A simulation model for evaluating the medical and economic outcomes of screening strategies for colorectal cancer

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Mathematical models have been shown to be useful in predicting the cost-effectiveness of cancer screening programmes. We designed a computer macro-simulation model aimed at predicting the cost-effectiveness of alternative colorectal cancer screening strategies. This model was built to determine the cost-effectiveness of a biennial screening programme using the Hemoccult® test in Burgundy (France). It was validated with data from the Danish randomized study. Estimates of our model showed an extremely close concordance with observed results in the Danish study. The observed mortality reduction was 18.0% and the estimated mortality reduction was 18.4%. Preliminary data from the Burgundy study predict a 14.6% colorectal cancer mortality reduction after 10 years. Sensitivity analyses were performed with different assumptions regarding the participation rates and the lead-time. This model can serve to assess the cost-effectiveness of a variety of screening modalities. ***European Journal of Cancer Prevention*** **12:77–84 © 2003 Lippincott Williams & Wilkins.**

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Introduction

To be eligible for mass screening, a cancer has to meet several criteria. These are met by colorectal cancer, which ranks first with breast cancer among incident cancers in France (Menegoz *et al.*, 1997). Despite advances in diagnosis techniques and treatment, the 5-year survival rate remains poor. In the EUROCARE study, the mean 5-year crude survival rate in Europe was estimated to be 37% for colon cancer and 35% for rectal cancer (Berrino *et al.*, 1999). There is a stage where the disease is confined to the bowel wall (TNM stage 1) which can be cured by surgical resection. Furthermore, a pre-cancerous lesion, the adenoma, can be discovered and removed by endoscopy. Converging data from case–control studies (Faivre *et al.*, 1999) and randomized controlled studies (Mandel *et al.*, 1993; Hardcastle *et al.*, 1996; Kronborg *et al.*, 1996) indicate that it is possible to reduce colorectal cancer (CRC) mortality in individuals who accept screening with faecal occult blood testing (FOBT) using the Hemoccult® test, followed by a colonoscopy in the case of a positive screening test. However, evidence of effectiveness in reducing disease-specific mortality is insufficient alone in justifying the implementation of a population-screening programme. Therefore, to be deemed a priority from a public health policy perspective, any new programme must prove itself cost-effective in relation to other alternatives. The aim of the present paper is to describe and evaluate a mathematical model, which has been designed to predict the medical and economic outcomes of different screening situations for CRC.

Material and methods

General structure of the model

A macro-simulation model was developed to assess the costs and effectiveness of a variety of screening modalities for CRC. This model, intended to simulate a biennial screening programme with the Hemoccult® test, is based on a decision tree analysis, using the Markov process. It estimates the annual medical and economic outcomes within a given cohort invited to participate in different screening strategies and within an unscreened cohort. Each cohort is followed from a given starting age, year by year until the age of 85 or until death.

The structure of the model is illustrated in Figure 1. For each year in a person's life, the model calculates several probabilities. Healthy individuals issued either from the screened or from the unscreened cohort may stay in a 'healthy' state (no diagnosis of cancer) or can directly experience a transition from this state to the 'death from other causes' state. Individuals can reach the CRC state through three different paths: first, a CRC presenting symptoms diagnosed in the screened or in the unscreened cohort; secondly, an asymptomatic CRC detected during one of the screening rounds; and thirdly, CRC diagnosed during the follow-up of patients with a large adenoma previously removed. From the CRC state,

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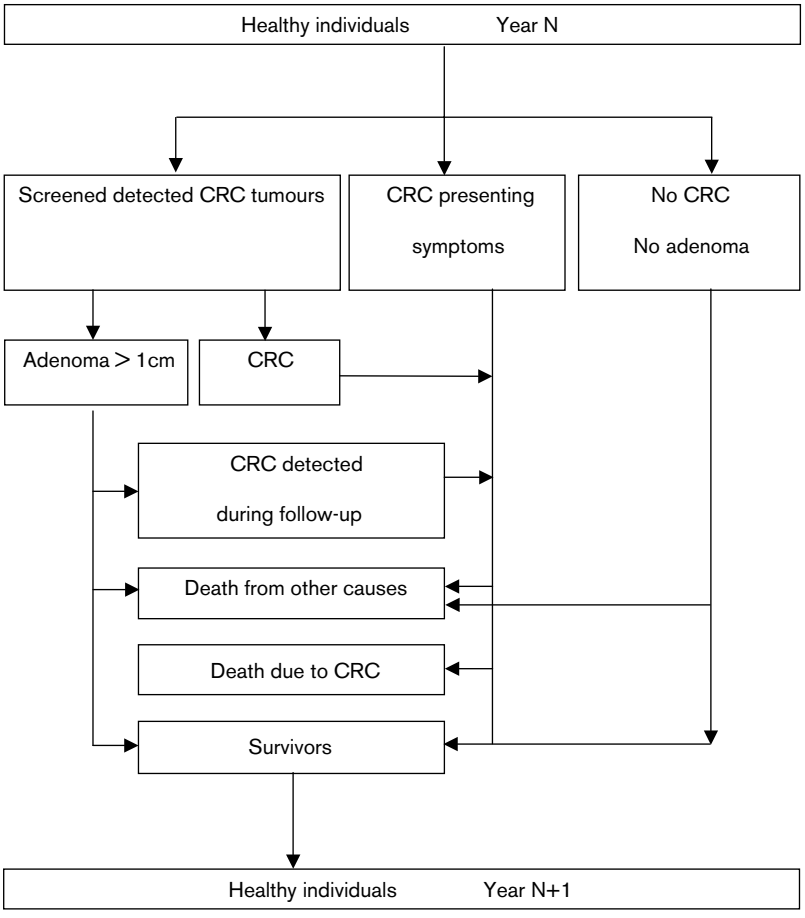
Fig. 1



Transitions between health states.

there are three possibilities: death from CRC, death from other causes or long-term survival.

Because the simulation model should represent reality as closely as possible, most variables can be modified to take into account new data or to test other strategies. The model assesses the number of CRC diagnosed, the number of CRC deaths in the screened and the unscreened populations. The final epidemiological output of the model is the number of life-years gained in the screened group, defined as the difference between the number of life-years lost due to CRC in the screened group compared with the unscreened group. The costs are used to estimate the cost per life-year gained.

Model parameters

Data provided by epidemiological and screening studies

Most parameter values were calculated directly from data provided by national population vital statistics and screening programmes. Data provided by vital statistics concerned the age and sex structure of the population at the beginning of screening, their age- and sex-specific mortality rates, and their age- and sex-specific life expectancy rates. The model also requires epidemiological data including the age- and sex-specific incidence rate for CRC, as well as the distribution of CRC by stage and the yearly survival rates by stage in the unscreened population .

Data provided by screening programmes included compliance to screening. We assumed that four types of participation behaviour were possible: those who participate in all screening rounds, those who participate in one round out of three, those who participate in two rounds out of three and those who never participate in screening. The model also requires the sensitivity of the screening test for CRC, the positivity rate of the screening test by sex, age group and screening round, the compliance to colonoscopy in case of a positive screening test, the

positive predictive value for large adenomas, the distribution of CRC by stage among interval cancers, cancers in nonresponders and the yearly survival rates by stage in the screened population.

Sojourn time and lead-time

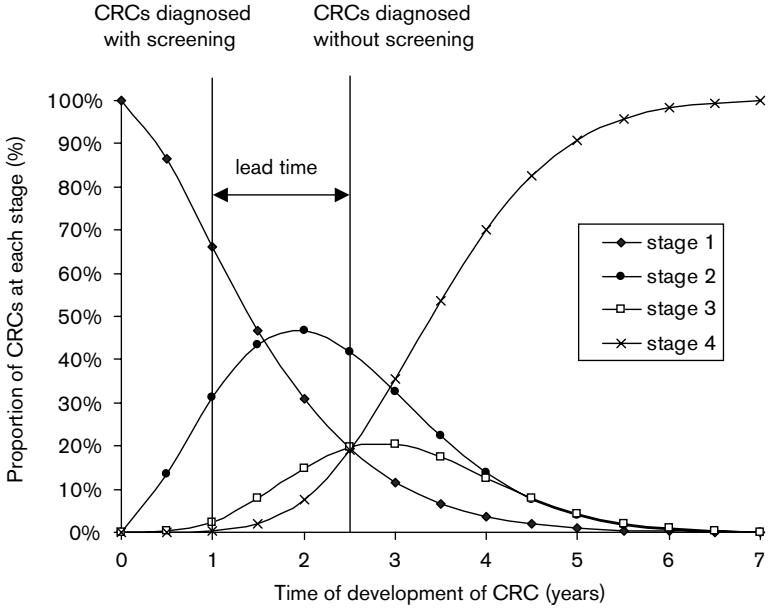
Some parameters have to be estimated by the model. This is the case of the dwelling time in each CRC stage, of the lead-time and of the distribution per stage of screened detected CRCs. A sub-model was developed to determine the stage distribution of CRCs according to the lead-time. Lead-time can be defined as the amount of time by which the detection of cancer has been moved forward thanks to the screening test. It was assumed that all CRCs developed from stage 1 to stage 2, 3 and 4 and that 100% of CRCs were at stage 1 at time $t = 0$. A Weibull distribution was implemented to model the dwelling time at each current CRC stage (Appendix 1). This distribution has already been tested in other modelling procedures (Habbema *et al.*, 1984). The normal and the exponential distributions were also tested, but they did not fit so well to the data. Figure 2 shows the modelling of the proportion of CRCs at each stage diagnosed in an unscreened population since the appearance of the cancer and obtained from a Weibull distribution: the distribution of CRCs by stage in the unscreened cohort was similar to the modelled distribution of cancers by stage observed after almost 2.5 years of evolution of the disease. These 2.5 years fitted with the 2.56 years mean sojourn time estimated by our data from the Burgundy trial (Jouve *et al.*, 2001). Figure 2 shows the modelling of the proportion of CRCs at each stage in a screened population according to lead-time. Several values of lead-time were tested as an input of the global model. The best fit of the model to the observed results of the screening programme was obtained with a 1.5-year lead-time. Then, this modelling was applied without any modification to the Danish screening programme. We observed that the distribution of cancers by stage observed in the unscreened population in Fünen was similar to the theoretical distribution of cancers by stage observed after almost 3 years of evolution of the disease and not 2.5 years as in France. A mean lead-time of 2 years was estimated. This lead-time fitted well with the mean 2.1 years lead-time estimated by Gyrd-Hansen *et al.* (1997).

Prevalence of CRC

To determine the number of detectable CRCs in the screened cohort, the model estimates for each screening campaign the prevalence of detectable CRCs. For a given screening campaign, the estimation of this prevalence depends on:

- CRC incidence, which can be easily calculated from the observed CRC incidence.
- Asymptomatic and detectable CRCs, which would have remained undiagnosed in the absence of screening. The estimation of their number depends essentially on the

Fig. 2



Modelling over time of the proportion of CRCs at each stage diagnosed in an unscreened population since the appearance of the cancer. The vertical line on the right determines the estimated distribution per stage of CRCs in an unscreened population. It corresponds to a sojourn time of 2.5 years. The vertical line on the left determines the estimated distribution per stage of CRCs in a screened population with a lead-time of 1.5 years.

estimated lead-time. These CRCs represent the real benefit of the screening programme.

Estimation of the number of CRCs after adenoma detection and polypectomy

Many uncertainties remain concerning the natural history of CRC. However, there is considerable evidence that a high proportion of CRC arises from adenomas. Autopsy studies indicate that adenomas are frequent. In an autopsy study performed in Burgundy, the prevalence of adenomas was 12% before the age of 54 and 46% after 74 (Michiels *et al.*, 1990). The risk of malignant transformation of adenomas is very low until they reach 1 cm in size (Hill *et al.*, 1978). It is estimated that only 10% of adenomas will reach this size (Faivre *et al.*, 1990). To simplify the model, it was assumed that CRCs, which developed from adenomas, would arise from adenomas > 1 cm in diameter. We used the data suggesting that the cumulative risk of cancer at any site within the colon in subjects with large adenomas left *in situ* was 4% after 5 years, 14% after 10 years and 35% after 20 years (Stryker *et al.*, 1987). The positive predictive value for large adenomas is commonly reported in most studies of mass screening for CRC. Thus, our model uses this input to predict the number of adenomas > 1 cm that will be detected during screening campaigns among the screened population following a positive Hemoccult® test and a total colonoscopy. Data from the National Polyp Study and the Fünen study were used to determine CRC incidence after removal of a large adenoma (Jorgensen *et al.*, 1993; Winawer *et al.*, 1993). The stage distribution of CRC arising in patients followed after excision of at least one large adenoma was reported in the National Polyp Study (Winawer *et al.*, 1993).

All epidemiological parameters are summarized in Appendix 2.

Economic data

Cost-effectiveness analyses are possible using the model. The model requires the following data: the fixed cost of the structure organizing screening, the cost of the general practitioner's training (GP), the cost of the informing of the whole medical profession, the cost of the screening test, the cost related to invitations for screening (letter + information leaflet), the cost of distribution of the tests by GPs followed by the mailing of the test to the nonconsultants and if necessary a reminder letter, the cost of the analysis of FOBTs, the cost of colonoscopy (in case of a positive test), the cost of treatment of diagnosed cancer by stage, the cost of follow-up of CRCs and large adenomas. The cost in the unscreened population is the sum of the cost of diagnosis, treatment and follow-up of incident cases. Data on costs is provided by the Burgundy screening trial. They have not been used in this paper, aimed at validating the effectiveness of the model.

Results

Validation of the model with Danish data

Our model was validated using data from the Danish randomized study performed in the County of Fünen. A total of 30 967 people aged 45–75 were assigned to screening with a nonrehydrated faecal occult blood test, the Hemoccult® test, over a 10-year period (five rounds) and another 30 966 were assigned to no screening. The following parameters were used: age distribution at entry in the screened and control populations, CRC incidence without screening, compliance rates to the Hemoccult® test and to colonoscopy in the case of a positive test, sensitivity of the screening test for CRC, positive predictive value for large adenomas, the stage distribution of CRCs among interval cases, cases in nonresponders and in the unscreened population, 10-year observed survival rates in the screened and the controlled groups, and estimated mean lead-time.

These inputs allowed us to calculate the expected number of CRCs, the expected number of deaths by CRC in the screened and unscreened populations (Table 1). The number of CRCs by stage estimated by our model in the screened group and in the control group was close to the reported data in the Danish study. The number of deaths from CRC was estimated by our model to be 201 in the screened group and 248 in the unscreened group. The difference between the observed and expected mortality reduction was nonsignificant (chi-squared test). The mortality reduction reported in the Danish cohort was 18.0%. It was estimated to be 18.4% by our model.

Estimation of the effectiveness of screening in the Burgundy study

We used data derived from the first five screening rounds in the Burgundy study to estimate the expected reduction in CRC mortality after 10 years. Results are given in Table 2. The estimated number of life-years gained was 839 and the estimated mortality reduction was 14.6%.

Sensitivity analyses were performed. First, the impact of compliance variation was studied (Table 3). Absolute

Table 1 **Comparison of observed and simulated results of the Danish colorectal cancer screening study**

	Study		Model	
	Test*	Control	Test*	Control
CRC detected (*n*)	481	483	513	481
stage 1	21.8%	11.2%	23.8%	11.2%
stage 2	34.1%	36.6%	36.9%	36.6%
stage 3	18.7%	23.0%	16.4%	23.0%
stage 4†	25.4%	29.2%	22.9%	29.2%
Deaths from CRC (*n*)	205	249	201	248
10-year mortality reduction	18.0%		18.4%	

*The test cohort includes participants and nonresponders.
†Includes patients with visceral metastases or patients with unresected cancers.

Table 2 **Estimation of the incidence of and mortality from colorectal cancer in the Burgundy screening study**

	Test*	Control
CRC detected (*n*)	661	655
stage 1	27.5%	21.0%
stage 2	31.8%	25.5%
stage 3	20.3%	26.0%
stage 4	20.3%	27.5%
Deaths from CRC (*n*)	304	358
10-year mortality reduction	14.6%	
Number of life-years gained	839	

*The test cohort includes participants and nonresponders.

Table 3 **Sensitivity analysis performed on the participation rate in the Burgundy study**

	−20%	−10%	Reference*	+10%	+20%
CRC detected (*n*)	654	657	661	662	663
stage 1	21.9%	24.4%	27.5%	31.0%	34.4%
stage 2	31.3%	31.5%	31.8%	32.4%	32.5%
stage 3	22.9%	21.7%	20.3%	18.3%	16.4%
stage 4	23.9%	22.3%	20.3%	18.4%	16.6%
Deaths from CRC (*n*)	321	313	304	291	279
10-year mortality reduction	10.1%	12.1%	14.6%	18.3%	21.7%
No. of life-years gained	586	701	839	1 046	1 239

*The reference value corresponds to a compliance of 55% at the first screening campaign. Compliance in successive screening rounds takes into account the initial compliance value.

decreases or increases of 10% and 20% at the first screening campaign were tested. We took account of this variation compliance in the successive screening campaigns. The increase of the compliance rate improved the CRC stage distribution in the screened group. Consequently, the mortality reduction from CRC increased from 10.1% (with a decrease in compliance of 20%) to 21.7% (with an increase in compliance of 20%).

Secondly, a sensitivity analysis on the lead-time was performed (Table 4). Four values were attributed to the mean lead-time: 0.5 years, 1 year, 2 years and 2.5 years. The increase of the lead-time improved the number of detected CRCs and their distribution per stage. The mortality reduction rose from 10.2% with a 0.5-year lead-time to 19.8% with a 2.5-year lead-time.

Discussion

Screening must be shown not only to be clinically effective in reducing disease specific mortality but also cost-effective. Ideally, the cost-effectiveness analysis should be based on real data collected in controlled studies designed to evaluate the effectiveness of screening strategies. Such studies have limited objectives and they are not suitable in responding to all practical questions. Moreover, the very long period between the start of a controlled study and its first results (about 10 years) and the important size of the population needed for such studies make it difficult to test many policy

Table 4 **Sensitivity analysis performed on the mean lead time in the Burgundy study**

	0.5 years	1 year	1.5 years	2 years	2.5 years
CRC detected (*n*)	646	647	661	676	687
stage 1	21.8%	23.9%	27.5%	32.6%	39.0%
stage 2	30.2%	31.6%	31.8%	30.6%	27.6%
stage 3	23.6%	22.1%	20.3%	18.5%	16.7%
stage 4	24.4%	22.4%	20.3%	18.3%	16.7%
Deaths from CRC (*n*)	320	311	304	295	286
10-year mortality reduction	10.2%	12.8%	14.6%	17.2%	19.8%
No. of life-years gained	597	741	839	980	1122

options. Simulation models able to predict the benefits and the costs of screening programmes can represent a useful complementary tool to aid in decision-making. Results of a controlled study can be extrapolated beyond the follow-up period of the study and predictions can be made for other screening strategies. Furthermore, through sensitivity analysis on key clinical and cost parameters, simulation models can be used to test variants in the screening programme: for example, the age limits of the target population, the time interval between screening rounds or the test to be selected. Models also have limits. The frequent lack of data on the natural history of the disease and the necessity to estimate some key factors can invalidate results.

Several models designed to evaluate CRC screening programmes are available (Eddy *et al.*, 1987; Wagner *et al.*, 1991, 1996; Neilson and Whynes, 1995; Gyrd-Hansen *et al.*, 1998; Loeve *et al.*, 1999). All these models except one used a macro-simulation technique. It consists of a sequence of possible and subsequent health states with subjects moving from one to another according to transition probabilities. The MISCAN-COLON (Loeve *et al.*, 1999) is the only model to use a micro-simulation programme by generating fictitious individual life histories governed by probability distributions making the simulation more flexible.

The validity of the results provided by models depends mostly on the accuracy of assumptions such as participation rates, performance of screening tests and the natural history of the disease.

Some models, like ours, used mostly real data derived from population-based studies (Gyrd-Hansen *et al.*, 1998; Whynes *et al.*, 1998), others have used data estimated from a variety of sources (Eddy *et al.*, 1987; Wagner *et al.*, 1991, 1996).

In scientific publications, there are important variations in the assumptions concerning the sensitivity of the screening test. The sensitivity of the screening test cannot be directly measured because Hemoccult®-negative individuals do not undergo examinations of the

large bowel. The sensitivity of the test must be estimated by mathematical model (Gyrd-Hansen *et al.*, 1997; Launoy *et al.*, 1997; Prevost *et al.*, 1998). The sensitivity of the Hemoccult® test used in our simulation model derives from modelling built with Burgundy screening data (Jouve *et al.*, 2001). In the Danish model, the test sensitivity was also modelled based on the results of the Fünen study (Gyrd-Hansen *et al.*, 1997). In most other published simulations, the test sensitivity derived from published sources (Eddy *et al.*, 1987; Wagner *et al.*, 1991, 1996).

Other differences between models often concern the assumptions made on the natural history of CRC, which is largely unknown, particularly the adenoma–carcinoma sequence. According to the study, the proportion of cancers arising in an adenoma varied from 57% (Wagner *et al.*, 1991) to 93% (Eddy *et al.*, 1987) and the duration of the adenoma–carcinoma sequence from 6 years (Wagner *et al.*, 1991) to 20 years (Loeve *et al.*, 1999). To simplify the model, we made the assumption, as in the Danish model, that all cancers following the adenoma–carcinoma sequence arose from an adenoma over 1 cm in diameter. More sophisticated models are available distinguishing between adenomas < 5 mm, adenomas from 5–9 mm and large adenomas over 10 mm (Loeve *et al.*, 1999). We did not consider such precision necessary. In the Danish and Burgundy models, the annual cumulative probability of cancer provided by Stryker's study (Stryker *et al.*, 1987) was used to estimate the number of CRC arising from a large adenoma.

The most important variable when dealing with natural history is the time taken by a colorectal cancer to move from one stage to another. These time periods are called dwelling times. They determine the number of opportunities for disease detection under screening at any stage. They are often assimilated to the sojourn time, that is the length of time during which the disease is in its pre-clinical phase and detectable by a given screening test. In some models, the time needed to pass from an early stage to a late stage was established without precise calculations to be 1 year (Wagner *et al.*, 1991) and 4 years (Eddy *et al.*, 1987; Wagner *et al.*, 1996). In other models, these durations resulted from simulation approaches (Neilson and Whynes, 1995). Other authors also attempted to determine the length of the pre-clinical detectable phase of CRC, that is, the sojourn time. The sojourn time was obtained by modelling with data obtained from existing screening programmes. Using Burgundy data, the sojourn time was estimated to be 2.56 years (Jouve *et al.*, 2001). These published data fitted well with the 2.5-year period of evolution of the CRC from its appearance until its diagnosis as estimated by our model. When using Danish data, a 3-year period of evolution of the CRC was estimated instead of 2.5 years in France. This result appeared logical according to the accepted fact that CRCs diagnosed in Denmark are often diagnosed at a later stage than in France because of a longer delay between the appearance of symptoms and treatment.

Reliable use of a model in the evaluation of different screening policies is possible when the model is validated. To achieve this objective, the model's assumptions should be tested against available data of existing screening trials. When we compared our model's predictions of colorectal cancer mortality with those of the Danish trial, we found a remarkable concordance thus lending reliability in our mathematical model. The validated model was then used to simulate the 10-year mortality reduction in the Burgundy study. Using preliminary data from this study, it was estimated to be 14.6%, a figure close to the reported colorectal cancer mortality reduction in Denmark.

Sensitivity analyses have been conducted on some parameters in order to verify the strength of the model and its underlying assumptions. The sensitivity analysis performed on the screening participation rate and the mean estimated lead-time demonstrated the strength of our model and showed that before taking into consideration the results of models, every hypothesis and data used must also be carefully checked. Our simulation model appears to be a good tool for representing the clinical reality of a screening programme. Cost-effectiveness analysis is now possible with our model. We are able to calculate the outcomes of screening with any combination of tests, in any order and frequency, in any risk group of individuals, starting and stopping the screening process at any age in terms of cost-effectiveness ratios.

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Appendix 1. Modelling of the proportion of CRCs at each stage

All CRCs were supposed to develop successively from stage 1 to 2, 2 to 3 and 3 to 4. Published studies showed that it seemed reasonable to assume that these three time dwelling times ($T_{ii+1}, i = 1, 2, 3$) followed a Weibull statistical distribution such that:

$$T_{ii+1} \sim \mathit{Weibull}(\alpha_i, \beta_i) \quad \text{with} \quad i = 1, 2, 3 \qquad (1)$$

where $\alpha_i > 0$ (respectively $\beta_i > 0$) represented the shape (respectively the scale) of the distribution.

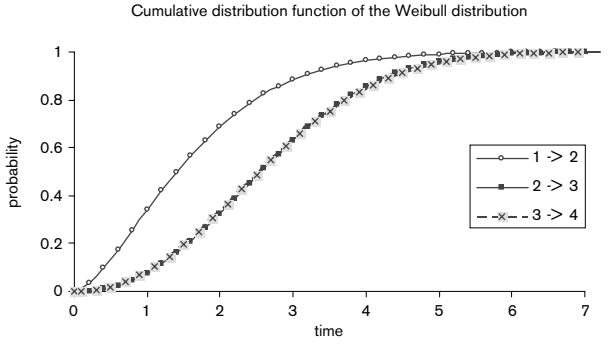
Under these hypotheses of distribution, it was strictly possible to calculate the probability for a CRC to develop from stage k to stage $k+1$ between two times t_0 and t_1 using the cumulative distribution function of the Weibull distribution (α, β) given by the following formula:

$$F(t) = 1 - e^{-\left(\frac{t}{\beta}\right)^{\alpha}} \tag{2}$$

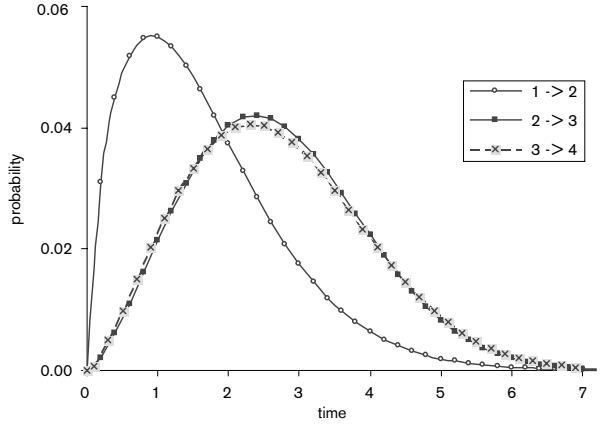
it follows that:

$$\begin{aligned} P(t_0 < T_{\ddot{\imath}+1} \leq t_1) &= P(T_{\ddot{\imath}+1} \leq t_1) - P(T_{\ddot{\imath}+1} \leq t_0) \\ &= \left(1 - e^{-\left(\frac{t_1}{\beta_i}^{\alpha_i}\right)^{\alpha_i}}\right) - \left(1 - e^{-\left(\frac{t_0}{\beta_i}\right)^{\alpha_i}}\right), \\ & i = 1, 2, 3 \end{aligned} \tag{3}$$

Because of the lack of raw data about dwelling times, the classical estimators of maximum likelihood could not be calculated. Then the estimations of the parameters (α_i, β_i), $i = 1, 2, 3$ were obtained by simulation of a statistical sample of each dwelling time and adjusted by published results. The figure below represents the three estimations of cumulative distribution of each dwelling time.



The estimation of the probability for a CRC to develop from stage k to stage $k+1$ between two time periods is illustrated by the following figure.



Assuming that 100% of CRCs were at stage 1 at time $t = 0$, the model was then able to calculate the CRC stage distribution at regular intervals for every point in time from the beginning of the disease until stage 4, as shown in Figure 2.

Appendix 2. Epidemiological parameters used in the model

Variables	References
Demographic data	
Sex-age specific mortality rate	French vital statistics
Sex-age specific life expectancy	French vital statistics
Compliance	
FOBT	Burgundy screening
Colonoscopy	trial
Hemoccult® test performances	
Sensitivity for CRC	Burgundy screening
Positivity rate	trial
Large adenoma positive predictive value	
Natural history of the disease	
Sex-age specific CRC incidence rate	Cancer Registry data
Lead time (years)	Modelling
Large adenoma cumulating transformation malignant rate	Published studies
Relative risk of carcinoma after adenoma detection	Published studies
Data related to CRC	
Distribution per stage in the reference cohort	Burgundy screening
Distribution per stage among nonresponders to screening	trial
Distribution per stage among interval CRC	
Distribution per stage among participants in screening	Modelling
10-year survival rate in the screened cohort	Burgundy screening
10-year survival rate in the reference cohort	trial

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