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Bayesian evaluation of breast cancer screening using data from two studies

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SUMMARY

The mean sojourn time (the duration of the period during which a cancer is symptom free but potentially detectable by screening) and the screening sensitivity (the probability that a screen applied to a cancer in the preclinical screen detectable period will result in a positive diagnosis) are two important features of a cancer screening programme. Little data from any single study are available on the potential effectiveness of mammographic screening for breast cancer in women with a family history of the disease, despite this being an important public health issue. We develop a method of estimation, from two separate studies, of the two parameters, assuming that transition from no disease to preclinical screen detectable disease, and from preclinical disease to clinical disease, are Poisson processes. Estimation is performed by a Markov chain Monte Carlo algorithm. The method is applied to the synthesis of two studies of mammographic screening in women with a family history of breast cancer, one in Manchester and one in Kopparberg, Sweden. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS: breast cancer; screening; sojourn time; sensitivity; MCMC; synthesis

1. INTRODUCTION

The aim of breast cancer screening by mammography is to reduce mortality due to breast cancer by causing cancers to be detected at an earlier, and hence more treatable stage. Studies of the effectiveness of mammography tend to be randomized controlled trials with an unscreened control group, but with populations deemed to be at high risk (because of a known family

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history of breast cancer) this may not be ethically practicable. We therefore have to rely on more circumstantial evidence, such as observational studies, in such populations.

Two studies which have been carried out into the effectiveness of mammography in preventing death from breast cancer in women at a higher risk than the normal population are a study carried out in Manchester [1] and the family history subset of the study group in the Swedish two-county study [2].

Two questions which arise generally in cancer screening, and in these studies in particular, are:

1. What is the mean sojourn time (MST) in these subjects?
2. What is the sensitivity (S) of screening in these subjects?

The first question relates to the 'window of opportunity' for screening to advance the time of diagnosis of a tumour to a more successfully treatable stage. The mean sojourn time is that interval of time during which a tumour is asymptomatic but potentially detectable by a screening test. Clearly, the longer this period is, the greater the potential for screening to advance the diagnosis of the tumour. The second question relates to the effectiveness of screening in detecting those tumours which are in the preclinical screen-detectable phase. Although the values of both the MST and S are well-documented for the general population, these cannot be assumed to hold for women with a family history of breast cancer, as the latter group tends to have different biological types of breast cancer than the former [3].

In this paper we show how data from the two studies can be used to obtain estimates of their screen sensitivities and the mean sojourn time which is assumed to be common to them. We do this by formulating a model for the data from both studies, obtaining the likelihood for that data under this model and fitting the model from a Bayesian perspective using the BUGS program [4].

2. DESIGN OF THE TWO STUDIES AND COLLECTION OF DATA

The women in the two studies receive an initial or *prevalence* screen and may or may not then receive a number of subsequent, or *incidence* screens. For our analysis, we shall also find it useful to introduce more terminology for the incidence screens so that a woman who receives incidence screens receives a *first incidence screen* (that is, the first screen after her prevalence screen) and may or may not go on to receive a number of *subsequent incidence screens* (all her other screens).

We use data from two mammographic screening programmes for women with a family history of breast cancer. The first includes 2998 women with a family history of breast cancer in Manchester enrolled in a mammographic screening programme between 1987 and 1997. The second is a group of 3226 women with a family history of breast cancer within the invited arm of the Swedish two-county trial of mammographic screening for breast cancer. In the Manchester study annual invitation to screening was the initial policy, but this was superseded by two-yearly invitations in later years. In the Swedish study, women aged 40–49 years at recruitment were invited to two-yearly screening, and women aged 50 or more to screening every 2.75 years. Although both studies involved repeated invitations to screens over several years, in the Swedish study, only the prevalence screen data and the interval

cancer data are used, as we did not have family history status by attendance at incidence screens. The median age at recruitment was 52 years in the Swedish study and 41 years in the Manchester study.

3. MODELS, ASSUMPTIONS AND METHODS

3.1. Basic terminology

We introduce some terminology and notation. Let the Manchester and Swedish studies be studies 0 and 1, respectively. We model the natural history of breast cancer by a three-state continuous-time Markov chain so that a woman begins in state N (no detectable disease) and moves successively into states P, the *preclinical* state during which symptoms do not appear but the cancer may be detected at a screen, and then into state C, the *clinical* state in which symptoms appear. If a woman with preclinical breast cancer (that is, in state P) receives a screen, her cancer is detected with a study-dependent probability, S_i, known as the *sensitivity* of the screen. We assume that only transitions $\mathrm{N} \to \mathrm{P}$ and $\mathrm{P} \to \mathrm{C}$ are possible and that these occur as Poisson processes. We write λ_{1i} for the rate of progression from N to P in study i and λ_2 for the rate of progression from P to C, assumed to be common between the two studies. (We thus assume that the rate of progression from N to P, and the sensitivities, are different between the two studies and that the rate of progression from P to C is constant between them, an assumption we discuss in Section 5.)

Estimates of λ_{10} and λ_{11} in the screened population in the two studies are given in the papers describing the studies [1, 2]. These were 3.73/1000 for Manchester and 3.01/1000 for Sweden, reflecting the stronger family history of the Manchester cohort. These values were treated as constants in our estimation procedure.

In study i, a total of c_i cancers are detected, consisting of p_i cancers found at prevalence screens, n_i discovered at incidence screens and v_i which are not discovered until they become symptomatic at some point in time between two screens. The total number of cancers detected at any screen in study i is $s_i = p_i + n_i$. In the case of study 0, the Manchester study, we also write $n_0 = n_0^{\mathrm{E}} + n_0^{\mathrm{S}}$, where n_0^{E} is the number of cancers discovered at first incidence screens and n_0^{S} is the number of cancers discovered at subsequent incidence screens.

In study i there are a total of T_i screens, consisting of P_i prevalence screens and N_i, incidence screens. Again, we write $N_0 = N_0^{\mathrm{E}} + N_0^{\mathrm{S}}$ where N_0^{E} is the number of first incidence screens and N_0^{S} is the number of subsequent incidence screens in the Manchester studies.

The total person-years contributed to the periods since previous screen 0–1 years, 1–2 years and 2+years ('periods 0, 1 and 2') in study i are given by $\mathrm{PY}_i^0, \mathrm{PY}_i^1$ and PY_i^2, respectively. A woman contributes a complete person-year to each of these totals by surviving free of clinical breast cancer during the period, and a shorter period is contributed to the total by surviving cancer-free for a shorter length of time during that period; thus a woman who survives cancer-free for 2.4 years after a screen at which cancer was not detected contributes 1 year to each of PY_i^0 and PY_i^1 and 0.4 years to PY_i^2. During the periods between screens women may present with symptoms of breast cancer; such cancers are known as *interval cancers* and arise either because no cancer was present at the previous screen or because cancer was present but not detected. The number of cancers arising in period t of study i is v_i^t, so that $v_i = v_i^0 + v_i^1 + v_i^2$.

We wish to estimate λ_2, the rate of progression from P to C which we assume to be common to the screened population in both studies, and the sensitivities S_0 and S_1. We shall

Table I. Notation and data.

		Manchester	Sweden
Cancer states			
N No detectable disease			
P Preclinical			
C Clinical			
Parameters			
U_j Underlying true state at screen j			
O_j Observed state at screen j			
λ_{1i} Rate of transition from N to P in study i		0.00373	0.00301
λ_2 Rate of progression from P to C, same in both studies			
S_i Screening sensitivity in study i			
μ_i^t Mean of Poisson distribution for v_i^t			
Cancer numbers			
c_i Total number of cancers in study i		50	89
p_i Number of cancers found at prevalence screen in study i		15	15
n_0 Number of cancers found at incidence screens in Manchester study of which:		26	
n_0^{F} Number of cancers found at first incidence screen		3	
n_0^{S} Number of cancers found at subsequent incidence screens		23	
m_i Total number of screen-detected cancers at Manchester and total at all screens except the last in Sweden		41	29
v_i^t Number of interval cancers in study i during year t after a negative screen	Year 0–1	5	4
	Year 1–2	3	10
	Year 2+	1	1
Screen numbers			
P_i Number of prevalence screens in study i		2998	3226
N_i Number of incidence screens in study i		5278	
N_0^{F} Number of first incidence screens in the Manchester study		1899	
N_0^{S} Number of subsequent incidence screens in the Manchester study		3379	
a_i Mean age for prevalence screens in study i		41.64	54
PY_i^j Person-years contributed in period j since screening in study i	Year 0–1	6566	6259
	Year 1–2	2695	6259
	Year 2 +	875	3399
T_0 Time between screens in the Manchester study		1	

assume that in neither study is it possible for a woman to have two consecutive false negatives (another assumption which we discuss in Section 5).

The notation and data are summarized in Table I.

3.2. Likelihood for the prevalence screen detected cancers

The number of cancers detected at the prevalence screen of study i, p_i, satisfies

$$p_i \sim \mathrm{Bin}(P_i, q_i) \tag{1}$$

where q_i is the probability that a woman in study i is observed to be in state P (that is, is found to have cancer) at her prevalence screen, conditional on her having no previous

history of observed cancer (a condition of recruitment), and P_i is the number attending the prevalence screen in study i. If we make the approximating assumption that each woman in study i receives her prevalence screen at age a_i, the mean age for prevalence screens in that study (see Section 5), then we can derive the study dependent probability q_i by noting that if we assume that all women are born in state N, the probability that a woman of age a_i is in state P is $\Pr(\mathrm{P};\mathrm{N},a_i)$, where $\Pr(X;Y,t)$ is the probability that a woman is in state X a time t after being in state Y. Thus, since a woman attending a prevalence screen does not have clinical symptoms of cancer and therefore is in either state N or state P:

$$\begin{aligned} q_i &= \Pr(\text{probability that a woman in state P has cancer detected}) \\ &\quad \times \Pr(\text{probability that the woman is in state P}) \end{aligned}$$

$$\begin{aligned} q_i &= S_i \left\{ \frac{\Pr(\mathrm{P};\mathrm{N},a_i)}{\Pr(\mathrm{P};\mathrm{N},a_i)+\Pr(\mathrm{N};\mathrm{N};a_i)} \right\} \\ &= S_i \left\{ \frac{\frac{\lambda_{1i}\{\exp(-\lambda_2 a_i)-\exp(-\lambda_{1i}a_i)\}}{\lambda_{1i}-\lambda_2}}{\frac{\lambda_{1i}\{\exp(-\lambda_2 a_i)-\exp(-\lambda_{1i}a_i)\}}{\lambda_{1i}-\lambda_2}+\exp(-\lambda_{1i}a_i)} \right\} \end{aligned} \tag{2}$$

the last line being a direct application of standard continuous-time Markov chain theory [5].

3.3. Likelihood for the interval cancers

As shown by Prevost *et al.* [6], the number of interval cancers arising in study i period t (as defined in Section 3) after a screen at which cancer was not detected, v_i^t, may be modelled as having a Poisson distribution with mean μ_i^t given by

$$\begin{aligned} \mu_i^t &= \lambda_1^i \mathrm{PY}_i^t(1-\exp(\lambda_2(t-0.5))) \\ &\quad + \frac{m_i(1-S_i)}{S_i}\{\exp(\lambda_2(t-1))-(\lambda_2(t))\} \end{aligned} \tag{3}$$

that is, equal to the expected number of newly arising cancers plus the expected number of cancers which were present at the previous screen but not detected. In this equation the meanings of m_i are subtly different for $i=0$ (the Manchester study) and $i=1$ (the Swedish study). In the Manchester study it is the total number of cancers discovered *at all screens* while in the Swedish study it is the total number of cancers discovered at all screens *except the last*. This is because follow-up for diagnosis of breast cancer ceases after the final screen in the Swedish study, but continues in the Manchester study. In the case of the Swedish study, m_1 is estimated using the total number of screen-detected cancers in the whole study (except at the last study) and the proportion of women in the study with a family history.

3.4. Likelihood for the incidence screen detected cancers

The data from the Manchester study allows us to model the detection of cancers at incidence screens. We break the incidence screens into 'first incidence screen' and 'subsequent incidence

Table II. Estimate of sensitivity and mean sojourn time.

	Estimate	95 per cent CI
Sensitivity (Sweden)	94.6%	(88.5%, 99.3%)
Sensitivity (Manchester)	98.1%	(70.9%, 99.3%)
λ_2	0.56	(0.41, 0.75)
MST	1.80	(1.33, 2.45)

screens' as described in Section 3.1. Then the number of cancers detected at the first incidence screen, n_0^F, will be the sum of N_0^F (the number of first incidence screens) independent Bernoulli random variables each with the probability p^F that a cancer is detected at a first incidence screen. Similarly the number of cancers detected at subsequent incidence screens, n_0^S, is the sum of N_0^S (the number of subsequent incidence screens) independent Bernoulli random variables each with the probability p^S that a cancer is detected at a subsequent incidence screen. Equations for p^F and p^S are derived in Appendix A.

3.5. Bayesian modelling using BUGS

The expressions derived above and in the Appendices enable us to construct a model relating the unobserved parameters to the observed data. Very vague priors were placed on the parameters. Once the model has been constructed, the posterior distribution of the unknown parameters can be obtained by Gibbs sampling, one of the family of Markov chain Monte Carlo algorithms [7]. This was carried out within the BUGS program [4].

4. RESULTS

Table I shows the data available from the two studies. Table II shows the estimate of λ_2 and its inverse, MST, with separate estimates of S for each study, with 95 per cent credible intervals. The Markov chain was run for 15 000 iterations with a burn in of 1000 iterations. Convergence was assessed by the methods of Geweke [8], Raftery and Lewis [9] and Heidelberger and Welch [10].

Sensitivity was high at 98 per cent in the Manchester study and 95 per cent in the Swedish study. The slight difference may be due to the use of two-view mammography in Manchester and one-view in Sweden. However, the mean sojourn time was comparatively short at 1.80 years [11]. This reflects the fact that these studies are made up of women with a family history of disease. There is some evidence that tumours in this group tend to be more aggressive and faster progressing [2, 3].

5. DISCUSSION

This paper demonstrates the use of a stochastic model and estimation by MCMC to address a complex problem of some importance in public health, namely the sensitivity and potential lead time of mammographic screening in women with a family history of breast cancer.

No substantial body of single-centre data exists for purposes of such estimation, so it was necessary to synthesize results from two screening programmes with potentially varying breast cancer incidence and screening sensitivity. For any synthesis of evidence to be useful some assumptions of similarity between the data sources has to be made, and we have assumed a common λ_2. We feel that this can be justified by the fact that the MST, and thus λ_2, is a property of the natural history of breast cancer, and thus is unlikely to be different between the two populations. It is true that the age structures of the two screened populations are significantly different but Nixon *et al.* [2] show that the MST is largely independent of age in women with a family history of breast cancer. We allow λ_{1i} and S_i to be study dependent because λ_{1i} will depend on the risk of breast cancer in the particular population, and S_i is a function of the screening programme.

We have also assumed that no woman can have more than two consecutive false negative screens. This is clearly untrue but is arguably a reasonable approximation. Suppose that the sensitivity is 0.83 (a conservative estimate obtained from reference [12]), then the probability that a woman is in state P at one screen, remaining in state P until the next screen and being detected to have cancer at neither can be shown to be less than 2×10^{-5}.

It should be noted that the sensitivity and mean sojourn time are only two facets of the evaluation of screening. Other facets include mortality from cancer (the most important of all), rates of radical treatment, rates of recall for further investigation of mammographically detected lesions, particularly those which transpire to be non-malignant, stage of disease and psychosocial aspects. It is, however, worthwhile obtaining reliable estimates of sensitivity and mean sojourn time as part of the evaluation process.

Although the focus of this paper is the methodology of synthesis of the two studies, it is worth commenting briefly on our results. We found estimates of screening sensitivity of between 90 per cent and 100 per cent which are comparable with those observed in other studies [11, 13, 14]. The mean sojourn time estimate of 1.80 years is rather shorter than usually observed; even in pre-menopausal women [14, 15] Tabar *et al.* find mean sojourn times of at least 2.4 years in women of all ages. It therefore seems likely that the tendency of genetic and family history clinics to recommend more frequent screening of women with a family history of breast cancer is justified [16].

Ideally, one would wish to subdivide the studies by age group, but there are problems of stability of estimation from these complex models with relativity sparse data [2]. For age-specific results, more event-rich data would be required. In this case, we could, for example, have broken up the prevalence screen cancers into age groups instead of assuming that all women in study i have their prevalence screen at age a_i. However we feel that our assumptions and approximations allow the limited amount of data on this important topic to be usefully modelled.

APPENDIX A: DERIVATIONS OF PROBABILITIES p^{F} AND p^{S}

$$\begin{aligned} n_0^{\mathrm{F}} &\sim \mathrm{Bin}(N_0^{\mathrm{F}}, p^{\mathrm{F}}) \\ n_0^{\mathrm{S}} &\sim \mathrm{Bin}(N_0^{\mathrm{S}}, p^{\mathrm{S}}) \end{aligned} \tag{A1}$$

where p^{F} is the probability that a cancer is detected at a first incidence screen and p^{S} is the probability at a subsequent incidence screen. We now derive these probabilities.

We are assuming that:

1. no woman can have two consecutive 'false negatives';
2. a woman withdraws from screening immediately after a cancer is discovered, so that all the screens preceding any screen will have been (possibly false) negatives.

We shall simplify the argument by the approximation that:

3. all women receive their first screen at a_0, the mean age at first screen;
4. all screens are at time T apart.

To derive p^{S}, the probability that a cancer is detected at a subsequent incidence screen, note that a woman having a subsequent incidence screen must have had at least two screens previously at which she was in observed state N. Labelling these three screens $0, 1, 2$ in order and writing U_i and O_i for the underlying true state and the observed state, respectively, at screen i.

$$\begin{aligned}
p^{\mathrm{S}} &= \Pr(O_2=\mathrm{P}|O_0=\mathrm{N}, O_1=\mathrm{N}) \\
&= \Pr(O_2=\mathrm{P}|U_0=\mathrm{N}, O_1=\mathrm{N}) \text{ (assumption 1)} \\
&= \{\Pr(U_l 1=\mathrm{P}, U_2=\mathrm{P}|O_0=\mathrm{N}) \\
&\quad \times \Pr(O_2=\mathrm{P}|U_2=\mathrm{P}) \Pr(O_1=\mathrm{N}|U_1=\mathrm{P})\} \\
&\quad + \Pr(U_1=\mathrm{N}, U_2=\mathrm{P}|O_0=\mathrm{N}) \Pr(O_2=\mathrm{P}|U_2=\mathrm{P}) \\
&= \Pr(\mathrm{P};\mathrm{N},T) \Pr(\mathrm{P};\mathrm{P},T)(1-S_i)S_i + \Pr(\mathrm{N};\mathrm{N},T) \Pr(\mathrm{P};\mathrm{N},T)S_i \\
&= S_i \Pr(\mathrm{P};\mathrm{N},T)\{\Pr(\mathrm{P};\mathrm{P},T)(1-S_i) + \Pr(\mathrm{N};\mathrm{N},T)\} \\
&= S_i \frac{\lambda_{10}\exp(-\lambda_2 T) - \exp(-\lambda_{10}T)}{\lambda_{10}-\lambda_2} \\
&\quad \times (\exp(-\lambda_2 T)(1-S_i) + \exp(-\lambda_{10}T))
\end{aligned} \tag{A2}$$

To derive p^{F}, the probability that a cancer is detected at a first incidence screen, note that a woman having first incidence screen will have previously had a prevalence screen at which she was observed to be in state N. Label the prevalence screen 0 and the first incidence screen 1. Then

$$\begin{aligned}
p^{\mathrm{F}} &= \Pr(O_1=\mathrm{P}|O_0=\mathrm{N}) \\
&= \Pr(O_1=\mathrm{P}|U_0=\mathrm{N}) \Pr(U_0=\mathrm{N}|O_0=\mathrm{N}) \\
&\quad + \Pr(O_1=\mathrm{P}|U_0=P) \Pr(U_0=\mathrm{P}|O_0=\mathrm{N}) \\
&= S_0\{\Pr(U_1=\mathrm{P}|U_0=\mathrm{N}) \Pr(U_0=\mathrm{N}|O_0=\mathrm{N}) \\
&\quad + \Pr(U_1=\mathrm{P}|U_0=\mathrm{P}) \Pr(U_0=\mathrm{P}|O_0=\mathrm{N})\}
\end{aligned}$$

$$
\begin{aligned}
&= S_0\{\Pr(\mathrm{P};\mathrm{N},T)\Pr(U_0=\mathrm{N}|O_0=\mathrm{N}) \\
&\quad + \Pr(\mathrm{P};\mathrm{P},T)\Pr(U_0=\mathrm{P}|O_0=\mathrm{N})\} \\
&= S_0\{\Pr(\mathrm{P};\mathrm{N},T)(p(1-S_0)/(p(1-S_0)+(1-p))) \\
&\quad + \Pr(\mathrm{P};\mathrm{P},T)((1-p)/(p(1-S_0)+(1-p)))\} \\
&= S_0\left\{\frac{\lambda_{10}(\exp(-\lambda_2 T)-\exp(-\lambda_{10}T)\}}{\lambda_{10}-\lambda_2}(p(1-S_0)/(p(1-S_0)+(1-p))) \right. \\
&\quad \left. + \exp(-\lambda_2 T)((1-p)/(p(1-S_0)+(1-p)))\right\} \qquad \text{(A3)}
\end{aligned}
$$

where p is the probability that a woman who receives a prevalence screen at age a_0 is in true state P at that screen, and

$$
\begin{aligned}
p &= \frac{\Pr(\mathrm{P};\mathrm{N},a_0)}{\Pr(\mathrm{P};\mathrm{N},a_0)+\Pr(\mathrm{N};\mathrm{N},a_0)} \\
&= \frac{\frac{\lambda_{10}\{\exp(-\lambda_2 a_0)-\exp(-\lambda_{10}a_0)\}}{\lambda_{10}-\lambda_2}}{\frac{\lambda_{10}\{\exp(-\lambda_2 a_0)-\exp(-\lambda_{10}a_0)\}}{\lambda_{10}-\lambda_2}+\exp(-\lambda_{10}a_0)} \qquad \text{(A4)}
\end{aligned}
$$

APPENDIX B: A BUGS PROGRAM FOR THE OBSERVED DATA AND THE UNOBSERVED PARAMETERS

```
model twostudies;

#This BUGS programs fits a model which combines data from
#the two studies, and obtains posXsterior distributions for the
#means sojourn time (assumed to be constant between the two
#studies) and the screen sensitivites in the two studies.

const N.STUD0=3,N.STUD1=3;

var time.stud0[N.STUD0], time.stud1[N.STUD1],
  o.stud0[N.STUD0], o.stud1[N.STUD1],
  py.stud0[N.STUD0], py.stud1[N.STUD1],
  age.stud0, age.stud1,
  e.stud0[N.STUD0], e.stud1[N.STUD1],
   can.stud0, can.stud1,
  lam1.stud0, lam1.stud1, lam2,
  theta.new.stud0[N.STUD0], theta.new.stud1[N.STUD1],
  theta.obs.stud0[N.STUD0], theta.obs.stud1[N.STUD1],
  theta.und.stud0[N.STUD0], theta.und.stud1[N.STUD1],
```



```
  mst,
  can.scr.stud0, can.scr.stud1,
  n.scr.stud0,n.scr.stud1,
  p.scr.stud0, p.scr.stud1,
  sub.inc.screen.cancers.stud0, p.can.sub.inc.scr.stud0,
   sub.incidence.screens.stud0,
  first.inc.screen.cancers.stud0, p.can.first.inc.scr.stud0,
   first.incidence.screens.stud0,
  S.stud0, logit.S.stud0,
  S.stud1, logit.S.stud1,
  timegap.stud0;
data in "two_studies.dat";

{
# Prevalence screen detected cancers
# ==================================
#
# This section calculates the likelihood of the number of screen
# detected cancers.
# for study 0, this number has a binomial distribution with
# n = n.scr.stud0, the number of women screened
# p = p.scr.stud0, the probability the a woman having an initial screen

can.scr.stud0 ~ dbin(p.scr.stud0,n.scr.stud0);

# p.scr.stud0 is given by the expresion for q_0 in equation (2) in the paper.

p.scr.stud0 <- S.stud0*(lam1.stud0*(exp(-lam1.stud0*age.stud0) -
        exp(-lam2*age.stud0))/(lam2-lam1.stud0))/
      (exp(-lam1.stud0*age.stud0) +
      (lam1.stud0*(exp(-lam1.stud0*age.stud0)-exp(-lam2*age.stud0))/
      (lam2-lam1.stud0))) ;
# the likelihood for p.scr.stud1 is given by a similar argument.

can.scr.stud1 ~ dbin(p.scr.studl,n.scr.stud1);

p.scr.stud1 <- S.stud1*(lam1.stud1*(exp(-lam1.stud1*age.stud1) -
        exp(-lam2*age.stud1))/(lam2-lam1.stud1))/
      (exp(-lam1.stud1*age.stud1) +
      (lam1.stud1*(exp(-lam1.stud1*age.stud1)-exp(-lam2*age.stud1))/
      (lam2-lam1.stud1))) ;
# Interval cancers
#=================

#N.STUD0 is the number of years of follow-up in the Manchester study.
for(i in 1:N.STUD0){
```



```
#The observed number of interval cancers during year i of follow-up
#o.stud0[i], has a Poisson distribution
#with mean given by equation (4).

    o.stud0[i] ~ dpois(theta.obs.stud0[i]);
    e.stud0[i] <- lam1.stud0*py.stud0[i];

#As explained in the derivation of equation (5), the expected number
#of interval cancers is the sum of the expected number of cancers which
#appear after a false negative at a previous screen (ie when the woman
     already
#had cancer but this was missed at the previous screen) and the expected
#number of cancers which arise after a genuinely false screen (ie when cancer
#has developed since the last screen.

    theta.new.stud0[i] <- e.stud0[i]*(1-exp(-lam2*time.stud0[i]));

    theta.und.stud0[i] <-
      can.stud0*exp(logit.S.stud0)*(exp(-lam2*(time.stud0[i]-0.5))
             -exp(-lam2*(time.stud0[i]+0.5)));
    theta.obs.stud0[i] <- theta.new.stud0[i]+theta.und.stud0[i];
}

for(i in 1:N.STUD1){
    o.stud1[i] ~ dpois(theta.obs.stud1[i]);
    e.stud1[i] <- lam1.stud1*py.stud0[i];
    theta.new.stud1[i] <- e.stud1[i]*(1-exp(-lam2*time.stud1[i]));

    theta.und.stud1[i] <-
      can.stud1*exp(logit.S.stud1)*(exp(-lam2*(time.stud1[i]-0.5)
             -exp(-lam2*(time.stud1[i]+0.5)));
    theta.obs.stud1[i] <- theta.new.stud1[i]+theta.und.stud1[i];

}
#Interval Screen-detected cancers in the Manchester study
#=========================================================
#
#The number of cancers detected at the first incidence screen
#in the Manchester study has a binomial distribution with
#
# n= first.incidence.screens.stud0, the total number of first
#    incidence screens
#
# p= p.can.first.inc.scr.stud0,
# the probability that a woman faving a first incidence screen is found to have
# cancer.
```



```
first.inc.screen.cancers.stud0 ~
    dbin (p.can.first.inc.scr.stud0.first.incidence.screens.stud0);

# The expression for p.can.first.inc.scr.stud0
# is given in equation ()

p.can.first.inc.scr.stud0 <-
          S.stud0 * ( p.scr.stud0 * (1-S.stud0) /
          (p.scr.stud0 * (1-S.stud0) +
          (1 - p.scr.stud0))
          * exp(-lam2 * timegap.stud0) +
          ( 1 - p.scr.stud1 ) / ( p.scr.stud1 * (1-S.stud0)
          + ( 1 - p.scr.studl ) ) *
          (lam1.stud0 * (exp(-lam2*timegap.stud0) -
          exp(-lam1.stud1*timegap.stud0))/(lam1.stud0-lam2) ) )

#The number of cancers detected at subsequent incidence screens
#in the Manchester study has a binomial distribution with
#
# n= first.incidence.screens.stud0, the total number of subsequent
#    incidence screens
#
# p= p.can.sub.inc.scr.stud0,
# the probability that a woman having a subsequent incidence screen
  is found to have
# cancer.

sub.inc.screen.cancers.stud0 ~
     dbin(p.can.sub.inc.scr.stud0,sub.incidence.screens.stud0);

# The expression for p.can.sub.inc.scr.stud0
# is given in equation ()

p.can.sub.inc.scr.stud0<-(lam1.stud0 * (exp(-lam2*timegap.stud0)-
             exp(-lam1.stud1*timegap.stud0))/(lam1.stud0-lam2))*
             (S.stud0*(1-S.stud0)* exp(-lam2*timegap.stud0) +
             S.stud0* exp(-lam1.stud0*timegap.stud0));


# very vague priors for the parameters

logit.S.stud0 ~ dunif(-5,5);
S.stud0<-1/(l+exp(logit.S.stud0));

logit.S.studl ~ dunif(-5,5);
S.stud1<-1/(1+exp(logit.S.stud1));
```



```
lam2 ~ dgamma(0.001,0.001)I(0.005,2.0);
mst <- 1/lam2;
}

#Data file two_studies.dat

list(
timegap.stud0=1.0,
o.stud0=c(5,3,1),
o.stud1=c(4,10,1),
py.stud0=c( 6565.583, 2695.372, 875.4736),
py.stud1=c( 6259,6259,3399),
can.scr.stud0=15 ,
can.scr.studl=15, #a coincidence, not a typo
n.scr.stud0=2998,
n.scr.stud1=3226,
lam1.stud0=0.00373,
lam1.stud1=0.00301,
time.stud0=c(0.5,1.5,2.5),
time.stud1=c(0.5,1.5,2.27),
age.stud0=41.64,
age.stud1=54,
sub.inc.screen.cancers.stud0=23,
first.inc.screen.cancers.stud0=3,
can.stud0=41,
can.stud1=29,
sub.incidence.screens.stud0=3379,
first.incidence.screens.stud0=1899)
```

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