

HOW WILL SCREENING FOR GENETIC DISORDERS AFFECT LIFE INSURANCE?: A CASE STUDY OF COLORECTAL CANCER

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ABSTRACT

Colorectal cancer (CRC) is a major cause of death. If CRC is detected and treated early, the prognosis is good, which benefits the individual and life insurers alike. It is therefore a target for public health screening programs. (1) Some programs may screen the whole population, therefore detecting CRCs after onset. The detection of CRC earlier than would happen otherwise should reduce mortality: we assess the likely reduction in life insurance premiums. (2) A small proportion of CRC is caused by inherited gene mutations. Screening (by genetic testing) the relatives of CRC patients who carry causative mutations, followed up by frequent colonoscopies — called ‘cascade screening’ — has been trialled. Such screening, however, might enlarge the pool of relatively young persons with adverse genetic test results, inaccessible to insurers and exposing them to adverse selection. The idea that insurers’ interests should act to reduce the takeup of beneficial screening is discomfoting. We assess the possible costs and benefits to life insurers arising from CRC screening programs for hereditary non-polyposis colorectal cancer (HNPCC).

KEYWORDS

Cascade Screening; Colorectal Cancer; Genetic Tests; Life Insurance; Population Screening

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1. INTRODUCTION

1.1 *Genetics, Insurance and Screening Programs*

Genetic testing continues to throw up problems for the insurance industry. Most attention has been paid to the basic questions of: (a) personal privacy and protecting individuals from insurers’ adverse use of genetic test results; and (b) adverse selection arising from insurers’ enforced ignorance of genetic test results. The severe single gene disorders provide some concrete test cases, whereas the more common multifactorial diseases so far support more hypothetical actuarial research, because of the epidemiology available so far. See Macdonald (2007) for a recent review.

One of the most troublesome concerns about allowing insurers to use genetic test results is that it may deter individuals from taking part in valuable medical research that involves testing; or, worse, from being tested when their family history suggests that their own medical care could be improved by doing so. The latter concern is perhaps marginal in the case of an untreatable disorder, like Huntington’s disease. It becomes extremely important if effective treatments are available, and genetic testing may be offered as part of a screening program to identify high-risk

individuals at an early stage. It would surely be unacceptable if anyone declined to enter such screening programs because of concerns about insurability.

Lu *et al.* (2007) described an actuarial model for hereditary non-polyposis colorectal cancer (HNPCC), a rare inherited form of colorectal cancer (CRC). CRC often has a relatively good prognosis if detected early, but being a cancer of an internal organ the chances of doing so are limited. Carriers of gene mutations known to cause HNPCC can be given regular colonoscopies to detect the early stages of disease; hence genetic testing may be offered in various kinds of screening programs. Genetic epidemiology is now becoming available, measuring the outcomes of such programs; hence we can now try to evaluate the effect on insurance premiums of individuals choosing to participate in them. That is the aim of this paper.

1.2 Screening for Colorectal Cancer

CRC is the third most common form of cancer in men (after prostate and lung cancer) and the second leading cause of cancer-related death in the western world. CRC can be sporadic or hereditary. Approximately 6% of CRCs are hereditary, of which around 83% are accounted for by HNPCC, and the rest by familial adenomatous polyposis (FAP) (Lynch & Smyrk, 1996). Mutations in five DNA mismatch repair (MMR) genes, namely MSH2, MLH1, PMS1, PMS2 and MSH6 have so far been associated with most of HNPCC, with MLH1 and MSH2 mutations accounting for 90% of all cases (Lynch & de la Chapelle, 2003). HNPCC mutation carriers are also at increased risk of endometrial cancer (females), brain cancer, small bowel cancer, gastric cancer, upper urinary tract and extracolonic cancers, for example ovarian cancer (females).

CRC can take many years to develop and early detection of CRC greatly improves the chance of survival. Therefore, screening for the disease is recommended for individuals who have been identified as being at risk of CRC. In this paper, we model the impact of a CRC screening program on the onset rate of CRC, mortality caused by CRC and life insurance premiums.

There are two types of screening program.

- (a) In one, the entire population is screened. We will call these ‘population screening programs’ (PSPs). Genetic testing is not used; the aim is to identify persons with pre-cancerous or early-stage symptoms, who will benefit from early intervention. A pilot study for such a program has been undertaken in the UK, called the Bowel Screening Program (BSP). We describe this, and supporting studies, in Section 2.
- (b) In the other, members of families known to be at risk of HNPCC are screened. Genetic testing is used to identify mutation carriers, who are then offered regular check-ups to ensure early detection of symptoms followed by intervention. These are often called ‘cascade screening programs’ (CSPs, Mitchell *et al.* (2008)). An example, that we will use in our application, is the CRC Surveillance Program in Finland. We describe this, and related work, in Section 3.

In Sections 4 and 5, respectively, we study the effect of these examples of screening programs on life insurance. Our conclusions are in Section 6.

2. THE BOWEL SCREENING PROGRAM IN THE UK

The BSP originated in the UK Colorectal Cancer Screening Pilot (‘the Pilot’), conducted to determine the feasibility of screening for CRC in the UK population using faecal occult blood (FOB) testing. A key task of the Pilot has been to determine whether outcomes achieved in the trial settings can be repeated in population-based programs. The Pilot commissioned two sites, one in central England, the other in Scotland. Screening began at the Scottish site on

March 31, 2000 and at the English site on September 6, 2000. Up to February 2003, 486,355 people had been offered screening. The age range of the sampled population is 50 to 70 for both males and females. The final report on the UK Pilot ('the report') was made available online at <http://www.cancerscreening.nhs.uk/bowel/finalreport.pdf>. Some important conclusions of the report were as follows:

- (a) The Pilot achieved uptake of the FOB test of close to the target of 60%. However some sub-groups in the population showed lower uptake, including men, younger people, those from deprived areas and individuals of ethnic origin. Uptake was slight lower in Scotland than in England.
- (b) Staging distribution data indicated that the screening program helped to detect CRC at an earlier stage than in unscreened populations.

The report concluded that benefits had been observed in the Pilot, including CRC-specific mortality reductions, and that screening should be extended nationally, as the National Health Service Bowel Screening Program (NHS BSP). The website of the NHS BSP states the following:

- (a) The NHS BSP offers routine screening every one or two years to all men and women aged 60–69.
- (b) A faecal occult blood (FOB) test detects if any blood is present in faeces, at a much lower level than would be evident to the subjects.
- (c) Around 98% of people will receive a normal result and will be returned to routine screening. Around 2% will receive an abnormal result. They will be referred for further investigation and usually offered a colonoscopy.
- (d) A colonoscopy is a visual inspection of the lining of the large bowel, using a thin, flexible tube and a tiny camera. If polyps are found, most can be removed painlessly, using a wire loop passed down the colonoscope tube. These tissue samples are then checked for any abnormal cells that might be cancerous. Around 50% of referred colonoscopy subjects have a normal result, 40% have a polyp, and 10% are found to have cancer.

Also, a meta-analysis, Hewitson *et al.* (2007), identified 9 articles, covering 320,000 participants aged 45 and over, with follow-up ranging from 8 to 18 years, with the following conclusions:

- (a) Participants allocated to screening had a 16% reduction in the relative risk (RR) of CRC mortality (RR 0.84, CI: 0.78–0.90).
- (b) In three studies that used biennial screening, there was a 15% relative risk reduction (RR 0.85, CI: 0.78–0.92) in CRC mortality.

These results are more reliable than each individual study included, because of the much larger sample. Therefore, we will use them in our study of the effect on life insurance of reduced CRC mortality caused by screening.

3. THE COLORECTAL CANCER SURVEILLANCE PROGRAM IN FINLAND

The CRC Surveillance Program in Finland is a CSP, in which screening is extended to persons known to be at risk of HNPCC. We summarise the description in Järvinen (2006) as follows:

- (a) The CRC Surveillance Program begins with ascertainment of HNPCC families by careful inquiry about the family history of cancers in new patients (index patients) with CRC or endometrial cancer (EC). The Amsterdam Criteria, or other rules, might be used to ascertain HNPCC families. Definite diagnosis of HNPCC requires identification of mutations in

one of the MMR genes. If found, genetic testing of the first-degree relatives (FDRs) of the index patients will help identify mutation-positive persons predisposed to cancers. Then the detected mutation carriers will go through a cancer prevention program, in order to find and treat colorectal adenomas by colonoscopy before cancers develop.

- (b) For ascertained HNPCC family members, the optimal surveillance interval lies between one to three years beginning from the age of 25. For comparison, Bliss & Schroy (2004) suggested that mutation carriers should undergo surveillance every one to two years from age 20 and then annually after age 40.
- (c) The CRC Surveillance Program greatly reduces the risk for mutation carriers. Other papers, for example Renkonen-Sinisalo *et al.*, (2000), Bliss & Schroy (2004), Vasen *et al.*, (1993) and de Vos tot Nederveen Cappel *et al.*, (2002), drew the same conclusion.

Two important papers are Järvinen, Mecklin & Sistonen (1995) and Järvinen *et al.* (2000). In Järvinen, Mecklin & Sistonen (1995), 251 asymptomatic individuals, aged 20–66 years, belonging to 22 HNPCC families, were ascertained according to the Amsterdam criteria. The observation on these participants (with one individual added later) continued to the publication of the subsequent paper Järvinen *et al.* (2000). The studies both aimed to evaluate the efficacy of a long-term surveillance program by means of colonoscopy and polypectomies. Of the 252 (251 + 1) participants, 133 opted for colonic examination between 1982 and 1986 (study group), whereas the 119 control participants either declined screening (78) or could not be traced (41). Genetic tests for the mutation segregating in each particular family was offered for 205 individuals and performed in 193 between 1996 and 1998 (116 in the study group and 77 in the controls). Another 9 participants were classified as mutation-positive carriers without a genetic test. In total, there were 44 mutation-positive and 74 mutation-negative individuals in the study group compared with 46 positive and 38 negative in the controls. The examination was repeated at 3-year intervals, and the use of colonoscopy reached nearly 100%. Järvinen *et al.* (2000) concluded that in mutation-positive subjects alone, the onset rate of CRC was reduced by 56%. Unlike the BSP, which starts from ages above 45, the CRC Surveillance Program starts from age 20. Therefore, we assume the reduced CRC onset rate takes effect from age 20. Compared with the other papers listed above, Järvinen *et al.* (2000) included more patients in the study, had longer follow-up and carried out genetic tests to identify mutation carriers. Therefore, we choose to use the results of Järvinen *et al.* (2000) to evaluate the effect of a surveillance program on life insurance.

4. THE EFFECT OF A POPULATION SCREENING PROGRAM ON LIFE INSURANCE

We present a Markov model for pricing a life insurance policy in Figure 1, in order to evaluate the effect of a PSP (exemplified by the BSP) on life insurance.

This model splits the total population force of mortality into the force of mortality caused by CRC, ν_x^{01} , and that from other causes ν_x^{02} . We suppose that ELT15 represents the population mortality. Hence

$$\mu_x^{ELT15} = \nu_x^{01} + \nu_x^{02} \quad (1)$$

ELT15 was produced using Office of National Statistics (ONS) data during 1990–1992 (ONS, 1997 & 1999). We also use ONS data (ONS 1997, 1999) to estimate the intensity ν_x^{01} . Assume that θ_x^{ELT15} and E_x^{ELT15} are the numbers of deaths and the numbers exposed to risk at age x during 1990–1992. We can split the total number of deaths θ_x^{ELT15} into the numbers of deaths

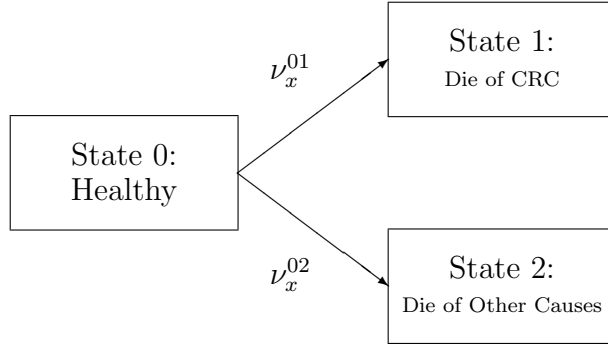


Figure 1: A Markov model of life history, differentiating mortality caused by CRC and other mortality.

caused by CRC, denoted $\theta_x^{ELT15,CRC}$, and by all other causes, denoted $\theta_x^{ELT15,Other}$. Hence the crude rate of the mortality caused by CRC, denoted $\dot{\nu}_x^{01}$, can be estimated as:

$$\dot{\nu}_x^{01} = \frac{\theta_x^{ELT15,CRC}}{E_x^{ELT15}}. \quad (2)$$

The crude rate $\dot{\nu}_x^{01}$ is then graduated to give a smoothed estimate ν_x^{01} . The total number of deaths caused by CRC, $\theta_x^{ELT15,CRC}$, was found from ONS (1999). We fitted polynomial functions as follows:

$$\begin{aligned} \text{Males: } \nu_x^{01} &= 5.943 \times 10^{-5} - 2.188 \times 10^{-5}x + 2.404 \times 10^{-6}x^2 \\ &\quad - 9.798 \times 10^{-8}x^3 + 1.576 \times 10^{-9}x^4 - 7.078 \times 10^{-12}x^5, \end{aligned} \quad (3)$$

$$\begin{aligned} \text{Females: } \nu_x^{01} &= -1.108592 \times 10^{-5} + 5.639 \times 10^{-6}x - 2.152 \times 10^{-7}x^2 \\ &\quad - 7.249 \times 10^{-9}x^3 + 3.589 \times 10^{-10}x^4 - 2.026 \times 10^{-12}x^5. \end{aligned} \quad (4)$$

The crude estimates and fitted functions are displayed in Figure 2.

Then the intensity ν_x^{02} is easily derived by subtracting the intensity ν_x^{01} from μ_x^{ELT15} . Based on Hewitson *et al.* (2007), we assume that the intensity ν_x^{01} is reduced by about 15% if people go through either annual or biennial screening, and the reduction takes effect from age 45 onward. We treat persons who choose not to take part in a screening program as standard risks.

In this model, insured applicants pay premiums continuously while remaining in State 0, and the claim is paid when they enter State 1 or 2. We assume a constant force of interest $\delta = 0.05$ and define the following probabilities:

$$\begin{aligned} {}_t p_x^{ij} &= \text{P[In state } j \text{ at age } x+t \mid \text{ In state } i \text{ at age } x \text{]} \\ {}_t \bar{p}_x^{\bar{ii}} &= \text{P[In state } j \text{ from age } x \text{ to age } x+t \mid \text{ In state } i \text{ at age } x \text{]}. \end{aligned}$$

We calculate the net level rate of premium P for a unit sum assured from:

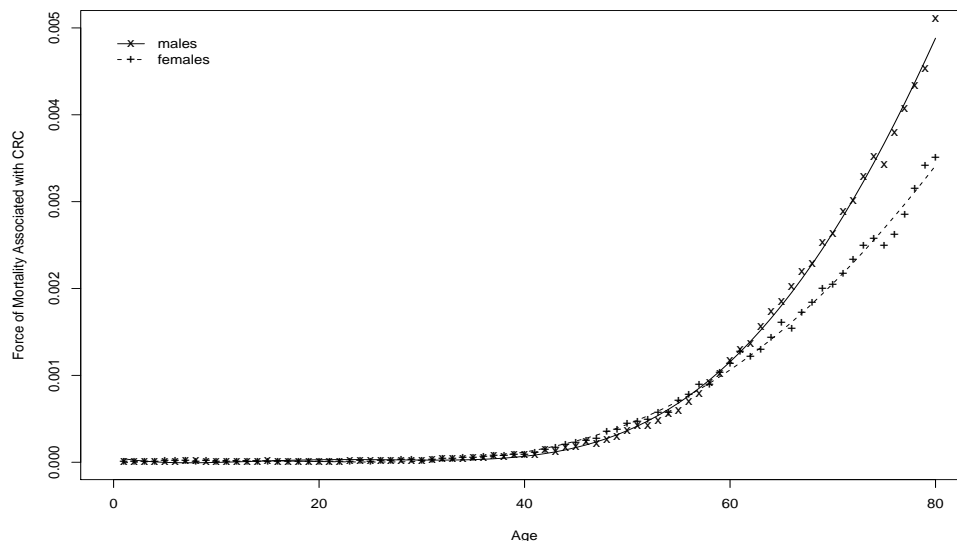


Figure 2: Observed and fitted age-related mortality caused by CRC for males and females.

$$P \int_x^{x+n} e^{-\delta t} {}_t p_x^{00} dt = \int_x^{x+n} e^{-\delta t} {}_t p_x^{00} (\nu_{x+t}^{01} + \nu_{x+t}^{02}) dt. \quad (5)$$

We calculate the premium rates for different entry ages and terms for both males and females. Table 1 shows the premium rates as a percentage of the premium rates for a standard risk. We can see the following features:

- (a) Premium rates fall by 1–2% for policies expiring at age 60, because CRC risk is greatest at high ages. For entry age 50 and term 10 years, for males, we observe a 2% reduction in premium rates.
- (b) The reduction seems greater for males than for females, probably because male CRC mortality (before any screening) is greater, especially at high ages (see Figure 2).

5. THE EFFECT OF A CASCADE SCREENING PROGRAM ON LIFE INSURANCE

5.1 A Semi-Markov Model of Life History

Cascade screening targets healthy blood relatives of persons who have had HNPCC and have been found to carry a relevant mutation (see Section 1.2). Only those found to carry the same mutation need to be monitored; we assume that non-carriers are normal risks.

Our starting point is a model of CRC onset depending on genotype. Moreover, mutations linked to HNPCC are also linked to increased risk of other cancers, (see Section 1.2) which must be included in the model. A semi-Markov model of a person's life history allowing for onset of CRC, onset of endometrial cancer (EC, females only) and onset of other extra-colonic cancers (OECC), is presented in Figure 3, for a sub-population labelled i defined by genotype.

- (a) The intensities of onset of CRC, EC and OECC depend on genotype. We use the same intensities (or in some cases, cumulative distributions from which intensities can be found

Table 1: Level net life insurance premium rates for persons not taking part in a screening program and taking part in a screening program.

Age	Term	No Screening Program				Screening Program			
		Females		Males		Females		Males	
20	10	0.000342	(100%)	0.000867	(100%)	0.000342	(100%)	0.000867	(100%)
	20	0.000459	(100%)	0.000973	(100%)	0.000459	(100%)	0.000973	(100%)
	30	0.000684	(100%)	0.001268	(100%)	0.000679	(99%)	0.001265	(100%)
	40	0.001066	(100%)	0.001874	(100%)	0.001052	(99%)	0.001861	(99%)
30	10	0.000653	(100%)	0.001148	(100%)	0.000653	(100%)	0.001148	(100%)
	20	0.001038	(100%)	0.001687	(100%)	0.001029	(99%)	0.001680	(100%)
	30	0.001681	(100%)	0.002737	(100%)	0.001654	(98%)	0.002713	(99%)
40	10	0.001679	(100%)	0.002592	(100%)	0.001656	(99%)	0.002574	(99%)
	20	0.002759	(100%)	0.004424	(100%)	0.002704	(98%)	0.004375	(99%)
50	10	0.004590	(100%)	0.007589	(100%)	0.004480	(98%)	0.007482	(99%)

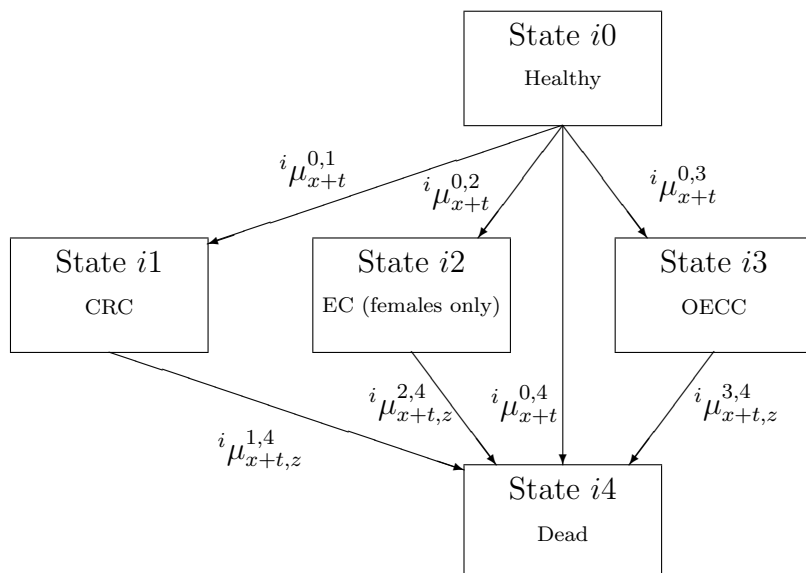


Figure 3: A semi-Markov model for HNPCC in life insurance for sub-population i , defined by genotype.

numerically) as in Lu *et al.* (2007), which for convenience are reproduced in the Appendix. We assume that onset rates of CRC for mutation carriers going through the CSP will be reduced by 56% (see Section 3), and that non-mutation-carriers not going through the CSP are standard risks.

- (b) Post-onset mortality intensities, depending on duration z since onset as well as age, are described in Section 5.2 below.

Following Lu *et al.* (2007) we stratify the whole population into the following three sub-populations:

- (a) sub-population 1: non-mutation carriers;
- (b) sub-population 2: mutation MLH1 carriers;
- (c) sub-population 3: mutation MSH2 carriers;

5.2 Post-Onset Mortality Intensities

Since mutations in MLH1 and MSH2 lead to the onset of cancers of several different sites (CRC, EC (female only) and OECC), we need post-onset mortality intensities in all three cases. In addition, HNPCC patients experience different mortality from sporadic CRC patients.

- (a) *Post-onset mortality associated with CRC:*

Watson *et al.* (1998) is one of the most comprehensive studies of post-CRC mortality, validating the hypothesis that patients with HNPCC have a better prognosis than sporadic CRC patients. Dr. Patrice Watson, the principal author, kindly allowed us to use the underlying data.

In Watson *et al.* (1998), HNPCC cases, as the study group, were selected from 98 HNPCC families in the registries at Roswell Park Cancer Institute and Creighton University. The Amsterdam criteria were used to ascertain the HNPCC patients. As the control group,

sporadic CRC cases were selected from the tumor registry (TR) of a single hospital affiliated with Creighton University. The diagnosis of CRC is taken as the start of survival analysis and the observation ends either because of death, or 10 years after the analysis. Kaplan-Meier methods were used for the survival analysis.

Figure 4 shows the Kaplan-Meier estimate of the survival probability after contracting CRC, with our fitted curve (top) and the corresponding intensity $\mu_z^{CRC,Mortality,MC}$ (bottom) for HNPCC patients. Figure 5 shows the Kaplan-Meier estimate of the survival probability after contracting CRC, with our fitted curve (top) and the corresponding intensity $\mu_z^{CRC,Mortality,NC}$ (bottom) for sporadic CRC patients. The superscripts *MC* and *NC* stand for mutation carriers and non-mutation carriers. Equations (6) and (7) show, respectively, our fitted survival functions (of duration since onset) for HNPCC patients and for sporadic CRC patients. When we use the associated intensities to calculate premiums, we will impose as a minimum mortality intensity that of the standard population, $\mu_x^{Standard}$, here assumed to be English Life Tables No.15.

$$S_z^{CRC,Mortality,MC} = 1 - 0.05973z + 0.003277z^2 - 9.982 \times 10^{-5}z^3 + 1.035 \times 10^{-6}z^4 \quad (6)$$

$$S_z^{CRC,Mortality,NC} = \begin{cases} 1 - 0.1893z + 0.02413z^2 - 0.001342z^3 & z \leq 15 \\ 21.32 \cdot \frac{0.03250^{1.099}}{\Gamma(1.099)} \cdot z^{0.09905} \cdot \exp(-0.03250z) & z \geq 20 \end{cases} \quad (7)$$

For non-carriers, we use a sine blending function for $15 < z < 20$.

(b) *Post-onset mortality associated with EC:*

Boks *et al.* (2002), from a case-control study, concluded that the survival probability of patients with EC from HNPCC families is not significantly different from that of patients with sporadic EC. The study group consisted of 50 patients with HNPCC-associated EC from the registry of the Netherlands Foundation for Hereditary Tumors. The control group consisted of 100 patients with sporadic EC registered in the Eindhoven Cancer Registry in the Netherlands. The observation time for each patient was from the date of diagnosis until death or the end of the study in December 2000. Post onset survival probabilities were estimated using Kaplan-Meier methods.

In the onset intensity analysis of Vasen *et al.* (2001), which was the basis of the onset intensities in Lu *et al.* (2007), the observation time was from birth until date of diagnosis of cancer, death, or to the end of the study on July 1st, 2000. Hence our models for pre-onset and post-onset events use consistent definitions of onset.

The disadvantage of the study by Boks *et al.* (2002) is that the follow-up was short, 5 years for the control group and 10 years for study group. We assume that the life insurance market operates between ages 20 and 60, hence we need to extrapolate the fitted survival function beyond 10 years. We used truncated Gamma functions for this purpose. Figure 6 shows the Kaplan-Meier estimate of the survival probability after contracting EC, with our fitted curve (top) and the corresponding intensity $\mu_z^{EC,Mortality,MC}$ (bottom) for mutation carriers. Figure 7 shows the Kaplan-Meier estimate of the survival probability after contracting EC, with our fitted curve (top) and the corresponding intensity $\mu_z^{EC,Mortality,NC}$ (bottom) for sporadic EC patients. Equations (8) and (9) show, respectively, the fitted post-onset survival probabilities associated with EC for HNPCC patients and for sporadic EC patients. As for CRC, we impose a minimum mortality intensity of $\mu_z^{EC,Mortality,NC}$ in premium calculations.

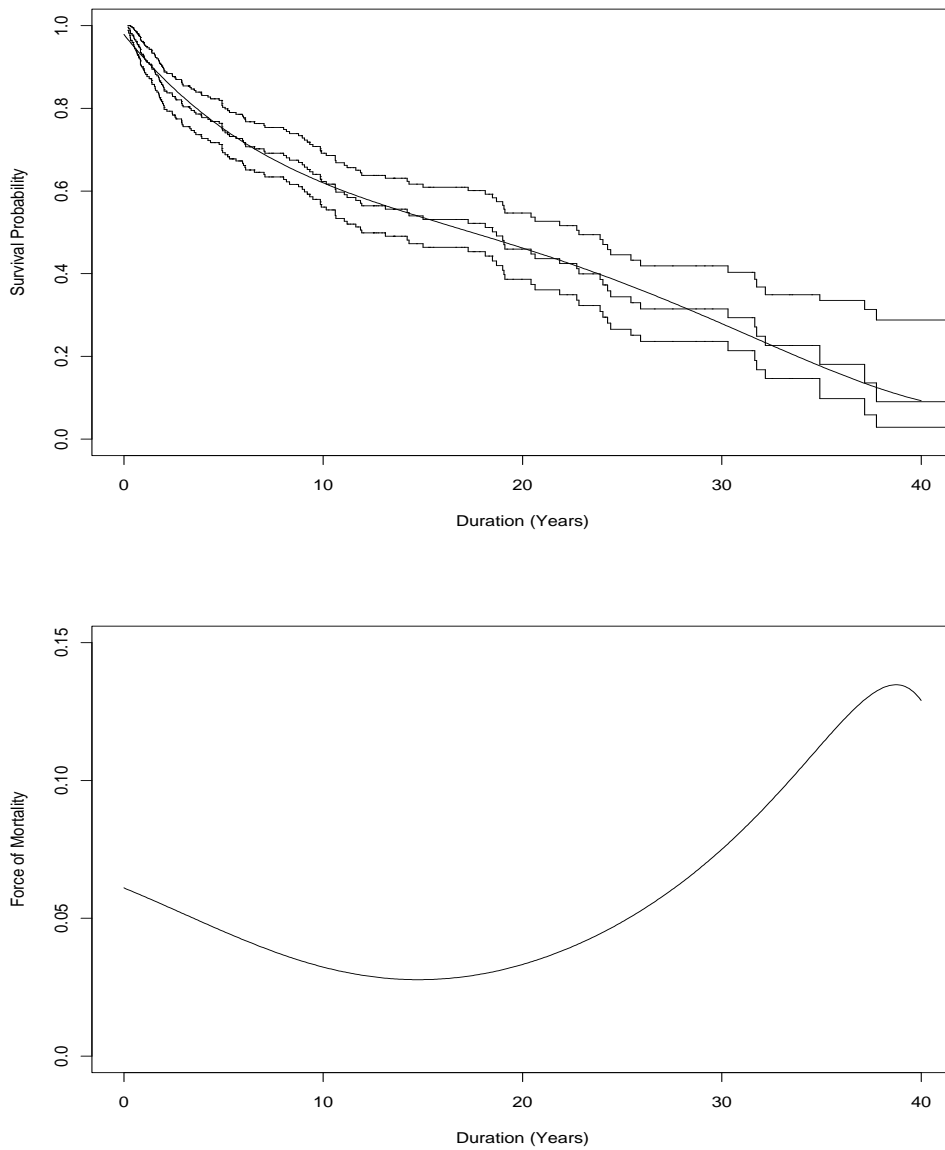


Figure 4: Kaplan-Meier estimates of survival probability after contracting CRC with fitted curve (top) and mortality intensity derived (bottom) for mutation carriers. Data source: Watson *et al.* (1998).

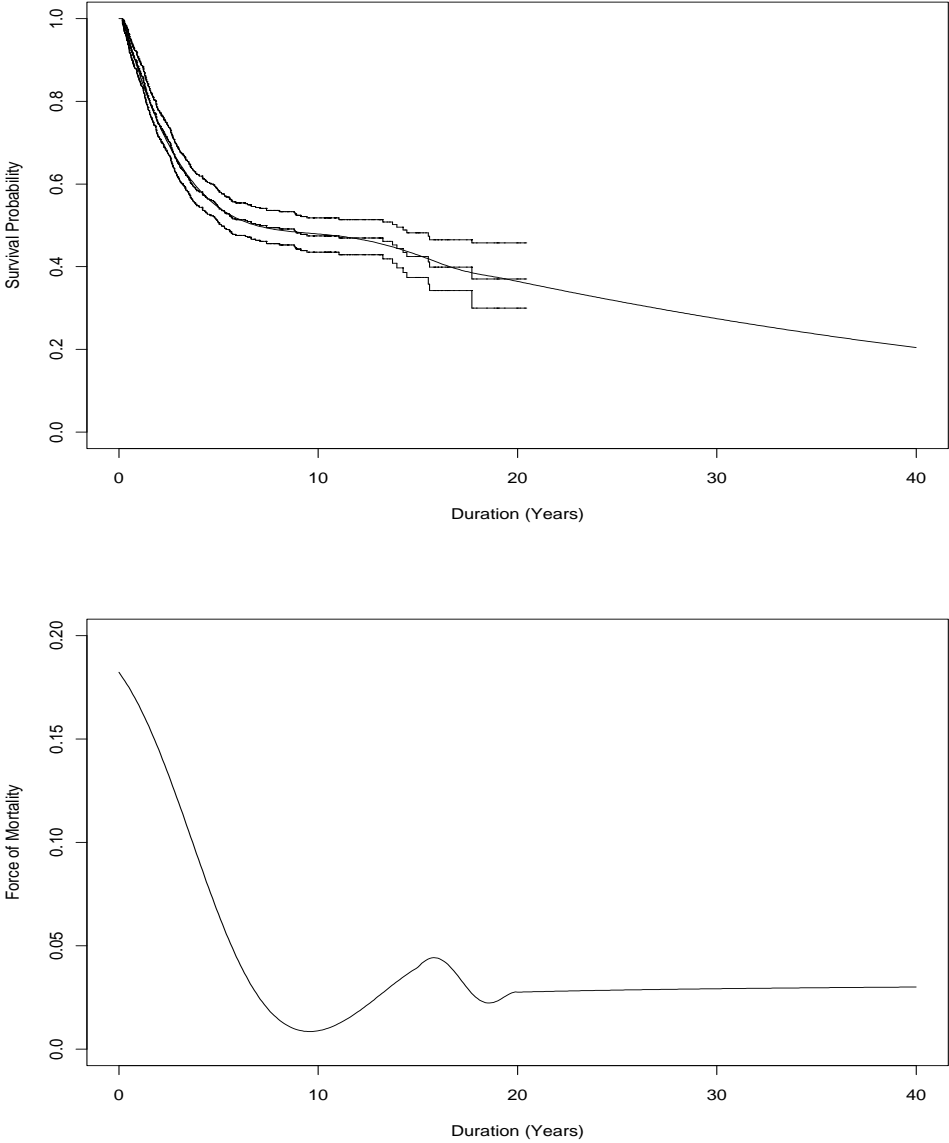


Figure 5: Kaplan-Meier estimates of survival probability after contracting CRC with fitted curve (top) and mortality intensity derived (bottom) for non-mutation carriers. Data source: Watson *et al.* (1998).

$$1 - S_z^{EC,Mortality,MC} = \frac{0.004918^{0.6083}}{\Gamma(0.6083)} \int_0^z t^{-1.608} \exp(-0.004918t) dt \quad (8)$$

$$1 - S_z^{EC,Mortality,NC} = \frac{0.01036^{0.6492}}{\Gamma(0.6492)} \int_0^z t^{-1.649} \exp(-0.01036t) dt. \quad (9)$$

(c) *Post-onset mortality associated with OECC:*

OECC includes cancer of the stomach, urinary tract, small bowel, ovarian (female only) and brain. Ideally, we would study the epidemiological literature on each type of cancer, as we did above in the case of CRC and EC. However, HNPCC-associated OECC is rare enough that there are no survival analyses in respect of some OECCs (such as urinary tract cancer and brain cancer), and in some other cases (such as stomach cancer, small bowel cancer and ovarian cancer), the reliability of results is in doubt due to the small number of samples. Let $\mu_z^{OECC,Mortality,NC}$ and $\mu_z^{OECC,Mortality,MC}$ be the post-onset mortality intensities associated with OECC for sporadic patients and HNPCC patients, respectively. In the absence of any better information, we assume that $\mu_z^{OECC,Mortality,NC} = \mu_z^{CRC,Mortality,NC}$ and $\mu_z^{OECC,Mortality,MC} = \mu_z^{CRC,Mortality,MC}$. Considering the relatively low onset rates of OECC, we believe this assumption will have a negligible effect on results. The alternative would perhaps be to ignore OECC altogether. As usual, the post-onset mortality associated with OECC should not be assumed to be lower than that of ELT15 in premium calculations.

5.3 Premium Rates

In this model, insured persons pay premiums continuously while remaining in states $i0$, $i1$, $i2$ or $i3$, and the claim is paid when they enter state $i4$. The simplest case is to suppose that the insurer can access genetic test results, including any taken as part of a CSP. Given the appropriate intensities, and assuming a constant force of interest $\delta = 0.05$, the EPVs of a unit premium, payable continuously, and a unit of benefit payable on death, assuming entry age x and policy term n , are respectively:

$$\text{EPV}[\text{Premium}] = \int_0^n e^{-\delta t} \cdot {}_i p_x^{\overline{00}} dt + \sum_{j=1,2,3} \int_0^n e^{-\delta t} \cdot {}_i p_x^{\overline{00}} \cdot {}_i \mu_{x+t}^{0j} \int_0^{n-t} e^{-\delta s} \cdot {}_s p_{x+t}^{\overline{jj}} ds dt \quad (10)$$

and

$$\text{EPV}[\text{Benefit}] = \int_0^n e^{-\delta t} \cdot {}_i p_x^{\overline{00}} \cdot {}_i \mu_{x+t}^{04} dt + \sum_{j=1,2,3} \int_0^n e^{-\delta t} \cdot {}_i p_x^{\overline{00}} \cdot {}_i \mu_{x+t}^{0j} \int_0^{n-t} e^{-\delta s} \cdot {}_s p_{x+t}^{\overline{jj}} \cdot {}_i \mu_{x+t+s}^{j4} ds dt. \quad (11)$$

The net level premium for a unit of benefit is $\text{EPV}[\text{Benefit}]/\text{EPV}[\text{Premium}]$. Table 2 shows these, for MLH1 and MSH2 mutation carriers taking part, or not, in the CRC Surveillance Program; Table 3 shows the same as a percentage of standard risks. The effect of taking part is to lower the onset rate of CRC, see Section 3. We comment as follows.

(a) Mutation carriers who choose not to take part in the CSP would be uninsurable in most cases, except for a few cases at high ages. Note that this means persons who have taken a genetic test, whether as part of the CSP or otherwise, but decline to undergo the regular colonoscopies. Those who choose to take part in the CSP have substantially decreased premiums, and most cases become insurable at increased premium rates.

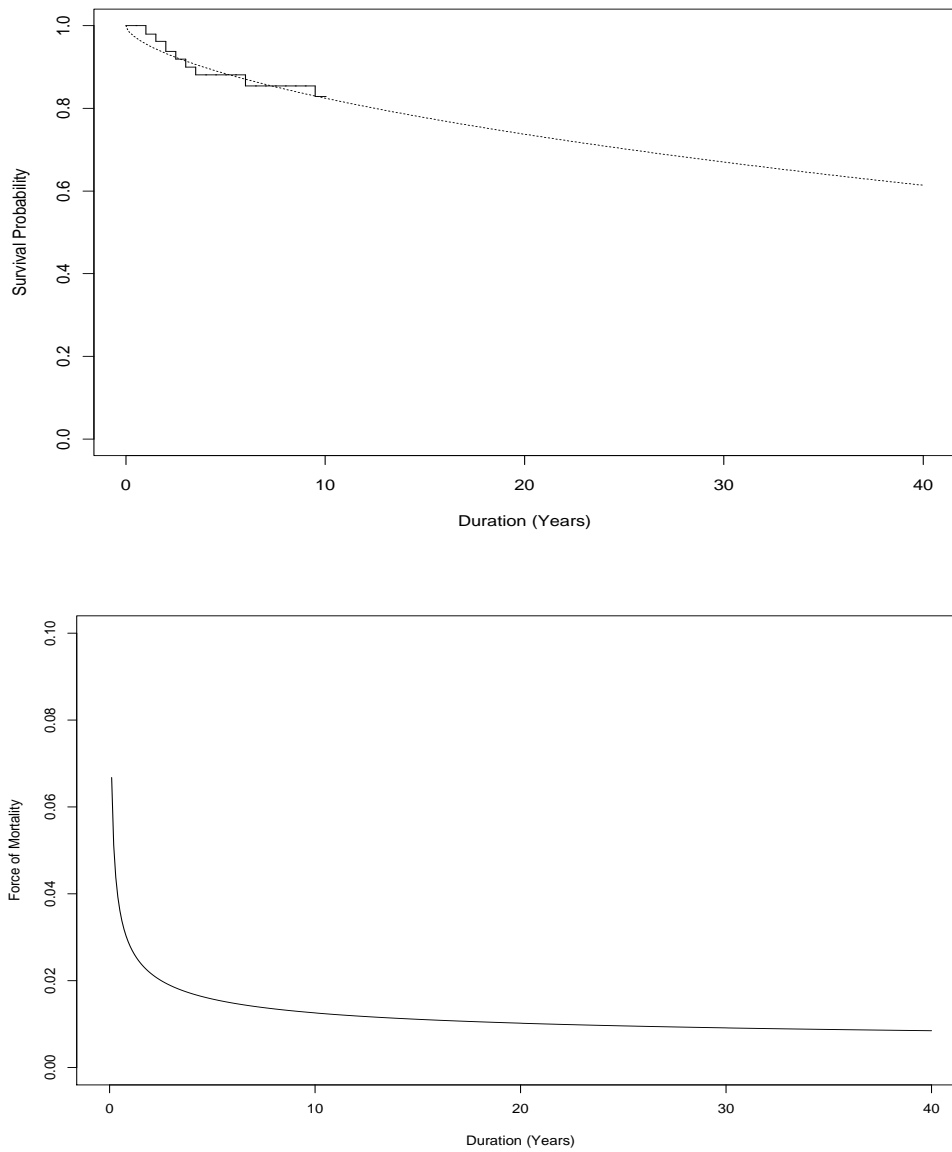


Figure 6: Kaplan-Meier estimate of the survival probability after contracting EC, with our fitted curve (top) and the corresponding mortality intensity (bottom) for HNPCC patients. Data source: Boks *et al.* (2002)

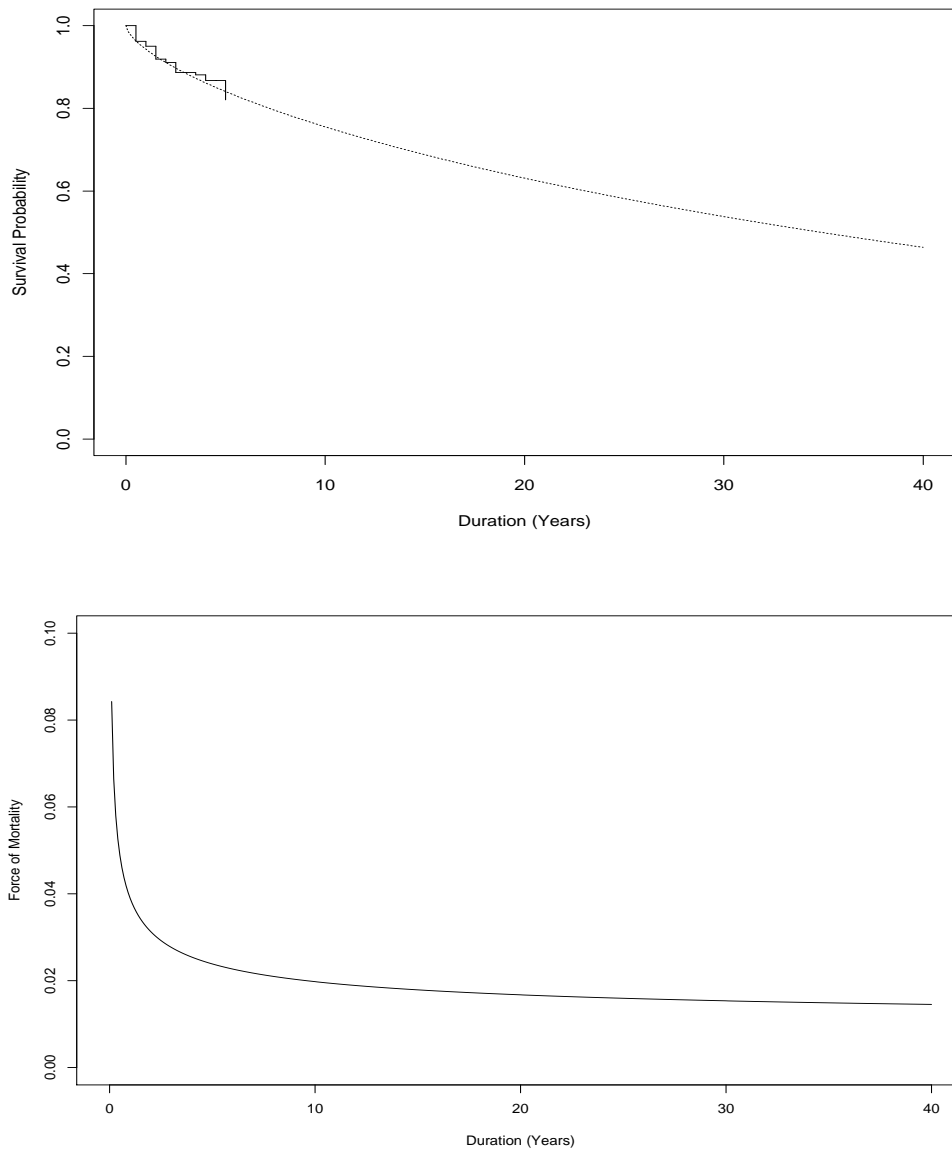


Figure 7: Kaplan-Meier estimate of the survival probability after contracting EC, with our fitted curve (top) and the corresponding mortality intensity (bottom) for sporadic EC patients. Data source: Boks *et al.* (2002)

Table 2: Level net life insurance premium rates for MLH1 and MSH2 mutation carriers not taking part in a CRC Surveillance Program and taking part in a Surveillance Program.

Age	Term	Not in Surveillance Program				In Surveillance Program			
		MLH1		MSH2		MLH1		MSH2	
		Females	Males	Females	Males	Females	Males	Females	Males
20	10	0.000976	0.001806	0.000755	0.001714	0.000624	0.001277	0.000634	0.001265
	20	0.002298	0.003404	0.001750	0.003447	0.001334	0.002069	0.001340	0.002136
	30	0.003566	0.004846	0.003251	0.005479	0.002180	0.002941	0.002444	0.003356
	40	0.004638	0.006095	0.004523	0.006939	0.003037	0.003918	0.003490	0.004536
30	10	0.003189	0.004358	0.002684	0.004956	0.001884	0.002577	0.001999	0.002889
	20	0.005293	0.006775	0.005350	0.008519	0.003310	0.004047	0.003947	0.005022
	30	0.006927	0.008714	0.007381	0.010775	0.004664	0.005623	0.005628	0.006922
40	10	0.005891	0.007298	0.007281	0.010341	0.004094	0.004726	0.005392	0.006289
	20	0.008700	0.010774	0.010725	0.014231	0.006384	0.007494	0.008221	0.009553
50	10	0.009622	0.012608	0.012094	0.015088	0.007745	0.009968	0.009617	0.011588

Table 3: Level net life insurance premium rates for MLH1 and MSH2 mutation carriers not taking part in the CRC Surveillance Program and taking part in the CRC Surveillance Program, expressed as percentages of standard risks.

Age	Term	Not in Surveillance Program				In Surveillance Program			
		MLH1		MSH2		MLH1		MSH2	
		Females %	Males %	Females %	Males %	Females %	Males %	Females %	Males %
20	10	285	208	221	198	182	147	185	146
	20	501	350	381	354	291	213	292	220
	30	521	382	475	432	319	232	357	265
	40	435	325	424	370	285	209	327	242
30	10	488	380	411	432	289	224	306	252
	20	510	402	515	505	319	240	380	298
	30	412	318	439	394	277	205	335	253
40	10	351	282	434	399	244	182	321	243
	20	315	244	389	322	231	169	298	216
50	10	210	166	263	199	169	131	210	153

- (b) Premium rates for female mutation carriers are smaller than those for males in absolute terms but larger as a proportion of the standard premium, because females have lower standard premium rates and because they are also at risk of EC, which is not screened for.
- (c) Table 2 and Table 3 are based on known genetic test results. However, underwriting based on adverse genetic test results is effectively banned in the UK. Insurers instead may ask about family history (FH), which in practice means any hereditary diseases suffered by the applicant's first-degree relatives (parents and siblings). In this case, the net level premium is found from an equation of value in which the EPVs (of unit benefit and unit annuity) are weighted averages of the EPVs for specific genotypes, the weights being the genotype probabilities given all known information whose use is permitted to insurers, in this case:

$$P[\text{genotype } g_i \mid \text{healthy at age } x, \text{ and with family history}] \quad (12)$$

for sub-population i . Examples of such premium rates for critical illness insurance were given in Lu *et al.* (2007), and we could extend these to allow for the CSP. However, the existence of the CSP changes the 'known information whose use is permitted to insurers'. In particular, insurers are allowed to take account of negative genetic test results (that is, when the mutation is absent) and underwrite such applicants as standard risks. This gives rise to the following plausible scenario, under which Tables 2 and 3 are a more realistic outcome.

- (1) A CSP is implemented nationally, with very high take-up because it is associated with significantly reduced mortality.
- (2) As soon as family history leads to a suspicion of HNPCC (for example, on the Amsterdam criteria) CRC sufferers are tested, hence the majority of families in which HNPCC mutations appear are eventually enrolled in the CSP.
- (3) Applicants with a family history and a negative test result report this to insurers and obtain normal underwriting.
- (4) Applicants with a family history who do not report a negative test result are presumed to have had an adverse test result, even though this is not reported.
- (5) Therefore, the genotype probabilities in (12) above are recast as:

$$P[\text{genotype } g_i \mid \text{healthy at age } x, \text{ and with family history, and CSP exists}] \quad (13)$$

which are all either 0 or 1. This is the case illustrated in Tables 2 and 3.

- (d) It is possible that mutation carriers enrolled in the CSP could enjoy much lower premiums than shown in Tables 2 and 3. This is because our post-onset survival rates take no account of the CSP, such epidemiology not yet being available. As well as reducing the onset rate of CRC, we would expect any CRCs that do occur to be diagnosed at earlier stages, and to have a much better prognosis.

6. CONCLUSIONS

Screening programs for some diseases might be introduced by national health services (however constituted) if they promise sufficient benefits. One such target is CRC, and we have reviewed two screening approaches. Our purpose has been to estimate, however crudely, the possible consequences for life insurance.

- (a) One approach to screening is to target the whole population, exemplified by the BSP in the UK. We estimated that this could perhaps reduce life insurance premium rates by about 1 to 2%. This small impact — easily swamped by other factors in a pricing basis or by secular changes in mortality — is because such screening improves outcomes for a small proportion of the whole population. Moreover, the individuals who may benefit are not identified at the point of purchase (of life insurance). We conclude that population screening might reduce life insurance premiums, but only in the same way as any other improvement to post-onset diagnosis and treatment might do.
- (b) The second approach — cascade screening — targets families in which the various gene mutations causing HNPCC are inherited. When a CRC patient is found to carry such a mutation, genetic testing is offered to FDR's, and healthy mutation carriers undergo a regular program of colonoscopies.

Epidemiology supports a greatly reduced onset rate of CRC (56%, Järvinen *et al.* (2000)) but not yet an improved prognosis post-onset, which we might reasonably expect in due course. In that sense, our results based on survival observed to date are conservative.

We found that a national CSP which enrolled a large proportion of families at risk of HNPCC would bring most at-risk persons within the normal limits of life insurance, albeit at an increased premium. As just noted, this made no allowance for improved prognosis, only reduced onset rates, so we expect these premium reductions to be conservative.

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APPENDIX

The onset rates of CRC, EC (females only) and OECC associated with HNPCC

The following are the fitted cumulative onset probabilities of contracting CRC for mutation MLH1 and MSH2 carriers, males and females (Lu *et al.*, 2007).

$$F(x)_{MLH1.m}^{CRC} = 0.3406 - 0.039040x + 0.001294x^2 - 0.000009611x^3 (22 \leq x \leq 70),$$

in which we assume $F(x)_{MLH1.m}^{CRC} = 0$ below age 22.

$$F(x)_{MLH1.f}^{CRC} = 0.2193 - 0.02570x + 0.0008584x^2 - 0.000006075x^3 (23 \leq x \leq 70),$$

in which we assume $F(x)_{MLH1.f}^{CRC} = 0$ below age 23.

$$F(x)_{MSH2.m}^{CRC} = \frac{\exp(-10.92 + 0.3512x - 0.002579x^2)}{1 + \exp(-10.92 + 0.3512x - 0.002579x^2)} (20 \leq x \leq 68).$$

$$F(x)_{MSH2.f}^{CRC} = \frac{\exp(-12.36 + 0.3498x - 0.002421x^2)}{1 + \exp(-12.36 + 0.3498x - 0.002421x^2)} (20 \leq x \leq 70).$$

The following are the fitted cumulative onset probabilities of contracting EC for mutation MLH1 and MSH2 carriers, females only (Lu *et al.*, 2007).

$$F(x)_{MLH1}^{EC} = \frac{\exp(-17.78 + 0.4975x^1 - 0.003655x^2)}{1 + \exp(-17.78 + 0.4975x^1 - 0.003655x^2)} (20 \leq x \leq 65).$$

$$F(x)_{MSH2}^{EC} = \frac{\exp(-4.307 - 0.1973x + 0.008763x^2 - 7.432 \times 10^{-5}x^3)}{1 + \exp(-4.307 - 0.1973x + 0.008763x^2 - 7.432 \times 10^{-5}x^3)} (20 \leq x \leq 65).$$

The following are the fitted cumulative onset probabilities of contracting OECC for mutation MLH1 and MSH2 carriers, males and females. OECC stands for extracolonic cancers, including the cancers of stomach, urinary tract, small bowel, ovary (female only) and brain (Lu *et al.*, 2007).

$$F(x)_{MLH1.m}^{OECC} = \frac{\exp(-30.6539 + 0.8128x^1 - 0.0058x^2)}{1 + \exp(-30.6539 + 0.8128x^1 - 0.0058x^2)} (20 \leq x \leq 70).$$

$$F(x)_{MLH1.f}^{OECC} = \frac{\exp(-18.76 + 0.4747x - 0.003334x^2)}{1 + \exp(-18.76 + 0.4747x - 0.003334x^2)} (20 \leq x \leq 70).$$

$$F(x)_{MSH2.m}^{OECC} = \frac{\exp(-7.1635 + 0.10027x - 2.3206 \times 10^{-4}x^2)}{1 + \exp(-7.1635 + 0.10027x - 2.3206 \times 10^{-4}x^2)} (42 \leq x \leq 65),$$

in which below age 42, the intensity corresponding to $F(x)_{MSH2.m}^{OECC}$ is extrapolated linearly to the origin.

$$F(x)_{MSH2.f}^{OECC} = \frac{\exp(-10.45 + 0.2501x - 0.001618x^2)}{1 + \exp(-10.45 + 0.2501x - 0.001618x^2)} (20 \leq x \leq 70).$$

The following are the fitted onset rates of CRC for populations, both males and females (Lu *et al.*, 2007).

$$\mu_{pop.m}^{CRC}(x) = 0.001401 \frac{\Gamma(10.196)}{\Gamma(8.196)\Gamma(x)} \left(\frac{80x}{89^2}\right)^{7.196} \left(1 - \frac{80x}{89^2}\right)$$

$$\mu_{pop.f}^{CRC}(x) = 0.001092 \frac{\Gamma(8.207)}{\Gamma(6.742)\Gamma(1.465)} \left(\frac{80x}{89^2}\right)^{5.742} \left(1 - \frac{80x}{89^2}\right)^{0.465}$$

The following are the fitted onset rates of EC for populations, females only (Lu *et al.*, 2007).

$$\mu_{pop}^{EC}(x) = \begin{cases} \exp(-17.32 - 0.09261x + 0.004273x^2 - 5.200 \times 10^{-5}x^3) & (20 \leq x \leq 54) \\ -4.665 \times 10^{-4} + 2.446 \times 10^{-5}x - 1.555 \times 10^{-7}x^2 & (57 \leq x \leq 89), \end{cases}$$

blended linearly between age 54 and 57.