but only in 0.3% of adenomas <5 mm in diameter. Other studies have shown the relation with size and severe dysplasia[30 31] and between growth of adenoma and the tendency to also become villous.[32] Therefore, we have used size as the major variable in our model for estimating growth rates. The growth rate model is meant to provide a simple prototype of initiation and growth of polyps that can be described in terms of observable variables, and can be more easily validated than previous models.

We describe the structure of the growth model, explain the estimation method, and describe the data used for the input variables, and the output expected from the model. Next we describe the methods used for validation of the model. Finally, we use the model to estimate the expected rates of CRC from the number and size of polyps at various years of surveillance and to determine changes in outputs when growth rate changes.

Methods

MODEL DESCRIPTION

The growth model was a simulation that began with a group of 500 people who have had an index colon examination with polyps removed and who will be under surveillance for clinically significant polyps. It estimated the expected number and size of adenomatous polyps that would occur annually over 10 years. Each person belonged to a particular risk group depending on the number of polyps at the index examination. During each year each person grew a random number of new polyps. Each polyp was assigned a random growth rate that was consistent with the distribution of growth rates found in observational studies and clinical trials.[33–35] Then the polyp grew each year as a function of its initial size and the average age of the population, consistent with the overall age specific growth rates reported by Hofstad *et al*.[33–35] As the size of a polyp increased, and the average age of the population increased, the growth rate of the polyp decreased to be consistent with data shown by Hofstad *et al*.[33–35] Then we used standard techniques to calculate rates of CRC from the size of the largest polyp in a person and to distribute these rates to people with large and small polyps using estimates from the scientific literature.[6] The rate of cancer in situ and malignancy arising in the polyps was also calculated each year as a function of the size of the polyps at the end of the previous year. The model is described in more detail below.

INPUT VARIABLES

The model was a mathematical simulation, which was used to grow a new population of recurrent polyps in a cohort of patients, assuming model inputs and values specified in table 1.

METHOD OF ESTIMATION

The growth model simulated polyp initiation, growth, and malignant transformation for 10 years. The simulation began with a population with a mean age of 55, and with ages uniformly distributed between 50 and 59 years old. People were divided into four risk classes as a function of number of polyps found at index colonoscopy. People were assigned a risk from the screening colonoscopy. Those with zero polyps were in the lowest risk class for recurrence of polyps, and people with 4 or more polyps were in the highest risk class. Those with 1 polyp were risk group 1 and with 2–3 polyps were risk group 2. The size of the population for each risk group was 500.

The number of the pre-existing polyps at the index screening colonoscopy was a function of the risk group and the miss rate of the examination. For example, people in risk group 1 were assigned the number of pre-existing polyps that would result in an observation of 1 polyp for each person given the miss rate of the examination. The size distribution of polyps at

Table 1 Baseline values of the variables

Variables	*Values*			
Pre-existing polyps used to assign distribution of risk groups	Risk group 0=41 Risk group 1=541 Risk group 2=1351 Risk group 3=2432			
Initial size and distribution of polyps	1 mm, or uniformly distributed between 0 and 1 mm			
Miss rate of the initial colonoscopy	10% missed at ⩽5 mm, 5% missed at >5 mm			
Mean annual arrival rate (AR)of new polyps after colonoscopy	Immediately after screening colonoscopy or uniformly distributed over the year after colonoscopy Risk group 0: AR= 0.095238 SE=0.013 Risk group 1: AR=0.33 SE=0.07 Risk group 2: AR=0.46 SE=0.08 Risk group 3: AR=0.95 SE=0.26			
Malignant annual transformation rate	/Person with at least one polyp ⩾10 mm=0.03 /Person with polyps 10 mm=0.00075			
CRC transformation rate	20%/year			
Sensitivity of colonoscopic examination	0.75			
Mean prevalence (%) of polyps (95% CI) by risk group		Risk 0 and 1	Risk 2	Risk 3
	Year 1	13 (10 to 16)	17 (13 to 22)	27 (21 to 33)
	Year 2	22 (18 to 27)	29 (24 to 35)	46 (40 to 53)
	Year 3	27 (22 to 32)	37 (31 to 43)	57 (51 to 63)
	Year 4	33 (27 to 39)	44 (38 to 51)	70 (64 to 75)
	Year 5	35 (29 to 41)	48 (41 to 54)	74 (69 to 79)
	Year 6	36 (30 to 42)	49 (42 to 55)	76 (71 to 81)
	Year 7	36 (30 to 43)	49 (42 to 56)	77 (72 to 82)
	Year 8	38 (31 to 46)	52 (44 to 59)	81 (76 to 85)
	Year 9	40 (32 to 48)	53 (45 to 61)	84 (79 to 88)
	Year 10	41(33 to 49)	55 (47 to 63)	87 (82 to 90)
Prevalence of adjustment factors for risk groups	Risk group 0 (no polyps at index examination)=0.77 Risk group 1 (1 polyp at index examination)=0.77 Risk group 2 (2–3 polyps at index examination)=1.04 Risk group 3 (⩾4 polyps at index examination)=1.62			

the initial screening was taken from a population based study of screening colonoscopies.[36] This is the only study that we know that gives the size distribution of individual polyps for a representative population undergoing colonoscopy examination. All polyps found at the index examination were removed except for an estimated miss rate for the index colonoscopy of 10% for polyps that were 5 mm or less in size, and 5% for those greater than 5 mm.[37–40] We chose an optimistic miss rate assuming colonoscopy by a gastroenterologist and varied it in sensitivity analysis. The miss rate was modelled as a Bernoulli random variable that randomly selected those polyps that were missed in the index examination. Those polyps that remained were assigned a random growth rate as described later.

The annual arrival rate by risk group of new polyps after index colonoscopy and polypectomy was taken from studies by Hofstad *et al* (table 1).[34 35] The annual arrival of total polyps for the population was a random variable assumed to be normally distributed, except for risk group zero which was assumed to have a binomial distribution. The cumulative prevalence of polyps by year after polypectomy was modelled by fitting the prevalence in three observational studies of polyp prevalence[41–44] following the logistic distribution as a function of time. Prevalence for each year for the population was randomly assigned using the SEM of the estimated annual prevalence. Information on the differential prevalence by risk group was used to adjust the polyp prevalence for that risk group relative to that for the population average. The number of polyps in people who have polyps was assumed to follow the geometric distribution, which is consistent with observed data.[44–46]

The simulation assumed that all polyps arrived immediately after the index colonoscopy and that the initial size was 1 mm. Missed polyps were assigned a growth rate according to their existing size and grow annually at that rate thereafter, just as other 1st year polyp growth was handled. No information was found on the timing of the arrival of new polyps within each year or the size distribution of the new polyps. Therefore the simulation allows alternate assumptions on these variables. The arrival of polyps can be assumed to be uniformly distributed within each year, and the initial size can be uniformly distributed between zero and 1 mm in size. However, these alternative assumptions have little effect on the results.

The growth of polyps was assumed to follow a log linear growth model:

$$\ln(\textit{polyp-size}(t+1)) = (\textit{age-factor} \times 0.41896) + 0.70654 \ln(\textit{polyp-size}(t)) + \textit{pe} \quad (1)$$

where *polyp-size*(*t*) is the size of the polyp in mm in year *t*, *age-factor* is the age adjustment factor, and *pe* is the regression prediction error.

The growth model specification and variables were estimated from a reanalysis of annual growth data taken from Hofstad *et al*.[33–35] The prediction error had a *t* distribution with 198 degrees of freedom to be consistent with the regression used to estimate the annual growth rate conditional on the size of the model. A growth rate was assigned by generating a random prediction error, *pe*, in the initial year. Because no information was available on the annual variation in the growth rate, the same random prediction error was retained across years. This implies no variation in the growth rate over time except for the age factor which was used to reduce the mean growth rate as a function of the increasing average age of the population following data presented in table 1.[34 35] The adjusted constant in the equation (1) was reduced by an average 15%/year to

*Table 2 Expected number of polyps by size, time of surveillance, and risk group at first colonoscopy in a population cohort of 500**

Year of surveillance	Risk group: 0 (no polyps) Mean	0 (no polyps) SEM	1 (1–2 polyps) Mean	1 (1–2 polyps) SEM	2 (3–4 polyps) Mean	2 (3–4 polyps) SEM	3 (>4 polyps) Mean	3 (>4 polyps) SEM
Polyps ⩾2 mm:								
1	49	10.478	196	32.29	326	38.46	626	122.88
2	93	12.785	348	45.52	535	54.38	1063	170.1
3	135	13.96	492	55.66	736	65.6	1482	204.5
4	174	14.98	628	64.45	924	73.87	1872	233.6
5	210	16.55	752	70.21	1096	79.7	2231	259.4
6	241	17.46	860	74.77	1247	84.6	2547	278.3
7	267	18	946	77.42	1367	88.9	2798	287.8
8	284	18.21	1004	77.7	1445	90.2	2960	288.5
9	289	18.53	1021	76.1	1467	87.7	3009	278.7
10	281	17.89	990	72.08	1420	82.2	2914	258.4
Polyps ⩾5 mm:								
1	4	1.88	39	6.19	96	9.34	165	12.57
2	32	7.21	140	21.22	245	26.61	466	77.01
3	63	10.02	247	31.95	394	38.66	777	117.69
4	91	11.53	342	39.04	526	47.53	1047	144.8
5	113	12.43	417	43.8	629	52.47	1258	162.2
6	127	12.84	366	45.51	695	54.92	1396	169.3
7	134	12.98	484	45.47	717	54.2	1444	165.8
8	130	12.66	470	42.9	691	50.88	1395	152.7
9	118	11.85	423	37.78	620	44.83	1255	131.8
10	98	10.55	353	31.7	516	37.61	1045	105.2
Polyps ⩾10 mm:								
1	0.83	0.84	9	3.02	23	4.57	38	5.96
2	6	2.49	38	6.77	81	9.4	145	16.05
3	21	5.37	92	14.04	164	17.96	311	46.88
4	36	7.02	145	19.61	237	24.51	464	68.16
5	48	7.71	183	22.57	288	28.15	569	79.1
6	53	7.88	200	23.36	308	28.91	612	80.87
7	53	7.9	196	22.08	297	27.41	593	74.78
8	47	7.35	174	19.73	261	23.88	523	63.96
9	38	6.56	140	16.62	209	19.61	420	50.5
10	28	5.57	103	13.14	152	15.73	308	36.95

*Double these means for a cohort of 1000.

be consistent with the reduction in growth rate with increasing age that was measured in Hofstad *et al*.[34] The maximum polyp size was assumed to be 50 mm, and polyps reaching that size were assumed to have a zero growth rate.

The transformation of a benign to malignant polyp was done/polyp bearing person/year following variables estimated by Eide *et al*.[6] The transformation from a person bearing a benign polyp to a person bearing a malignant polyp followed a Bernoulli process. For people with at least one polyp of 10 mm or more, the transformation rate was 3%/year. For people with smaller polyps, the transformation rate was 0.075%/year.

The transformation from cancer in situ to invasive malignant cancer was also calculated/person. The transformation rate was based on the assumption that the median time from initiation of a polyp to clinical cancer was 10 years. The mean time between initiation of a polyp and the development of carcinoma has been estimated to be 10–15 years.[21 22 29] The minimum is 5 years and the maximum 25 years.[29] We chose 10 years as the median time to produce conservative estimates of the cost in terms of the development of CRCs that occur because of longer waiting times between surveillance examinations. The median time for the development of a cancer in situ in the simulation was 6.9 years leaving 3.1 years as the median time from bearing a cancer in situ to the development of invasive malignant cancer. This implied a transformation rate of 20%/year for a person with a cancer in situ to a person with invasive malignant cancer. All people and their polyps were removed from the simulation upon development of clinical cancer.

The effect of chemopreventive treatment on the growth of polyps was modelled by reducing the arrival rate of the polyps and the constant log linear growth equation (1). For example, a drug therapy that reduced polyp arrival and growth by 50% was modelled by reducing the annual arrival rate of polyps by 50% and reducing the constant term in (1) by 50% (from 0.41896 to 0.20948).

The model was estimated with a Monte Carlo simulation consisting of 1000 random trials for each risk group. The model estimates were means (SEM) taken over the 1000 trials. Each trial described the 10 year history of a population of 500 people. In each trial the arrival and growth of individual polyps were modelled and then allocated to people in the population of patients. One draw of each random variable describing population variables was taken for each trial. A random growth rate was assigned to each polyp that arrived in each year of each trial. The simulations were done with Minitab and programmed in the Minitab Macro language.[47]

OUTPUTS

The outputs from the model were expected number of polyps and people with polyps of size ⩾1 mm, 2 mm, 5 mm, 10 mm, number of people with clinically significant or malignant polyps (polyps ⩾5 or ⩾10 mm), and number of colorectal cancers. The outputs were calculated annually for 10 years and were used to find the effects of waiting until that year (1–10) for the next colonoscopy examination. For example, we estimate the number of polyps of different sizes (by risk group) that would be expected if a colonoscopy and polypectomy were performed at years 1–10 after index colonoscopy. Based on this number and the factors already described, the model could also be used to find how many malignant polyps and CRCs would be already existing at an examination in that year, as well as how many malignant polyps and cancers could be avoided in the future by cleaning out the colon during an examination in that year.

Results

NUMBER OF POLYPS

This model has the advantage of showing the distributions of polyps and cancers by risk group, different growth rates, and for different years of surveillance.

With the growth model, table 2 shows the number of polyps of different sizes (in a cohort of 500 people) over different times waiting for surveillance of the colon, assuming a mean age of 55 years at the index colonoscopy and a baseline growth for different risk groups. The higher risk groups showed more polyps and there were more smaller than larger polyps for all risk groups.

Also, the number of polyps found from year 1 to year 10 was estimated, to indicate what the effect of delaying a follow up surveillance after

Table 3 Expected number (mean (SEM)) of clinical cases of colorectal cancer

	Risk group 0			*Risk group 1*			*Risk group 2*			*Risk group 3*		
Year	*Mean*	*SEM*	*Cases of colorectal cancer/ 100 000*	*Mean*	*SEM*	*Cases of colorectal cancer/ 100 000*	*Mean*	*SEM*	*Cases of colorectal cancer/ 100 000*	*Mean*	*SEM*	*Cases of colorectal cancer/ 100 000*
Baseline:												
1	0.014	0.056	2.92	0.055	0.103	11.00	0.106	0.153	21.15	0.204	0.200	40.75
2	0.025	0.057	4.93	0.096	0.128	19.23	0.188	0.188	37.56	0.365	0.254	72.99
3	0.062	0.106	12.50	0.235	0.202	47.10	0.423	0.269	84.67	0.754	0.366	150.88
4	0.160	0.166	31.92	0.474	0.285	94.90	0.766	0.362	153.24	1.342	0.488	268.30
5	0.300	0.220	59.32	0.771	0.357	154.26	1.188	0.445	237.52	2.032	0.589	406.40
6	0.430	0.262	85.93	1.048	0.420	209.62	1.592	0.489	318.38	2.697	0.679	539.34
7	0.567	0.293	113.49	1.288	0.459	257.68	1.914	0.535	382.80	3.212	0.718	642.32
8	0.661	0.309	132.27	1.476	0.475	295.22	2.152	0.558	430.46	3.640	0.729	728.10
9	0.726	0.304	145.29	1.603	0.488	320.68	2.346	0.568	469.12	3.961	0.720	792.14
10	0.732	0.300	146.43	1.701	0.478	340.26	2.456	0.560	491.12	4.200	0.726	840.10
25% Growth:												
1	0.009	0.044	1.84	0.018	0.060	3.64	0.032	0.079	6.48	0.056	0.101	11.24
2	0.018	0.058	3.59	0.032	0.077	6.47	0.061	0.104	12.22	0.109	0.141	21.79
3	0.032	0.074	6.39	0.047	0.092	9.37	0.082	0.116	16.41	0.152	0.157	30.43
4	0.050	0.09	9.91	0.060	0.102	12.10	0.106	0.128	21.12	0.185	0.170	37.10
5	0.066	0.104	13.25	0.082	0.117	16.32	0.132	0.142	26.46	0.240	0.193	47.99
6	0.081	0.115	16.16	0.101	0.125	20.13	0.166	0.155*	33.25	0.300	0.217*	59.91
7	0.098	0.126	19.65	0.118	0.134	23.71	0.187	0.162*	37.44	0.365	0.235*	73.00
8	0.112	0.132	22.32	0.141	0.140*	28.24	0.210	0.167*	41.95	0.441	0.259*	88.20
9	0.126	0.135	25.21	0.161	0.149*	32.23	0.242	0.1838*	48.48	0.532	0.285*	106.31
10	0.137	0.141	27.45	0.178	0.156*	35.50	0.285	0.191*	56.98	0.622	0.313*	124.32
50% Growth:												
1	0.012	0.049	2.36	0.009	0.044	1.84	0.013	0.051	2.52	0.084	0.134	16.79
2	0.020	0.062	4.05	0.017	0.056	3.35	0.021	0.062	4.29	0.180	0.180	36.11
3	0.038	0.084	7.60	0.034	0.082	6.80	0.042	0.086	8.514	0.290	0.213	58.00
4	0.055	0.094	11.00	0.054	0.095	10.72	0.072	0.112	14.49	0.440	0.262	88.11
5	0.083	0.118	16.59	0.088	0.123	17.61	0.130	0.154	25.91	0.656	0.330	131.12
6	0.114	0.136	22.71	0.142	0.160	28.33	0.208	0.186*	41.64	0.900	0.379	179.96
7	0.142	0.152	28.41	0.221	0.196	44.22	0.325	0.222*	65.02	1.182	0.446	236.34
8	0.167	0.157	33.37	0.308	0.222	61.61	0.452	0.254*	90.37	1.484	0.503	296.9
9	0.186	0.164	37.25	0.394	0.247	78.80	0.577	0.298*	115.49	1.752	0.546	350.42
10	0.197	0.162	39.32	0.489	0.266	97.79	0.706	0.328*	141.3	2.021	0.569	404.28
75% Growth:												
1	0.014	0.053	2.72	0.033	0.078	6.64	0.070	0.113	13.96	0.140	0.170	27.95
2	0.023	0.066	4.65	0.070	0.110	14.11	0.145	0.167	29.08	0.286	0.228	57.27
3	0.046	0.093	9.26	0.148	0.164	29.52	0.306	0.240	61.25	0.577	0.313	115.40
4	0.091	0.130	18.16	0.294	0.231	58.81	0.548	0.302	109.70	1.017	0.418	203.40
5	0.162	0.173	32.48	0.483	0.296	96.55	0.833	0.375	166.54	1.569	0.487	313.80
6	0.241	0.205	48.22	0.702	0.352	140.30	1.168	0.427	233.54	2.136	0.563	427.24
7	0.307	0.230	61.49	0.916	0.377	183.10	1.441	0.454	288.20	2.674	0.606	534.84
8	0.363	0.240	72.79	1.081	0.394	216.28	1.692	0.488	338.34	3.110	0.667	622.04
9	0.393	0.244	78.67	1.226	0.408	245.14	1.872	0.482	374.34	3.516	0.686	703.20
10	0.409	0.234	81.79	1.322	0.406	264.50	2.003	0.486	400.58	3.830	0.699	766.06

*p<0.05, Significant difference from base case with Bonferroni's test correction.

colonoscopy would be at each year. For example, for those with no polyps found at index colonoscopy (risk group 0), only 28 polyps of 10 mm or more were found if the next colonoscopy was done in 10 years in the cohort of 500 people. This is only 0.056 polyps/person. However, for the highest risk group, by year 10 with no surveillance, as many as 308 high risk polyps (⩾10 mm) were found in our group of patients or 0.61/person and as many as 2914 polyps of 2 mm or more were found (5.8/person). Looking into the colon earlier, of course would show fewer polyps and potentially allow reductions in risk if all polyps were removed earlier.

CASES OF COLORECTAL CANCER

Table 3 shows the modelled numbers and rates of clinical cases of CRC derived from the initial data from the risk groups, three different growth rates, and year of surveillance. The cases of CRC followed a similar pattern to the number of polyps from which they were derived. Rates of CRC ranged from 3–146/100 000 population for risk group zero, to 41–840/100 000 for risk group 3 depending on the year that an examination was done. These data could support different surveillance frequencies depending on the risk groups, especially for those with zero polyps at index colonoscopy (risk group 0) who may only need repeat colonoscopy as recommended for those at average risk (7–10 years), and those with more than one polyp (risk groups 1–3) who will need the next colonoscopic surveillance more often (3–5 years).

VALIDATION

The model was validated by two methods by comparing our output results with those available in the scientific literature. Firstly, we compared the size distribution of polyps produced by the model to empirical distributions. Secondly, we compared rates of CRC simulated by the model to empirically observed rates. Validation of the distribution of polyps was done by comparing the simulated number of polyps at the beginning of 2 and 3 years to the empirically observed rates in several studies[39 46 48 49] between 2 and 3 years. Figure 1 shows that the simulations are close to the polyp proportions shown in the three studies for the three groups with different polyp size. Our simulations match fairly well with the results of Hixson *et al* except that they found more polyps of 2 mm and slightly less at 3 and

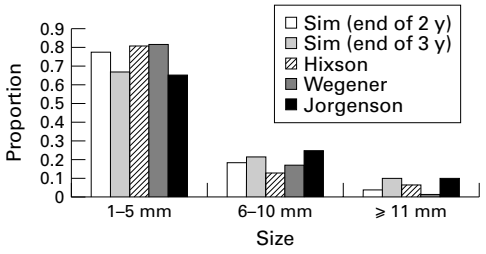

Figure 1 Simulation model validation: size distribution at 2 and 3 years from model, simulated (Sim), and existing studies, Hixon et al, Jorgenson et al, and Wegener et al.[48 48 49]

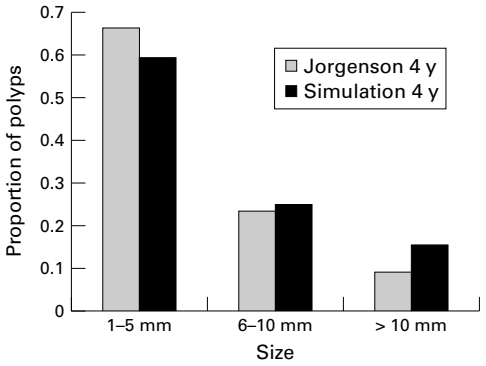

Figure 2 Distribution of polyps at 4 years: model simulation compared with Jorgenson et al.[48]

4 mm.[46] Figure 2 shows a comparison of the model's simulated size distribution with that of Jorgenson *et al* at 4 years.[48] This shows a fairly good match but with slightly fewer small polyps and slightly more large polyps in our simulation. Jorgenson *et al* started with a population without a verified clean colon, so we would expect his data to show higher rates of polyps in the earlier years as is seen in figure 1 for the larger polyps. Missed polyps will have a greater influence on the size distribution in the initial years after the index colonoscopy and therefore data at 4 years in figure 2 show more large polyps than do the earlier data. Therefore the validation is consistent with the results from Jorgenson *et al*.[48] We are not aware of any studies of longer periods of polyp growth after a clean colon for further validation comparisons.

The second type of validation study compared simulated rates of CRC after 5 and 10 years with empirically observed rates reported in the SEER data base (fig 3). A problem with doing this tyle of simulation is that the simulation is calculated by risk group, but the empirical studies are for actual populations that consist of several risk groups. Therefore the empirical results must be compared with simulation of risk classes as defined by the risk group distributions found in the population (risk group 0 = 0.70, risk group 1 = 0.168, risk group 2 = 0.096, and risk group 3 = 0.036).[37] This allowed us to better match our population to that of the SEER population according to risk group. Figure 3 shows the distribution of CRC cases generated by our model compared with that in the SEER data bases. SEER CRC rates fall within the standard error (SE) of CRC rates generated by our model. The shape

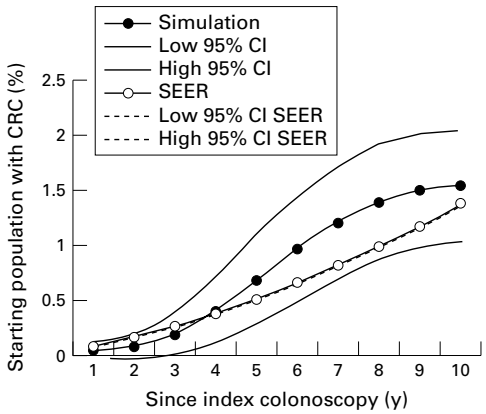

Figure 3 Simulated and SEER cumulative incidence of colorectal cancer.

of the SEER CRC curve is slightly different from that of the model, however. Most of the differences may be explained by differences in the populations represented by our model and that of SEER. For example, the SEER CRC rates would be expected to be somewhat lower than ours because it is reflecting a combination of the screened and unscreened populations whereas our population begins with an index colonoscopy and clean colon and then includes no further screening until the year selected for colonoscopy.

We also compared our simulated CRC rates with that of an existing study of CRC rates, the population of which matches ours more closely (fig 4).[50] This is important as the high rates of CRC often reported are based on populations that include people with existing polyps.[50] Lofti *et al* looked at rates of CRC in a population with one or more existing polyps which were removed and then followed up for up to 25 years. We compared the simulated rates of CRC for risk groups that had at least one polyp to match the population of Lofti *et al* (fig 4). Their cumulative incidence rates of CRC fell within the model simulation confidence intervals for most years. Their data were based on only 20 cases of cancer over this period which accounts for the large confidence interval for their incidence data and may account for the sudden rise in cases at year 2 and lack of cases of CRC in years 3 and 4. The cumulative incidences of CRC from Lofti *et al* at 10 years were similar to ours with observed rates of 3.8% and expected rates of 1.7% (fig 4).[50] Our model estimated rates of CRC of 0.1% at 1 year (Lofti *et al* report 0.3%), 1.4% at 5 years (Lofti *et al* report 1.7%), and 2.9% at 10 years (Lofti *et al* report 3.9%) for those with at least one polyp (risk groups 1–3).[50] These validation studies show that our model compares well with existing empirical rates of CRC from similar populations.

Finally, we also validated our model by comparing the ratio of observed to simulated number of polyps for five different studies, each at several time points. These studies varied widely in observed rates of polyps. In general, we showed that the observed rates at 1.5 years were 0.5–2.9 times our simulated rates, at 2 years 0.4–1.9 times the simulated rates, and at 4 years 55%–61% of the simulated rates of

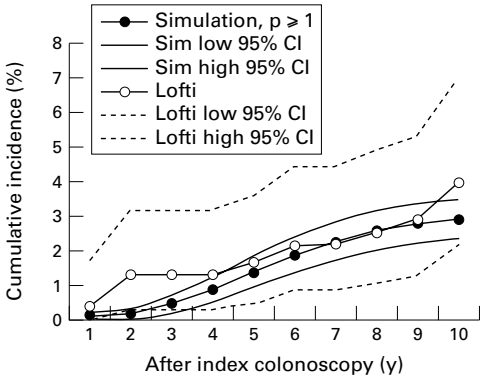

Figure 4 Cumulative incidence (% stimulation) compared with Lofti et al.[50]

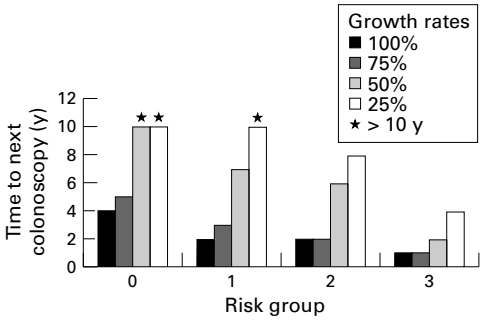

Figure 5 Delay (y) to next colonoscopy with changes in growth rates of polyps and a constant rate of 50 cases of colorectal cancer/100 000 people in that interval.

polyps.[31 46 48 49] Overall, the observed to simulated rates of polyps are 0.4–2.4 times the simulated rates, showing that our data are about midway between the range of observed rates in different study populations.

CHANGE IN GROWTH RATES OF POLYPS

An important use of our simulation model is that we can estimate changes in distributions of polyps and CRCs that result from changing the growth rate of polyps. This allows us to model changes that might occur with changes due to chemoprophylactic agents. Table 3 shows the change in numbers of cases and rates/100 000 of CRC when the estimation of the arrival and growth rates of polyps are 25%–75% of baseline. The NSAIDs are thought to be able to reduce both the number of polyps and rates of CRC by up to 50%[3 8–10] with no difference in rates between mice and humans. A mouse study of human cancer cell lines showed that cox-2 inhibitors reduced growth by 85%–90%.[20] Studies of people with familial polyposis measure polyp regressions by number of polyps and diameter of polyps rather than growth rate, and show 35%–44% changes in these variables after 9 months on NSAIDs. So although further study is needed to measure exactly the changes in growth rate of polyps induced by NSAIDs, a feasible range for these changes that could be induced by chemoprophylaxis should be somewhere between 50% and 90%. Our model showed that at year 10 a growth rate of 50% of baseline results in differences in 2 mm polyps of 85 versus 281 compared with baseline for risk group 0, 311 versus 990 for risk group 1462 versus 1420 for risk group 2, and 930 versus 2914 for risk group 3 in 500 patients (not shown but available from author). This is a reduction in number of polyps of 67%–70% depending on the risk group. A 25% growth rate reduces the number of 2 mm polyps at year 10 by about 88% for each risk group, and a 75% growth rate reduces polyps by 38%–40%. So the effect of chemoprophylaxis with non-selective or selective NSAIDs could have the effect of reducing growth rates to 25%–75% according to our model (not shown but available from authors).

CHANGES IN RATES OF COLORECTAL CANCER RESULTING FROM CHANGES IN GROWTH RATE

Table 3 shows the changes in rates of CRC/100 000 for different growth rates by year of surveillance. This is shown for all risk groups. Cancer rates at a 25% growth rate at year 10 for risk group zero show that the risk of cancer decreases from the baseline rate of 146/100 000 to only 57/100 000. If growth is reduced to only a 75% growth rate then the cancer rates decrease from a baseline of 146/100 000 to 82/100 000 for risk group zero. For risk group 3 rates of CRC at year 10 decrease from a baseline of 840/100 000 to 124/100 000 (25% growth rate), 404/100 000 (50% growth rate), and 766/100 000 at a 75% growth rate. Therefore reducing growth rate can be an important method for decreasing rates of CRC and the effect is logarithmic and so greater than a linear effect. Also, the ability of a growth rate approach such as ours to show the effects of a shift in surveillance frequencies with chemoprophylaxis for different risk groups could also affect the prognosis for CRC. Tests were computed for significant differences at the 5% level in cases of CRC comparing each growth rate and year by risk group with the baseline rates (table 3). Clinical differences in risk of CRC may be more important than the significance tests indicate. For example, for risk group 3 with baseline growth rates, surveillance might be recommended at 1–3 years but with a 25% growth rate this could be delayed until 5–6 years with the same risk of cancer.

CHANGES IN SURVEILLANCE INTERVALS

Figure 5 shows the change in acceptable intervals between surveillance colonoscopies. Chemoprevention treatments that reduce the rate at which CRC develops (by changing polyp growth rates) potentially could enable longer intervals between surveillance colonoscopies without increasing the cost in terms of cases of CRC that develop during the waiting interval. The model can be used to estimate the effect of chemotherapy on the duration between surveillance colonoscopies without increasing the number of cases of CRC within that period. Figure 5 shows the magnitude of the increased waiting time between colonoscopies for different reductions in rates of polyp growth and initiation, for a threshold of acceptable risk of

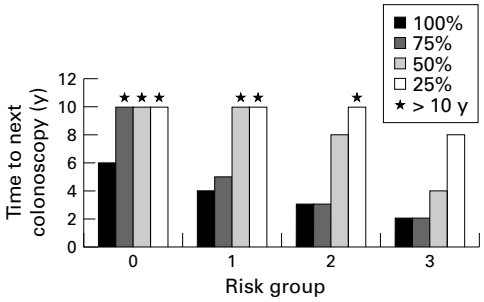

Figure 6 Delay (y) to next colonoscopy with a constant rate of 100 cases of colorectal cancer/100 000 people in that interval.

developing cases of CRC between examinations. The threshold of 50 cases/100 000 people was chosen to be conservative compared with current surveillance intervals. This threshold yields 0.5–1 cancers/1000 people; about 15% of the rate found over 6 years in patients under surveillance.[37] Savings in year intervals between colonoscopies with a 50% growth rate are as much as 2–7 years later for risk group 1 and 2–6 years for risk group 2. A 25% growth rate reduces this testing frequency even further, from 2–10 years in risk group 1, from 2–8 years in risk group 2 and from 1–4 years in risk group 3. Figure 6 shows the same data for a threshold of 100 cases/100 000 people. This model is the only model that we know of that can estimate savings due to chemopreventive effects which potentially slow polyp growth.

Discussion

This model describes polyp initiation, growth, and transformation to CRC that can be described by observable variables, and can be more easily validated than previous models. Observable variables that are independent of current characteristics of examination protocols, are easy to validate, and reduce the likelihood of introducing the spurious results from model calibration used to estimate unobservable variables. This prototype model uses the growth rate of polyps as the main variable to estimate the effects of different polyp surveillance intervals and the effects of chemotherapy that reduces growth on the incidence of malignant polyps and clinical CRC. This is the first model, to our knowledge, that is based on growth rates of polyps, a key variable affected by chemopreventive agents. The main use of this model is in estimating the effects of advances in chemopreventive agents that reduce the initiation and growth rate of polyps. For example, chemotherapeutic agents, which affect initiation and growth rates of polyps, may allow longer waiting periods before a repeat examination is necessary and data from our model provide some of the first evidence for weighing the risk and benefits of changes in growth rates. Although the exact growth rate is unknown, changes in growth rates of polyps to 50% of normal with the use of chemopreventive agents could change the need for the next colonoscopy surveillance from 2 to 7 years in risk group 1, and from 2 to 10 years if growth rate was reduced to 25% of the observed rates. These data can assist in the calculation of the cost effectiveness of using agents to delay surveillance frequencies or to reduce CRC cases.

There are two main weaknesses of the model. Firstly, we are modelling growth rates for a period of 10 years based on empirical data for up to 3–4 years only. Secondly, the predictions of size of polyps are based on growth rates shown in polyps equal to or less than 10 mm in size.[33–35] Long term growth rates are modelled from growth data found during only 3 years and under 10 mm in size. The implicit assumptions behind the model are that: (*a*) growth rates are constant over time and equal to the mean growth rate over the first 3 years of the polyps existence and (*b*) growth rates for larger polyps are equal to the mean rate for those 10 mm or less in size. Our results match the distribution of polyp sizes for up to 3–4 years. Unfortunately we do not know of any data describing the distribution of data for polyps for longer periods; therefore validation of the model must use other measures—such as the cumulative incidence of clinical colorectal cancer. The validation of the model indicates that it performs well over the initial 10 years; however, the results should be used with caution until further validation. The most useful part of the model is probably in the first 5–6 years because this is currently the accepted interval between colonoscopies for those with one or more polyps, and it is also the period for which the model is the most accurate. However, the uncertainty increases as the years without colonoscopy increase.

We used optimistic miss rates in our model which are rates attributable to colonoscopy performance by gastroenterologists rather than experienced primary care endoscopists, whose miss rates are 2–3 times higher.[51 52] When we tripled our baseline miss rates, however, we found for risk group 3 only a 0.05%–0.35% increase in cases of CRC up to year 5 and no difference in rates of CRC after that. Therefore our model is not sensitive to this factor as it only concerns polyps missed at the index colonoscopy, which constitute a very small percentage of the polyps that exist several years after the index colonoscopy.

We are uncertain of the exact change in growth rates of polyps with the use of chemoprevention. The scientific literature on familial polyposis provides data on number and size of polyps rather than growth rates and the 50% changes in rates of CRC discussed in this paper are generally from case-control studies. With our model we also looked at the relation between changes in growth and changes in predicted rates of CRC. Although this is highly variable depending on risk group and year of surveillance, for risk group 2 at year 10 after index colonoscopy, a 25% growth reduces cases of CRC by 59% and for risk group 3 somewhere between a 25% and 50% growth rate results in about a 50% reduction in CRC. Therefore we think that the range of growth rates shown here (25%–75% growth rate compared with baseline) is adequate. Also, the value of this model is that it can show

the changes in CRC with any change in growth rate by running the simulation with the rates desired. Further data are needed on the growth rate changes in sporadic CRC with the use of chemopreventive agents.

Our rates of polyps and CRCs seem to be in line with what is found in the literature as is shown in the validation studies, which support the accuracy of the model. These data show support for different surveillance frequencies depending on the risk groups. For example, for risk group 0, even taking miss rate into account, waiting until year 10 for a repeat colonoscopy yields only 0.7 CRCs in 500 people or a rate of 146/100 000 population. This cancer rate is found between 4 and 5 years for those in risk group 1, between 3 and 4 years for those in risk group 2 and between 2 and 3 years for those in risk group 3. Therefore this model approach may be useful in supporting different surveillance frequencies depending on risk groups. The model is fairly consistent with current surveillance guidelines for people of average risk.[53] Any interpretations of the results of the model must consider that guidelines may have specific recommendations for polyps that are excessively large or of a specific histological type that would warrant a different risk classification than that based on size alone. Our model suggests that for those with risk group zero (no polyps found at index colonoscopy) surveillance with colonoscopy may be recommended as for any person at average risk (7–10 years), whereas those with one or more polyps need more frequent colonoscopic examinations, 2–5 years depending on the risk group.

This model is unique in the use of growth rates as a basic variable, a key variable affected by chemopreventive agents, and begins to include growth rates in the clinical question of surveillance strategies. Finally, it must be stressed that a model such as this is only a planning tool that must be combined with both clinical data and experience to help to provide information for future research and clinical policies. The forecasts of the model should be applied when it is calibrated to the epidemiological characteristics of the population in question. However, this model is the first model that we are aware of which can describe the clinical implications of chemotherapeutic regimens that change the fundamental growth variables of colorectal polyps and do so in terms of observable variables.

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