

APPENDIX 1.

The model includes the following definitions and assumptions:

1. An individual has colorectal cancer (CRC) if his/her disease has manifested clinically. If an individual was screened and had a polyp removed before the polyp became cancerous, that individual is not considered a CRC case.
2. An individual has an observed CRC family history if at least one of his/her parents was diagnosed with CRC; the likelihood that both parents are diagnosed with CRC is considered negligible. While observed family history in real life is a time dependent variable, for simplicity in this model we considered it as a fixed characteristic. That is, family history of the disease is fixed before the individual is at risk for CRC.
3. In any generation, all couples have exactly two children. The population size of the generations is therefore maintained (i.e. population replacement).
4. In the absence of screening, the risk of developing CRC for an individual is assumed to depend on his/her CRC family history.
5. Colorectal screening is assumed to prevent some fraction of diseases by enabling the removal of precancerous lesions.
6. Individuals with an observed CRC family history are assumed to be screened at a higher rate than those without an observed CRC family history.
7. Screening is introduced at the second generation and used in all generations thereafter.

These conditions are specified by the following parameters:

T denotes the total population size in any given generation.

α denotes the risk of developing CRC in the absence of screening. For individuals with a CRC family history, $\alpha_1 = 13\%$. For individuals without a family history of the disease, $\alpha_0 = 6.5\%$ (i.e., $\alpha_1 = \alpha_0 \times 2$). That is, in the absence of screening, the group with a CRC family history is assumed to have a two-fold increased risk of CRC relative to the group without a CRC family history.

γ denotes the proportion of colorectal cancers that can be prevented by screening.

f denotes the proportion of the population receiving screening. Screening fractions are specified as f_1 for individuals with an observed CRC family history and f_0 for those without an observed CRC family history.

i denotes the generation under study.

$r(i)$ denotes the observed CRC risk in generation i . This quantity is denoted as $r_1(i)$ for those with an observed CRC family history and $r_0(i)$ for those without an observed CRC family history.

$rr(i)$ denotes the observed relative risk for the association between observed CRC family history and CRC at generation i , such that $rr(i) = r_1(i) / r_0(i)$. In generation 1, this quantity is set equal to 2.0.

APPENDIX 2.

The number of individuals with an observed CRC family history in this second generation is equal to the number of individuals who developed CRC in generation 1 multiplied by 2 (each couple assumed to have two children)

[i.e. $N_{11}(2) = 2\alpha_1[N_{11}(1)] + 2\alpha_0[N_{00}(1)]$]. Therefore, the number of individuals without an observed CRC family history in generation 2 is: $N_{00}(2) = T - N_{11}(2)$.

The relative distribution of the N_{11} and N_{00} subgroups in generation 2 is the same as in generation 1 [i.e. $N_{11}(2) = N_{11}(1)$ and $N_{00}(2) = N_{00}(1)$]. This equality can be solved as follows:

$$N_{11}(1) = N_{11}(2) = 2\alpha_1[N_{11}(1)] + 2\alpha_0[N_{00}(1)] = 2\alpha_1[N_{11}(1)] + 2\alpha_0[T - N_{11}(1)]$$

$$N_{11}(1) = N_{11}(2) = \frac{2\alpha_0}{1 - 2\alpha_1 + 2\alpha_0} \times T = 0.15 \times T$$

$$N_{00}(1) = N_{00}(2) = \frac{1 - 2\alpha_1}{1 - 2\alpha_1 + 2\alpha_0} \times T = 0.85 \times T$$

In order to calculate the relative risk for CRC associated with an observed CRC family history in this generation, we compare the risk of CRC in those with an observed family history to the risk in those without an observed family history. The former of these two risks, $r_1(2)$, can be calculated as follows:

$$r_1(2) = \frac{\alpha_1\{(1-\gamma)f_1 + (1-f_1)\} \times N_{11}(2)}{N_{11}(2)}$$

That is, in generation 2, the risk of disease for individuals with an observed CRC family history is found by adding together the risk of developing CRC in those who did not receive screening, $[\alpha_1(1 - f_1)]$, plus the risk of developing CRC in those who did receive screening, $[\alpha_1 f_1(1 - \gamma)]$, where the inclusion of a $(1 - \gamma)$ term accounts for

decreased risk due to screening. This quantity is multiplied by $N_{11}(2)$ to determine the expected number of cases in generation 2 among those with an observed CRC family history. Similarly, the risk in those without an observed CRC family history is calculated as:

$$r_0(2) = \frac{\alpha_0[(1-\gamma)f_0 + (1-f_0)] \times N_{00}(2)}{N_{00}(2)}$$

In this generation, the relative risk for the association between an observed CRC family history and CRC incidence is therefore:

$$rr(2) = \frac{\alpha_1[(1-\gamma)f_1 + (1-f_1)]}{\alpha_0[(1-\gamma)f_0 + (1-f_0)]} = rr(1) \times \frac{1-\gamma f_1}{1-\gamma f_0}$$

APPENDIX 3.

The number of individuals that will fall into each subgroup in generation 3 is as follows:

$$\begin{aligned}N_{11}(3) &= [2\alpha_1(1 - \gamma f_1)N_{11}(2)] + [2\alpha_0(1 - \gamma f_0)N_{00}(2)] \\N_{01}(3) &= [2\alpha_1\gamma f_1N_{11}(2)] + [2\alpha_0\gamma f_0N_{00}(2)] \\N_{00}(3) &= T - N_{11}(3) - N_{01}(3)\end{aligned}$$

The first of these quantities, $N_{11}(3)$, includes only the children of those in generation 2 who developed CRC that was observed; this group is smaller than in generation 2 as a result of the screening effect. For example, the $N_{11}(3)$ subgroup differs from the $N_{11}(2)$ subgroup by the inclusion of a factor of $(1 - \gamma f_1)$ to reflect the altered risk of developing CRC in the second generation due to the introduction of screening.

The size of the $N_{01}(3)$ subgroup is determined by screening uptake, f_1 and f_0 , as well as screening efficacy, γ . In the absence of screening (i.e. $f_1=f_0=\gamma=0$), $N_{01}(3)$ returns to zero, and the subgroup of individuals with an observed family history, $N_{11}(3)$, will be equal to $N_{11}(2)$ and $N_{11}(1)$.

The number of expected cases in generation 3 within each subgroup defined by observed CRC family history and screening status is provided in Table 2. For example, the number of individuals screened in the group with an observed CRC family history is $f_1N_{11}(3)$; among those individuals, $\alpha_1(1 - \gamma)f_1N_{11}(3)$ CRC cases are expected to be diagnosed. Based on the estimations described above (and values in Table 2), calculation of the risk for CRC in both the numerator, $r_1(3)$, and denominator, $r_0(3)$, for generation 3 takes on the following form:

$$r_1(3) = \frac{\alpha_1[(1-\gamma)f_1 + (1-f_1)] \times N_{11}(3)}{N_{11}(3)}$$

$$r_0(3) = \frac{\alpha_1[(1-\gamma)f_0 + (1-f_0)] \times N_{01}(3) + \alpha_0[(1-\gamma)f_0 + (1-f_0)] \times N_{00}(3)}{N_{01}(3) + N_{00}(3)}$$

Thus, the relative risk in generation 3 takes on the following modified form:

$$rr(3) = \frac{\frac{\alpha_1[(1-\gamma)f_1 + (1-f_1)] \times N_{11}(3)}{N_{11}(3)}}{\frac{\alpha_1[(1-\gamma)f_0 + (1-f_0)] \times N_{01}(3) + \alpha_0[(1-\gamma)f_0 + (1-f_0)] \times N_{00}(3)}{N_{01}(3) + N_{00}(3)}}$$

Or, equivalently, as:

$$rr(3) = \frac{(1-\gamma f_1)}{(1-\gamma f_0)} \times \frac{\alpha_1}{\frac{\alpha_1 \times N_{01}(3)}{N_{01}(3) + N_{00}(3)} + \frac{\alpha_0 \times N_{00}(3)}{N_{01}(3) + N_{00}(3)}}$$

$$rr(3) = \frac{rr(2)}{rr(1) \times \frac{N_{01}(3)}{N_{01}(3) + N_{00}(3)} + \frac{N_{00}(3)}{N_{01}(3) + N_{00}(3)}}$$

Expected Colorectal Cancer (CRC) Cases in Generation 3 According to Screening Status, Observed CRC Family History, and Family History in the Absence of Screening

	Observed CRC Family History		No Observed CRC Family History			
	Screened	Not-screened	Observed Family History in Absence of Screening		No Observed Family History in Absence of Screening	
			Screened	Not-screened	Screened	Not-screened
Cases	$\alpha_1(1-\gamma)f_1N_{11}(3)$	$\alpha_1(1-f_1)N_{11}(3)$	$\alpha_1(1-\gamma)f_0N_{01}(3)$	$\alpha_1(1-f_0)N_{01}(3)$	$\alpha_0(1-\gamma)f_0N_{00}(3)$	$\alpha_0(1-f_0)N_{00}(3)$
Total	$f_1N_{11}(3)$	$(1-f_1)N_{11}(3)$	$f_0N_{01}(3)$	$(1-f_0)N_{01}(3)$	$f_0N_{00}(3)$	$(1-f_0)N_{00}(3)$
