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Identification of the Fraction of Indolent Tumors and Associated Overdiagnosis in Breast Cancer Screening Trials

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It is generally accepted that some screen-detected breast cancers are overdiagnosed and would not progress to symptomatic cancer if left untreated. However, precise estimates of the fraction of nonprogressive cancers remain elusive. In recognition of the weaknesses of overdiagnosis estimation methods based on excess incidence, there is a need for model-based approaches that accommodate nonprogressive lesions. Here, we present an in-depth analysis of a generalized model of breast cancer natural history that allows for a mixture of progressive and indolent lesions. We provide a formal proof of global structural identifiability of the model and use simulation to identify conditions that allow for parameter estimates that are sufficiently precise and practically actionable. We show that clinical follow-up after the last screening can play a critical role in ensuring adequately precise identification of the fraction of indolent cancers in a stop-screen trial design, and we demonstrate that model misspecification can lead to substantially biased estimates of mean sojourn time. Finally, we illustrate our findings using the example of Canadian National Breast Screening Study 2 (1980–1985) and show that the fraction of indolent cancers is not precisely identifiable. Our findings provide the foundation for extended models that account for both in situ and invasive lesions.

breast neoplasms; identifiability; mammography; medical overuse; model-based inference; natural history; stochastic modeling

Abbreviations: API, adequately precise identification; CNBSS-2, Canadian National Breast Screening Study 2; MLE, maximum likelihood estimate; MST, mean sojourn time; PCI, profile confidence interval.

The problem of overdiagnosis associated with cancer screening has received much attention in the clinical literature and news media. Overdiagnosis occurs when a screening test detects a cancer that would never have surfaced symptomatically in the absence of screening. Treatment of an overdiagnosed lesion cannot help the patient; to the contrary, it can cause unnecessary harm in the form of treatment-associated complications and side effects. Because most newly diagnosed cancers are treated, it is rarely possible to directly observe whether a cancer detected by screening has been overdiagnosed or not. In the absence of direct empirical evidence, disease-specific overdiagnosis rates are estimated using statistical methods (1, 2).

A common estimation method approximates the frequency of overdiagnosis via the excess incidence of disease in screened populations as compared with unscreened populations (3–7). However, this approach can yield biased estimates even in the setting of randomized screening trials (8, 9). A second method uses mathematical modeling to leverage the close link between overdiagnosis and disease natural history (10–12). Since overdiagnosis occurs when the period of disease latency, or sojourn time, of a screen-detected case extends beyond the date of other-cause death, the frequency of overdiagnosis can be derived on the basis of an estimate of disease natural history (13).

The estimation of disease natural history in cancer and other chronic diseases has a long history in the statistical literature (13–15). With some exceptions (16–18), these works have primarily focused on estimating sojourn times based on a progressive disease model—that is, under the assumption that asymptomatic, screen-detectable lesions will become symptomatic after a finite amount of time. For example, in the case of breast cancer, progressive

model fits based on multiple cancer screening trials indicate a consensus median sojourn time of 2–4 years (8, 19).

As our understanding of cancer progression evolves, the possibility that some tumors may be nonprogressive or indolent is becoming more apparent (20). In a recent commentary, Baker et al. (1) critiqued the existing literature on natural history estimation because it does not accommodate nonprogressive natural histories. Accommodating a positive fraction of indolent tumors requires modeling a natural history that is a mixture of progressive and indolent disease, with nonprogressive tumors having infinite sojourn times. Valid estimation of natural history parameters—in this case, the fraction of indolent cases and the distribution of sojourn time among progressive cases—requires that the estimation problem be statistically identifiable from the available data. Indeed, identifiability is a key consideration when linking mechanistic models with data (21, 22); it addresses the important question of whether parameters can be uniquely estimated from a given model and data. We distinguish 2 categories of identifiability: *Structural identifiability* considers a best-case scenario of noise-free, continuously measured data, while *practical identifiability* is concerned with more realistic scenarios that bear the usual features of real-world data, such as measurement error and a limited number of sample times. Identifiability analysis evaluates which parameters can or cannot be inferred from a given model and data, and is thus a critical first step in every estimation process.

Here, we investigate the identifiability of a mixture model of disease progression that explicitly accounts for a nonprogressive fraction of screen-detectable tumors. This is a critical step in determining whether the modeling approach may provide a valid alternative to excess incidence in estimating overdiagnosis. We provide a detailed analysis of the mixture model's validity in making inferences about natural history and, by extension, of overdiagnosis in the setting where grouped data on screen and interval diagnoses are available from a randomized screening trial. We complement analytical results with simulation studies, and we illustrate our methods using data from Canadian National Breast Screening Study 2 (CNBSS-2) (23).

METHODS

Model specification

Disease progression. Cancer progression was modeled on the basis of a mixture model with 3 disease states (Figure 1): a cancer-free or susceptible state (S), a preclinical state with asymptomatic but screen-detectable disease (P), and a clinical state with symptomatic disease (C). The transition from S to P was assumed to be exponentially distributed with rate w. A mixture model was used to describe the transition from P to C, accounting for a fraction ψ of preclinical tumors that do not progress to symptomatic disease. The transition time for the remaining, progressive preclinical tumors was assumed to be exponentially distributed with rate λ. This specification reduces to the specification of Shen and Zelen (15, 19) for $\psi = 0$.

Screening program. We focused on a stop-screen trial design for a cohort of N asymptomatic trial participants who received $J+1$ screens at consecutive times $t_0, t_1, \ldots, t_J$ and were followed for clinical incidence until time t_{J+1}. The majority of breast cancer screening trials and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (24) have followed a stop-screen design. Calendar time was chosen to reflect participant age so that age at first screening was t_0. In addition to incidence of screen-detected tumors, we kept track of tumors that were clinically diagnosed between consecutive screenings, referred to as interval cancers. The screening sensitivity β, defined as the probability of detecting a lesion given that the individual was in state P, was assumed to be equal for indolent and progressive lesions. The complete set of parameters was denoted by $\theta = (\psi, \lambda, w, \beta)$.

Estimation procedures

To estimate the model parameters θ based on simulated or actual trial data, we used maximum likelihood estimation. Following previous work (15, 19), we used an inference scheme based on grouped trial data which summarizes each of the screening rounds with (n_j, s_j, r_j), where n_j is the number of subjects entering the jth screening round, s_j is the number of screen-detected cases at time t_j, and r_j is the number of clinically detected interval cases in time interval $[t_j, t_{j+1}]$. The full derivation and final expression of the likelihood are given in Web Appendix 1 (available at https://academic.oup.com/aje). All computations were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Confidence intervals and profile likelihoods

To construct confidence intervals for the parameter estimates, we used a profile likelihood approach (25), as follows. First, denote by $\mathcal{L}(\theta)$ the likelihood function of the model and by θ^* the maximum likelihood estimates (MLEs) of the model parameters θ. Then define the profile likelihood of parameter i as a function $x \mapsto \hat{\mathcal{L}}_i(x) \equiv \mathcal{L}(\theta_{-i}|\theta_i = x)$, which maximizes $\mathcal{L}(\theta)$ over all parameters but the ith parameter while keeping the latter fixed at x. Exploiting the asymptotic χ^2 distribution of the likelihood ratio statistic, define the 95% profile confidence interval for θ_i, at significance level α, as

$$\{x: \log\mathcal{L}(\theta^*) - \log \hat{\mathcal{L}}_i(x) < \Delta_\alpha/2\},$$

where Δ_α is the $(1-\alpha)$th percentile of the χ^2 (df) distribution with df degrees of freedom (22). Pointwise confidence intervals for θ_i were obtained by setting df equal to 1. The likelihood-based

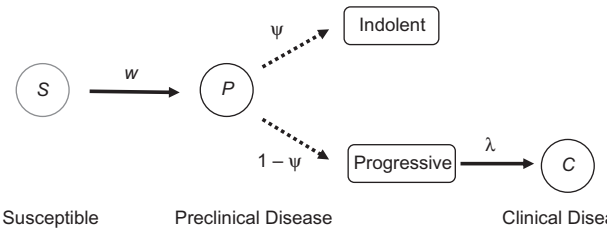

Figure 1. Mixture model of the natural history of breast cancer. Disease-free, susceptible (S) individuals are at risk of developing preclinical disease (P), which is either indolent nonprogressive with probability ψ or progressive otherwise (dotted arrows). Progressive lesions progress to clinically detectable disease (C) at rate λ.

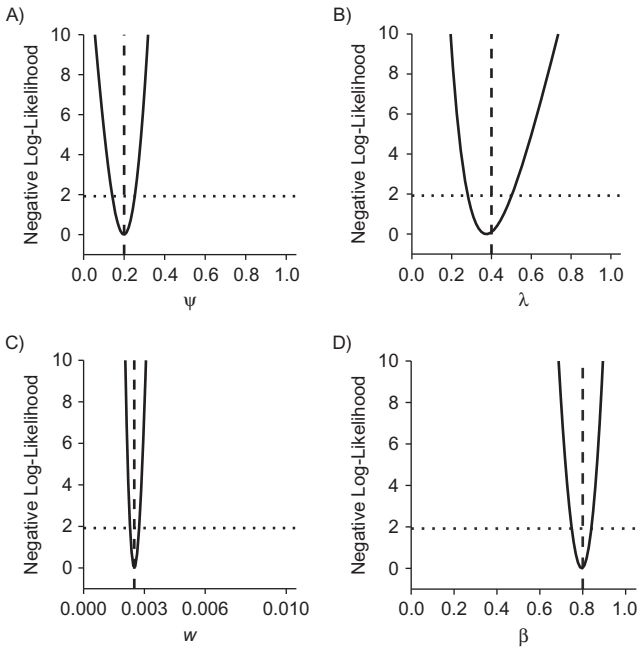

Figure 2. Practical identifiability of a mixture model of breast cancer disease progression. A stop-screen trial with 50,000 subjects was simulated with annual screening at ages 50–54 years, with follow-up to age 60 years. The outcomes were grouped by screening round to estimate the natural history parameters and screening sensitivity. The parameter values used to generate the synthetic data are indicated by vertical dashed lines, and the point estimates of the 4 parameters are close to the minima of the negative (profile) log-likelihoods. A) ψ; B) λ; C) w; D) β. For each parameter, the intersection of the profile likelihood with the horizontal dotted line defines the 95% profile confidence interval.

95% profile confidence interval is best visualized on the basis of the relative negative log-likelihood scale (Figure 2). Indeed, the 95% profile confidence interval for parameter θ_i corresponds to the neighborhood of its MLE where the relative negative log-likelihood stays below the $\Delta_\alpha/2$ threshold (Figure 2, dotted lines). The relative negative log-likelihood and confidence intervals were computed on the basis of the algorithm outlined by Eisenberg and Hayashi (26).

Structural and practical identifiability

Structural identifiability addresses the question of parameter identifiability in a hypothetical scenario of perfectly measured and noise-free data. Assuming such an ideal setting, structural identifiability is achieved if all model parameters can be uniquely recovered from the data. To evaluate the structural properties of the mixture models (21), we derived the backward Kolmogorov equations and employed a differential algebra approach to evaluate model identifiability and determine identifiable parameter combinations (27, 28). (See Web Appendix 2 for details.)

Structural identifiability is a necessary condition for practical identifiability, defined as parameter identifiability in real-world scenarios with imperfect and noisy data. In principle, a structurally identifiable but practically nonidentifiable model can be rendered practically identifiable by collecting suitable additional data.

For a formal definition, we say that a parameter θ_i is practically nonidentifiable if the profile likelihood does not exhibit a minimum or it admits a minimum at $\hat{\theta}_i$ but its 95% profile confidence interval is infinitely extended to either side or both sides of $\hat{\theta}_i$ (21, 22). In other words, a parameter is practically nonidentifiable if the relative negative log-likelihood stays below the $\Delta_\alpha/2$ threshold on either side of the MLE (Figure 2).

Adequately precise identification

In theory, practical (and hence structural) identifiability of a model ensures that point estimates and confidence intervals can be properly estimated from the available data. In practice, however, if the confidence regions are too large, the resulting information may not be actionable for practitioners. For example, if the model-based estimate of the time to progression from preclinical disease to clinical disease is 10 years with a 95% profile confidence interval of (0.1, 100.0) years, the practitioner is unlikely to use the information for clinical or public health recommendations. For this reason, we introduce a notion of practical utility for parameter estimates from a structurally identifiable model, namely that of adequately precise identification (API). We say that a model parameter satisfies API if its 95% profile confidence interval is contained within a meaningful range of the MLE. Furthermore, we say that the model satisfies joint API if all model parameters satisfy API. Here, we define a meaningful range to be $[\max(0, \theta_i - 0.2), \min(1, \theta_i + 0.2)]$ for parameters contained in $[0, 1]$ (e.g., ψ, β) and $[\frac{\theta_i}{3}, 3\,\theta_i]$ for parameters contained in $[0, \infty)$ (e.g., w, λ). Clearly, these choices depend on the application considered and the degree of precision needed for practical purposes.

Simulation study

We simulated data from a stop-screen trial with 50,000 trial subjects who received 5 annual screenings between the ages of 50 and 54 years and were followed for clinical cancer incidence for a specified number of years. The rate of preclinical disease onset w was set to 0.0025, and the screening sensitivity β was assumed to be 80%. We assumed no competing mortality or loss to follow-up. To characterize estimator properties, we performed Monte Carlo simulations ($n = 1{,}000$) to estimate the bias and standard error of the MLEs. We used this framework to conduct a systematic evaluation of API. We varied the duration of follow-up after the last screening and the key natural history parameters that drive overdiagnosis, namely the fraction of indolent cancers (ψ) and the rate of progression to invasive disease (λ). For each pair of ψ and λ, we calculated the fraction of simulation runs yielding API and estimated the corresponding probability of rejecting the null hypothesis of a purely progressive disease, H_0: $\psi = 0$. Finally, we conducted Monte Carlo simulations ($n = 1{,}000$) to determine the bias resulting from fitting a purely progressive model to the data generated by the mixture model.

CNBSS-2 data

To illustrate our methods, we analyzed data from CNBSS-2 (1980–1985). CNBSS-2 was implemented as an individually randomized trial with the goal of evaluating the reduction in

Table 1. Results of Monte Carlo Simulations Carried Out to Estimate the Bias and Standard Error of the Maximum Likelihood Estimators of the Model Parameters in a Mixture Model of Breast Cancer Disease Progression[a]

Parameter Type	Maximum Likelihood Estimator								Type II Error[b]
	Fraction of Indolent Tumors		Rate of Progression to Clinical Disease		Rate of Onset of Preclinical Cancer		Screening Sensitivity		
	ψ	SE($\hat{\psi}$)	λ	SE($\hat{\lambda}$)	w	SE($\hat{w}$)	β	SE($\hat{\beta}$)	
Target	0.2000		0.4000		0.0025		0.8000		
Estimate	0.2002	0.0270	0.4056	0.0593	0.0025	0.0001	0.8007	0.0231	0.000

Abbreviation: SE, standard error.
[a] Example target and estimated parameters based on 1,000 Monte Carlo simulations.
[b] Where the null hypothesis, H_0: $\psi = 0$, was not rejected.

mortality produced by combined annual mammography screening and clinical breast examination over clinical breast examination alone (23). CNBSS-2 enrolled women aged 50–59 years, and 19,711 women randomized to the screening arm underwent the first screening examination (see Web Table 1 for the grouped data). Model fitting was performed as described above in the "Estimation procedures" section, subject to the following assumptions: 1) Because of a lack of granular age data, we assumed average age at enrollment to be 55 years; 2) the incidence rate w of preclinical disease was assumed to be zero prior to age Δ_0 years, where Δ_0 was set to 45 years for the baseline scenario and was varied from 35 years to 50 years for sensitivity analyses; and 3) the parameter β was assumed to capture the combined sensitivity of mammography and clinical breast examination. Finally, the different models' goodness of fit to the trial data was assessed on the basis of a χ^2 test.

RESULTS

Structural identifiability

Under the assumption that the incidence rate of preclinical disease is lower than the rate of progression from preclinical disease to clinical disease ($w < \lambda$), we provided a rigorous proof of the structural identifiability of the mixture model (see theorem 2.2 in Web Appendix 2). We showed that a single screening round in conjunction with clinical follow-up over an arbitrary finite time interval is sufficient to ensure global structural identifiability of the mixture model. Finally, we note that $w < \lambda$ is invariably satisfied in breast cancer natural history.

Practical identifiability

Next, we focused on practical identifiability in scenarios with limited data via simulation studies. Setting the fraction of indolent preclinical tumors to 20% and the mean sojourn time (MST) to 2.5 years, we found all 4 model parameters to be practically identifiable with finite limits of the 95% profile confidence intervals (Figure 2). In particular, because the 95% profile confidence interval for the fraction of indolent cancers did not contain $\psi = 0$, the likelihood ratio test correctly indicated that the fraction of indolent cancers was positive. Results of Monte Carlo simulations carried out to estimate the bias and standard error of the MLEs (Table 1) showed that estimators for all parameters were unbiased with small standard errors.

Clinical utility of estimates

On the basis of a stop-screen trial design with 50,000 participants and 1 year of follow-up after the last screening, we found that a high probability of API was only achieved over a limited portion of the (ψ, λ) plane (Figure 3, top left). Increasing the duration of follow-up from 1 year to 6 years substantially enlarged the portion of the (ψ, λ) plane with a high probability of API (Figure 3, top right). In general, API of the estimates was reduced when the fraction of indolent cancers was large and when the progression rate was either very small or very large.

For the same trial scenarios, we evaluated the corresponding probability of rejecting the null hypothesis of a purely progressive disease, H_0: $\psi = 0$, across the (ψ, λ) plane (Figure 3, bottom row). The rate of type I errors—which corresponds to rejecting H_0 when $\psi = 0$—was negligible for all scenarios considered. With the exception of very small ψ and λ values, the rate of type II errors—which corresponds to the probability of not rejecting H_0 when $\psi > 0$—was negligible; equivalently, the statistical power of the test was high (over 90%). Finally, systematic analysis of estimator bias and standard error for the above trial settings (Web Figures 1 and 2) showed that loss of API occurred primarily in ψ and λ, when either or both of these parameters was particularly small or large. In contrast, the estimators of w and β exhibited minimal bias and standard error across the examined domain.

The role of follow-up

The above results suggest that the duration of follow-up after the last screening can have a substantial impact on the probability of API (Figure 3). For further study of this aspect, we examined API for clinical follow-up ranging from 1 year to 10 years, both for a 6-month MST (Figure 4A) and for a 4-year MST (Figure 4B). Longer follow-up intervals invariably increased the probability of the model's satisfying joint API. The impact of follow-up on API was most pronounced for larger values of ψ. A closer look at the estimators of the different parameters revealed that the low API for short follow-up was primarily driven by shallow profile likelihoods for the progression rate λ (Figure 5). This indicated that the 1-year intervals between screenings were insufficient to

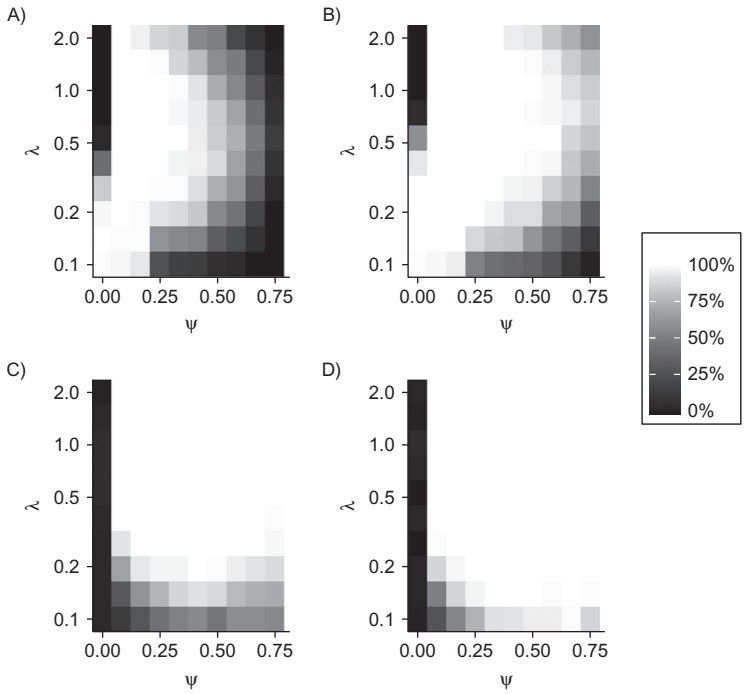

Figure 3. Adequately precise identification (API) and type I/II errors in a simulation study of stop-screen trials. Model performance over a range of values for the indolent fraction (ψ) and the progression rate of progressive cancers (λ) is visualized as (top row) percentages of 100 simulations achieving joint API for all 4 model parameters and (bottom row) percentages of 100 simulations that reject the null hypothesis, H_0: $\psi = 0$. Performance is visualized for 50,000 women screened annually at ages 50–54 years (5 screenings each) with follow-up to age 55 years (left column) or age 60 years (right column), assuming a constant risk of onset of preclinical cancer of $w = 0.0025$ per year and a sensitivity of screening to detect preclinical cancer of $\beta = 80\%$.

properly inform the tail of the progression time distribution. To capture the tail behavior, clinical follow-up after the last screening needed to be longer than the MST. Indeed, API as a function of clinical follow-up was found to increase at a higher rate for shorter sojourn times (Figure 4A) as compared with longer sojourn times (Figure 4B).

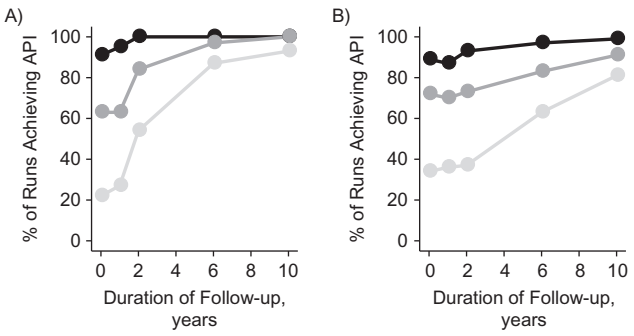

Figure 4. Adequately precise identification (API) as a function of follow-up in a simulation study of stop-screen trials. The graph shows percentages of simulations ($n = 100$) achieving joint API for all 4 model parameters (ψ, λ, w, β) in a stop-screen trial with 50,000 women screened annually at ages 50–54 years, by duration of follow-up after the last screening. Mean sojourn times were 6 months (A) and 4 years (B), respectively. Lines connect evaluations under ψ set equal to 20% (dark circles), 40% (medium circles), and 60% (light circles), assuming a constant rate of onset of preclinical cancer of $w = 0.0025$ per year and a sensitivity of screening to detect preclinical cancer of $\beta = 80\%$.

Bias due to model misspecification

Many published estimates of natural history and screening parameters have been derived on the basis of progressive models (i.e., $\psi = 0$). If the cancer in question is subject to a nonnegligible fraction of indolent preclinical cases, such model misspecification may lead to biased parameter estimates. Simulating natural histories with varying fractions of indolent tumors, we found that fitting a purely progressive model generally leads to substantial overestimation of both the incidence rate w and the MST among progressive cases, $1/\lambda$ (Figure 6). Overestimation of w results from the progressive model's attempt to fit an increased prevalence of preclinical cancers at the first screening (because of the presence of indolent tumors not accounted for by the model). Overestimation of the sojourn time in turn compensates for the inflated estimate of w when fitting the observed incidence of interval cases. Finally, all parameters exhibited minimal bias and standard error when the mixture model was applied to a purely progressive disease (Web Figures 1 and 2).

Parameter estimates for CNBSS-2

The mixture model yielded a good fit to the grouped data from the CNBSS-2 trial (goodness of fit: $P = 0.8$). Neither the fraction of indolent cancers nor the screening sensitivity

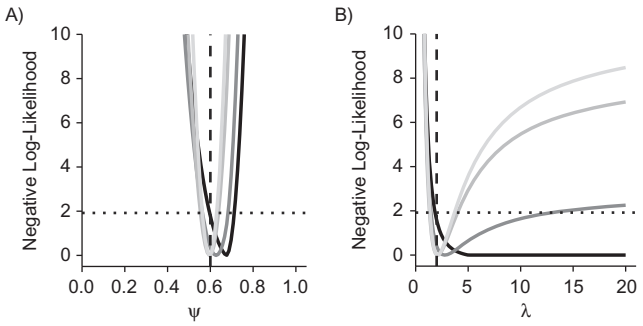

Figure 5. Identifiability of model parameters as a function of follow-up in a simulation study of stop-screen trials. The graph shows profile likelihoods of ψ (A) and λ (B) for representative realizations of the ψ = 60% scenario in Figure 3A. With 0 years of follow-up (black lines), λ is practically nonidentifiable. With 2 years of follow-up (dark gray lines), λ is practically identifiable but does not satisfy the requirements for adequately precise identification (API). With 4 and 6 years of follow-up (gray and light gray lines), λ clearly provides API. The remaining parameters β and *w* provide API under all follow-up scenarios considered (not shown). Simulation parameters are as follows: n = 50,000 trial participants, λ = 2, w = 0.0025, and β = 80%. Vertical dashed lines correspond to the true parameter values. The intersection of the relative negative log-likelihood with the horizontal dotted line indicates the 95% profile confidence interval.

provided API (Figure 7). With estimates of 0.0% (95% profile confidence interval (PCI): 0.0, 56.6) and 80.6% (95% PCI: 42.4, 100.0) for ψ and β, respectively, both had wide 95% profile confidence intervals. The imprecise estimate for ψ shows that the grouped data are not sufficiently rich to determine the fraction of indolent cancers. This lack of identifiability is further illustrated by examining the goodness of fit when constraining the model to a range of different positive fractions ψ of indolent cancers (Web Table 2). Indeed, even increasing ψ up to 40% does not change the goodness of fit substantially ($P = 0.6$).

With an estimate of 3.3 years (95% PCI: 1.4, 10.2), the MST provided borderline API, while the preclinical onset rate w was clearly API, with an estimate of 3.1×10^{-3} (95% PCI: 2.3×10^{-3}, 3.6×10^{-3}) per year. These estimates are consistent with values obtained by Shen and Zelen (15), who estimated a screening sensitivity of 78% for CNBSS-2 and an MST of 3.8 years under a progressive disease model. The slight discrepancy between their estimates and ours may be attributed to their assumption of a uniform rather than an exponential distribution for preclinical onset, in addition to the absence of an indolent fraction in their model.

Finally, we performed a sensitivity analysis for the above estimates with respect to the earliest average age of onset of preclinical disease (Web Table 3). Varying the latter between 35 years and 50 years led to slight variations in numerical parameter estimates but the same qualitative conclusions. Independent of the first average age of onset, the incidence of disease onset and the screening sensitivity continued to provide API; P values for the corresponding goodness of fit ranged from 0.3 to 1 for ages of onset of 35 years and 50 years, respectively.

DISCUSSION

We have presented an in-depth exploration of identifiability issues that arise when inferring disease natural histories from cancer screening studies. Our investigation was motivated by the problem of quantifying overdiagnosis in cancer and the recognition of weaknesses of methods based on excess incidence. On the basis of simulations and application to real-world data, we showed that adequately precise parameter estimation is not guaranteed in practice, even for a relatively simple model structure. Because more complex model extensions will naturally be less identifiable, our findings provide an important foundation for researchers inferring cancer natural histories using complex model designs.

By combining analytical and numerical techniques, we derived insights that have direct implications for model-based estimation

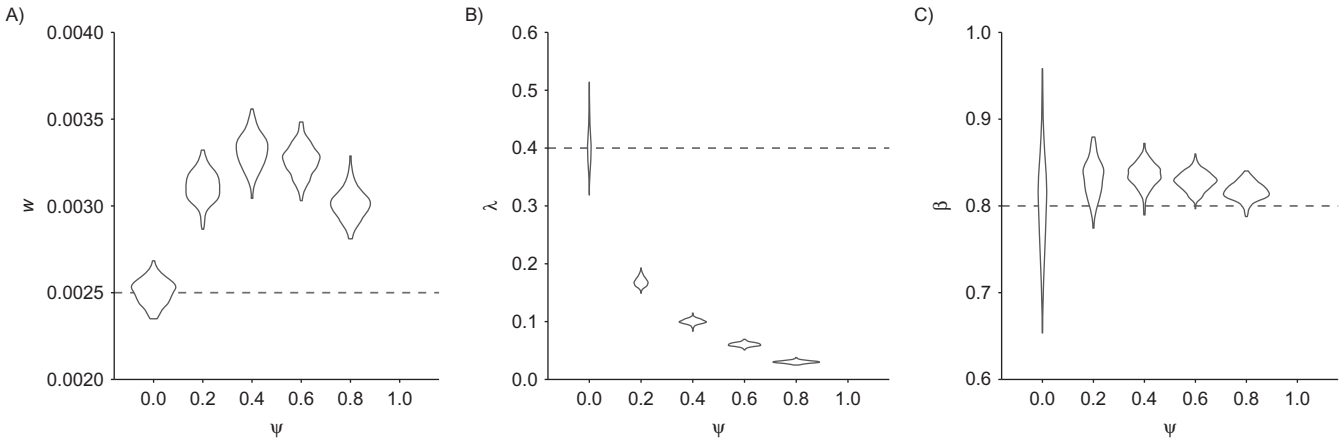

Figure 6. Model misspecification in a simulation study of stop-screen trials. The graph shows violin plots of maximum likelihood estimates for the parameters w (A), λ (B), and β (C) in a progressive model (i.e., one that assumes $\psi = 0$) fitted to data generated using a mixture model with selected values of $\psi \geq 0$, assuming that 50,000 women are screened annually at ages 50–54 years with follow-up to age 60 years and that the screening test has 80% sensitivity. Dashed horizontal lines indicate true parameter values. Results were based on 200 simulations per ψ value.

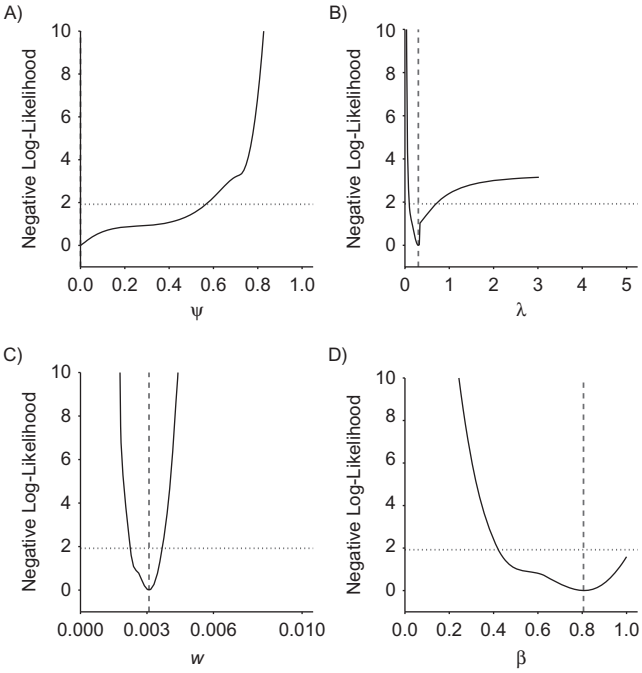

Figure 7. Profile likelihood for the parameters of a mixture model in an analysis of grouped data from Canadian National Breast Screening Study 2 (CNBSS-2), 1980–1985. The graph shows the relative negative log-likelihoods for the natural history parameters ψ (A), λ (B), *w* (C), and β (D) based on fitting of the mixture model to CNBSS-2 data (see also Web Table 1). Vertical dashed lines correspond to maximum likelihood estimates. The intersection of the relative negative log-likelihood with the horizontal dotted line indicates the 95% profile confidence interval.

of overdiagnosis rates from cancer screening trials. First, we formally proved that the mixture model is structurally identifiable. More precisely, given a sufficiently large number of trial participants, the model parameters can in theory be uniquely estimated from a single screening round with clinical follow-up. On the basis of simulation studies, we then demonstrated that in practice, identifiability and API of the model critically depend on both the underlying disease dynamics and the trial protocol, including the number of screenings and the duration of clinical follow-up after the last screening. In a mixture setting, natural histories with relatively short progressive sojourn times are more likely to be adequately identifiable than natural histories with long progressive sojourn times. To properly infer the tail behavior of the sojourn time distribution, the trial design needs to provide ample opportunity for interval case ascertainment and post-screening follow-up. Our simulation studies further suggest that increased follow-up after the last screening can compensate for a smaller number of screening rounds. This is a striking insight given that follow-up for clinical incidence is considerably less resource-intensive than recruiting trial participants for thousands of additional screenings.

Another key result with implications for the field concerns model misspecification. Natural history modeling has a long history in screening trials, but many published studies are based on the assumption that the disease is purely progressive. We found that for a mixture of progressive and indolent preclinical lesions, fitting a purely progressive disease model can lead to systematically biased estimates of MST, disease incidence rate, and screening sensitivity. These findings are aligned with the recent commentary emphasizing the need for mixture models when studying cancer overdiagnosis (1).

By definition, overdiagnosis occurs in patients who have nonprogressive lesions or who die from other causes before progression to a clinical state. Therefore, viable model-based estimation of overdiagnosis requires that the fraction of indolent tumors and the sojourn time distribution of progressive lesions be estimated with sufficient precision. Our findings suggest caution when applying mixture models to real data from screening studies for the purpose of overdiagnosis estimation. Awareness of the identifiability issue is critical, and we recommend that analyses be accompanied by a clear statement of all modeling assumptions and the presentation of profile likelihoods or other diagnostics as evidence for API (Figure 2).

In breast cancer, most published estimates of overdiagnosis bypass natural history modeling by directly estimating the excess incidence of cancers in screened cohorts compared with unscreened cohorts (3–6). Because the nonparametric excess incidence approach can lead to biased estimates of overdiagnosis (9), model-based approaches provide an attractive alternative, as long as the trial data are sufficiently rich to ensure API. For example, applying the mixture model to the CNBSS-2 data revealed that the fraction of indolent disease was not adequately precisely identifiable, indicating that more data were needed to draw reliable conclusions about the natural history of disease progression and the extent of overdiagnosis.

Identifiability poses an even bigger problem for more complex natural histories, such as the combination of in-situ and invasive cancers (12, 29). For complex models that remain analytically tractable, structural identifiability analyses such as those described here may be conducted, but they may be technically challenging. To the extent that a likelihood can be derived, practical identifiability analyses based on profile likelihoods are advised. For likelihood-free models (e.g., microsimulation models), practical identifiability can be explored using Bayesian methods (30). Furthermore, the analysis of constrained versions may provide guidance for the analysis of the full models. In the case of in-situ breast cancer, such simplifications could include specifying that all tumors go through the in-situ stage or assuming a known screening sensitivity (17). Irrespective of model complexity, identifiability should be verified or modifications to achieve identifiability should be made before making any inferences from the data.

Limitations of our approach include the fairly stringent parametric assumptions of exponential distributions for disease onset and progression. The latter can, in principle, be replaced with more flexible distributions as long as adequately precise verification can still be assured. Another limitation is the use of grouped trial data instead of individual screening histories. The advantage of this data configuration, which has previously been used for inference based on progressive models (15, 31), is that it is often readily available from published studies. While the resulting likelihood is relatively easy to construct, it assumes that persons who participate in the *k*th round of screening have participated in all prior rounds. This can be addressed by using an individual-level likelihood (32); however, the latter requires access to individual-level data. Finally, we

assumed a single screening sensitivity for indolent and progressive lesions. It is possible that this parameter depends on lesion type, and alternative parameterizations may be used (17, 33).

In conclusion, this work adds materially to the literature on the use of model-based approaches for estimating the natural history of disease progression as a precursor to quantifying overdiagnosis. Our findings confirm the potential for these methods to provide valuable insights into natural history and overdiagnosis in cancer screening programs. Most importantly, our approach highlights what types of data are needed for obtaining clinically relevant parameter estimates and provides insights into sources of bias under model misspecification. We conclude that application of a mixture natural history model to screening data should be accompanied by a thorough investigation of practical identifiability and an assurance that the model parameters can indeed be estimated from the available data.

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Web Materials for:

Identification of the Fraction of Indolent Tumors and Associated Overdiagnosis in Breast Cancer Screening Trials

Marc D. Ryser, Roman Gulati, Marisa C. Eisenberg, Yu Shen, E. Shelley Hwang, and Ruth B. Etzioni

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Web Appendix 1

In this section, we derive the likelihood function used for maximum likelihood estimation of the model parameters. Inference is performed in the stop-screen trial setting whereby the participants undergo a set number of screens and then are followed for clinical incidence after the last screen.

Model development and notation

Consider a cohort of individuals who undergo $J+1$ screens at times $t_0 < \ldots < t_J$, and let t_{J+1} denote the follow-up time after the last exam. In this setting, we can identify calendar time t with patient age. For the j-th screening round, we let n_j be the number of individuals undergoing the screen, s_j the number of screen-detected cancers, and r_j the number of clinically detected interval cancers diagnosed in the interval (t_j, t_{j+1}). Thus the summary data associated with the j-th interval are (n_j, s_j, r_j). Note that for the last screening round, we further dissect the follow up interval into L equally sized subintervals and denote the number of clinically detected cases in the l-th subinterval by r_J^l, i.e., $\sum_{l=1}^{L} r_J^l = r_J$. The reason for binning the data is that it simplifies computational aspects while providing more information than would be conveyed by the total number of follow up cases.

Organs are only at risk of preclinical disease after their developmental is completed, e.g., the risk of preclinical breast cancer is negligible before mammogenesis. Therefore, we assume that the rate of onset of preclinical disease becomes positive after age t^*, where $0 \leq t^* < t_0$. We denote by $w > 0$ the (constant) hazard rate for onset of preclinical disease after t^*, and denote by T the (random) age of onset of preclinical disease. Of note, the probability density function (pdf) of T is

$$\mathbb{P}(T \in [t, t+dt]) = \begin{cases} 0, & t \in [0, t^*], \\ we^{-w(t-t^*)}dt, & t > t^*. \end{cases} \tag{1}$$

To allow for a fraction of individuals with indolent cancers that will never progress to clinical disease, we consider a mixture distribution of sojourn times U from onset of preclinical disease to clinical disease,

$$\mathbb{P}(U > t) = \psi + (1-\psi)\mathbb{P}(U > t | U < \infty), \tag{2}$$

where ψ is the fraction of indolent cancers with infinite progression time. We assume that the sojourn time among progressive cases is exponentially distributed, i.e. $(U|U < \infty) \sim Exp(\lambda)$, with rate parameter $\lambda > 0$. We denote by Q and q the survival function and probability density

function (pdf) of U, and by Q_1 and q_1 the survival function and pdf of U conditioned on progression, $U|U < \infty$. Finally, let β be the sensitivity of the screening exam, assumed to be equal for progressive and indolent preclinical disease.

In summary, the four model parameters are $\theta := (w, \psi, \lambda, \beta)$, and the data used for inference of θ is grouped as (n_j, s_j, r_j). To prepare the likelihood function, we first need to calculate two key probabilities, namely the probability $D_j(\theta)$ of screen-detected preclinical disease at screen j, and the probability $I_j(\theta)$ of interval detected clinical cancer between screens j and $j+1$. The latter will be treated in two separate sections for $j = 0, 1, \ldots, J-1$ and $j = J$, respectively.

$D_j(\theta)$: screen-detected preclinical disease at screen t_j

We start with $D_0(\theta)$, the probability to find preclinical disease at the baseline screen. We note that for this to happen, we need (i) $T \in [0, t_0]$, (ii) $T+U > t_0$, and (iii) and a true-positive baseline screen. More precisely,

$$\begin{aligned} D_0(\theta) = \beta\, \mathbb{P}(T < t_0, T+U > t_0) &= \beta \int_0^\infty \mathbb{P}(T < t_0, T+U > t_0 | T = t)\mathbb{P}(T = t)dt \\ &= \beta \int_{t^*}^{t_0} \mathbb{P}(U > t_0 - t)\mathbb{P}(T = t)dt \\ &= \beta\, w \int_{t^*}^{t_0} e^{-w(t-t^*)} Q(t_0 - t)dt, \end{aligned} \tag{3}$$

where we recall that Q is the survival function of U. Applying a similar reasoning to subsequent screens, we easily derive a general expression by summing contributions from all intervals preceding t_j (with the convention that $t_{-1} := t^*$)

$$D_j(\theta) = \beta\, w \sum_{k=0}^{j} (1-\beta)^{j-k} \int_{t_{k-1}}^{t_k} e^{-w(s-t^*)} Q(t_j - s)ds, \qquad j = 0, 1, 2, \ldots, J \tag{4}$$

$I_j(\theta)$: clinical disease in interval (t_j, t_{j+1})

We first calculate $I_0(\theta)$, the probability of a clinically detected interval cancer in (t_0, t_1). There are two contributions to $I_0(\theta)$. (i) The first contribution stems from preclinical tumors arising in $[t^*, t_0)$ that go undetected at the first screen and then progress to clinical disease in (t_0, t_1). Since the first screen is false-negative with probability $1-\beta$ and the lesion is progressive with probability

$1-\psi$, we find the following contribution (recall that q_1 is the pdf of $U \,|\, U<\infty$),

$$\begin{aligned}(1-\beta)\mathbb{P}(T<t_0, t_0<T+U<t_1) &= (1-\beta)\int_{t^*}^{t_0}\mathbb{P}(t_0-t<U<t_1-t)\mathbb{P}(T=t)dt \\ &= w\,(1-\beta)(1-\psi)\int_{t^*}^{t_0} e^{-w(t-t^*)}\int_{t_0-t}^{t_1-t} q_1(s)dsdt \\ &= w\,(1-\beta)(1-\psi)\int_{t^*}^{t_0} e^{-w(t-t^*)}\int_{t_0}^{t_1} q_1(s-t)dsdt.\end{aligned} \tag{5}$$

(ii) The second contribution is from preclinical tumors that appear after t_0 and progress before t_1,

$$\begin{aligned}\mathbb{P}(T>t_0, U+T<t_1) =& \int_{t_0}^{t_1}\mathbb{P}(U<t_1-t)\mathbb{P}(T=t)dt \\ =& w\,(1-\psi)\int_{t_0}^{t_1} e^{-wt}\int_{0}^{t_1-t} q_1(s)dsdt \\ =& w\,(1-\psi)\int_{t_0}^{t_1} e^{-w(t-t^*)}\int_{t}^{t_1} q_1(s-t)dsdt.\end{aligned} \tag{6}$$

Combining the two contributions (5) and (6) to get

$$I_0(\theta) = (1-\psi)\,w\,\left[(1-\beta)\int_{t^*}^{t_0} e^{-w(t-t^*)}\left(\int_{t_0}^{t_1} q_1(s-t)ds\right)dt + \int_{t_0}^{t_1} e^{-w(t-t^*)}\left(\int_{t}^{t_1} q_1(s-t)ds\right)dt\right]. \tag{7}$$

Next, we extend this formula to $I_j(\theta)$, for $j=0,1,\dots J-1$, by considering the same contributions (i) and (ii) as above (the case $j=J$ will be treated separately below). (i) The first contribution comes from preclinical progressive lesions that arise in the interval (t_{k-1},t_k) for $k=0,\dots,j$, are missed on all subsequent screens at $t_k,\dots,t_j$, and then progress to clinical disease in $[t_j,t_{j+1}]$,

$$\begin{aligned}&(1-\beta)^{j-k+1}\,\mathbb{P}(t_{k-1}<T<t_k, t_j<T+U<t_{j+1}) \\ =\,&(1-\beta)^{j-k+1}\int_{t_{k-1}}^{t_k}\mathbb{P}(t_j-t<U<t_{j+1}-t)\mathbb{P}(T=t)dt \\ =\,&(1-\psi)(1-\beta)^{j-k+1}\,w\int_{t_{k-1}}^{t_k} e^{-w(t-t^*)}\left(\int_{t_j}^{t_{j+1}} q_1(s-t)ds\right)dt.\end{aligned} \tag{8}$$

(ii) For the second contribution, consider progressive lesions that arise after t_j and progress to clinical before t_{j+1}. Similarly to above calculation for I_0, we find that this contribution is given by

$$(1-\psi)w\int_{t_j}^{t_{j+1}} e^{-w(t-t^*)}\left(\int_{t}^{t_{j+1}} q_1(s-t)ds\right)dt. \tag{9}$$

Summa summarum, we find for $j = 0, 1, \ldots, J-1$,

$$\begin{aligned} I_j(\theta) =&(1-\psi)\, w \sum_{k=0}^{j}(1-\beta)^{j-k+1} \int_{t_{k-1}}^{t_k} e^{-w(t-t^*)} \left(\int_{t_j}^{t_{j+1}} q_1(s-t)ds \right) dt + \ldots \\ &\ldots (1-\psi) w \int_{t_j}^{t_{j+1}} e^{-w(t-t^*)} \left(\int_{t}^{t_{j+1}} q_1(s-t)ds \right) dt. \end{aligned} \tag{10}$$

$I_J^l(\theta)$: clinical disease after last screen

After the last screen at age t_J, enrolled individuals are followed for clinical disease until t_{J+1}. In keeping with the grouped data approach used for the screening rounds, we dissect the interval (t_J, t_{J+1}) into L equally spaced subintervals and calculate the corresponding probabilities $I_J^l(\theta)$ of a clinical diagnosis during the l-th follow-up interval. To keep notation at a minimum, we assume here that $t_{J+1} - t_J = L$, such that each subinterval has unit length (using units of years is thus convenient). After some algebra, we find

$$\begin{aligned} I_J^l(\theta) =&w(1-\psi) \sum_{k=0}^{J}(1-\beta)^{J-k+1} \int_{t_{k-1}}^{t_k} e^{-w(t-t^*)} \int_{t_J+l-1}^{t_J+l} q_1(s-t)dsdt \ldots \\ &\ldots + w(1-\psi) \int_{t_J}^{t_J+l} e^{-w(t-t^*)} \int_{(t_J+l-1)\vee t}^{t_J+l} q_1(s-t)dsdt, \end{aligned} \tag{11}$$

where $a \vee b := max(a, b)$.

Likelihood

Before we can assemble the above terms into the likelihood function, we have to account for the fact that only asymptomatic individuals are eligible to enter a new screening round. Because we treat the screening rounds independently, this means that for each screening round, we have to condition on not having been diagnosed prior to the screen in question. By Bayes' rule, the conditioning corresponds to adjustment of $D_j(\theta)$ and $I_j(\theta)$ as

$$D_j^c(\theta) := D_j(\theta)/\xi_j(\theta), \qquad I_j^c(\theta) := I_j(\theta)/\xi_j(\theta), \qquad j = 0, \ldots, J-1, \tag{12}$$

where $\xi_j(\theta)$ is the probability that an individual has not yet been diagnosed with preclinical or clinical disease upon entering the j-th screening round at t_j. Similarly, for the last screening round with clinical follow up we have

$$D_J^c(\theta) := D_J(\theta)/\xi_J(\theta), \qquad I_J^{l,c}(\theta) := I_J^l(\theta)/\xi_J(\theta). \tag{13}$$

Next, we need to calculate the $\xi_j(\theta)$. For the first screening round at t_0, we have $\xi_0(\theta) = \mathbb{P}(T+U > t_0)$. After some algebra, we find

$$\xi_0(\theta) = \mathbb{P}(T + U > t_0) = \psi + (1 - \psi)\left[e^{-w(t_0-t^*)} + \frac{w}{\lambda - w}\left(e^{-w(t_0-t^*)} - e^{-\lambda(t_0-t^*)}\right)\right]. \tag{14}$$

For all subsequent screens, we have the general expression

$$\xi_j(\theta) = \xi_0(\theta) - \sum_{k=0}^{j-1}\left(D_k(\theta) + I_k(\theta)\right) \tag{15}$$

At last, we can now assemble the likelihood. From the first J screening rounds, we have trinomial contributions to the log-likelihood function proportional to

$$l^{(i)}(\theta) \sim \sum_{j=0}^{J-1} s_j \log D_j^c(\theta) + r_j \log I_j^c(\theta) + (n_j - r_j - s_j)\log(1 - D_j^c(\theta) - I_j^c(\theta)). \tag{16}$$

reflecting the three possible events per individual: either a preclinical cancer is screen-detected, an interval cancer is diagnosed before the subsequent screen, or no cancer (screen-detected or clinical) is diagnosed before the next screen. For the last screen at t_J, we have to account for the clinical follow up incidence (see previous section). The corresponding multinomial contribution to the log-likelihood function is

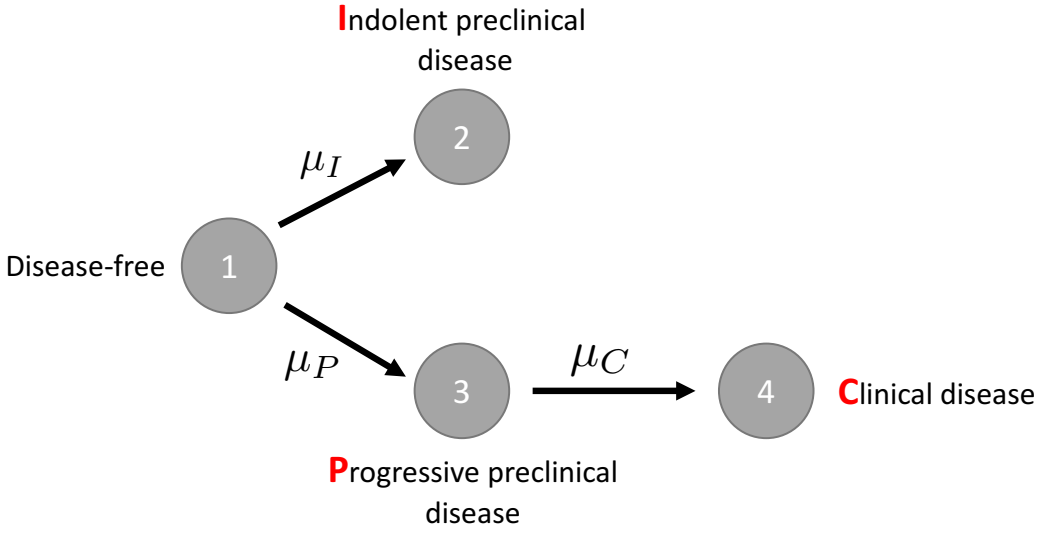
$$l^{(ii)}(\theta) \sim s_J \log D_J^c(\theta) + \sum_{l=1}^{L} r_J^l \log I_J^{l,c} + \left(n_J - s_J - \sum_{l=1}^{L} r_J^l\right)\log\left[1 - D_J^c(\theta) - \sum_{l=1}^{L} I_J^{l,c}(\theta)\right]. \tag{17}$$

Finally, the complete log-likelihood is given by

$$l(\theta) = l^{(i)}(\theta) + l^{(ii)}(\theta). \tag{18}$$

Web Appendix 2

In this section, we discuss structural identifiability of the natural history model as shown in the panel below.



Natural history model. Disease-free (1) individuals develop an indolent preclinical lesion (2) at rate μ_I, and a progressive preclinical lesion (3) at rate μ_P. Once in state (3), the lesion becomes clinically detectable (4) at rate μ_C.

Preliminaries

Before we address the specific problem at hand, we introduce the notion of structural identifiability. We largely follow [1, 2] and refer the reader to these references for a more detailed treatise of the problem. We start by considering an ordinary differential equation (ODE) model of the type

$$\begin{cases} \dot{\mathbf{x}} = & f(\mathbf{x}, t, \mathbf{p}), \quad \mathbf{x}(\mathbf{0}) = \mathbf{x_0}, \\ \mathbf{y} = & g(\mathbf{x}, \mathbf{p}), \end{cases} \tag{19}$$

where $\mathbf{x}$ is a vector of variables, $\mathbf{p}$ is a vector of model parameters, and $\mathbf{y}$ is a measurable model output. We start with two definitions.

Definition 0.1 (Structural identifiability)**.** *For a model of type* (19)*, an individual parameter p is globally structurally identifiable if for almost every value $\mathbf{p}^*$ and almost all initial conditions, the equation $\mathbf{y}(\mathbf{x}, \mathbf{t}, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, \mathbf{t}, \mathbf{p})$ implies $p = p^*$. A parameter p is said to be locally structurally identifiable if for almost any $\mathbf{p}^*$ and almost all initial conditions, the equation $\mathbf{y}(\mathbf{x}, \mathbf{t}, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, \mathbf{t}, \mathbf{p})$ implies that p has a finite number of solutions.*

Definition 0.2 (Input-output equation)**.** *An input-output equation for an ODE model of type* (19) *is a monic polynomial equation in* $\mathbf{y}$ *and its derivatives only. Thereby, the terms are ordered as* $\mathbf{y} < \dot{\mathbf{y}} < \ddot{\mathbf{y}} < \ldots$*, such that the highest derivative with a non-zero coefficient is the leading term of the polynomial equation.*

Our proof of structural identifiability will rest on the following result, see Theorem 4.1 in [Eisenberg]

Theorem 0.1. *The parameters of a rational function ODE model of type* (19) *are globally (respectively locally) structurally identifiable if and only if the map* $\mathbf{c}(\mathbf{p})$ *from the parameters to the coefficients of a set of input-output equations is injective (respectively, the fibers contain finitely many elements), regardless of how the input-output equations are generated.*

To make use of these results we need to reformulate our model accordingly. First, we introduce two competing progression events from disease-free to indolent disease, and from disease-free to progressive pre-clinical disease, with rates μ_I and μ_P, respectively. Note that the fraction of indolent cancers ψ used in the original model formulation corresponds to the ratio $\psi = \mu_I/(\mu_I + \mu_P)$. To use the formalism of Markov branching processes, we introduce the state indicator functions $Y_i(t) = \mathbf{1}_{\{\text{patient in state } i\}}(t)$, where the states $i = 1, 2, 3, 4$ are defined as in the panel at the beginning of the web appendix.

Next, we cast the evolution of the Markov model in an ODE framework by deriving the backward Kolmogorov equations. First, we introduce the probability generating functions

$$\Phi_1(y_1, y_2, y_3, y_4; \tau, t) = \mathbb{E}\left(y_1^{Y_1(t)} y_2^{Y_2(t)} y_3^{Y_3(t)} y_4^{Y_4(t)} | Y_1(\tau) = 1, Y_2(\tau) = 0, Y_3(\tau) = 0, Y_4(\tau) = 0\right),$$

and similarly for Φ_2, Φ_3 and Φ_4. The backward Kolmogorov equations for this problem are easily derived as

$$\begin{cases} \frac{\partial \Phi_1}{\partial \tau} = & (\mu_I + \mu_P)\,\Phi_1 - \mu_I \Phi_2 - \mu_P \Phi_3 \\ \frac{\partial \Phi_2}{\partial \tau} = & 0 \\ \frac{\partial \Phi_3}{\partial \tau} = & -\mu_C\,(\Phi_4 - \Phi_3) \\ \frac{\partial \Phi_4}{\partial \tau} = & 0, \end{cases} \tag{20}$$

with initial conditions

$$\Phi_i(y_1, y_2, y_3, y_4; t, t) = y_i,$$

where y_i is the probability that the patient is in state i at time $t = 0$. We can now state and prove the main result.

Main Result

Theorem 0.2 (Structural identifiability.)**.** *Consider the cancer progression model shown at the beginning of the web appendix and such that $\mu_I + \mu_P < \mu_C$. We assume a screening sensitivity β for preclinical lesions, and let $0 \leq t_1 < t_2 < \infty$. If perfect data is available for a single screen at time t_1 and clinical incidence during the subsequent interval $[t_1, t_2]$, then the four model parameters $(\mu_I, \mu_P, \mu_C, \beta)$ are globally structurally identifiable.*

Remark 0.3. *Note that the assumption $\mu_I + \mu_P \leq \mu_C$ is invariably satisfied in cancer screening: the incidence rate of preclinical disease (progressive or indolent) is much lower than the rate of progression to invasive disease among progressive cases. Indeed, the former is usually of the order of 10^{-4} to 10^{-3} and the latter is of the order of 10^{-1} to 10^{0}.*

Proof of Theorem 0.2. We first derive the input-output equations for screening and clinical incidence, respectively, and then combine them to conclude.

Clinical incidence. We denote by T the time of arrival (possibly infinite) in the clinical disease compartment. It follows that the survival function $S(t) := \mathbb{P}(T > t)$ can be expressed as

$$\begin{aligned} S(t) &= \sum_{(l_1,l_2,l_3,0)} \mathbb{P}(Y_1(t) = l_1, Y_2(t) = l_2, Y_3(t) = l_3, Y_4(t) = 0 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1) = \\ &= \sum_{(l_1,l_2,l_3,l_4)} \mathbb{P}(Y_1(t) = l_1, Y_2(t) = l_2, Y_3(t) = l_3, Y_4(t) = l_4 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1)\, 1^{l_1}\, 1^{l_2}\, 1^{l_3}\, 0^{l_4} \\ &= \mathbb{E}\left(1^{Y_1(t)}\, 1^{Y_2(t)}\, 1^{Y_3(t)}\, 0^{Y_4(t)} | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1\right) \\ &= \Phi_1(1, 1, 1, 0; 0, t). \end{aligned} \tag{21}$$

Therefore, if we set $x(s) := \Phi_1(1, 1, 1, 0; t-s, t)$, then $x(t) = S(t)$ is the survival function. Similarly, we define $x_i(s) := \Phi_i(1, 1, 1, 0; t - s, t)$ for $i = 2, 3, 4$. Substituting the latter into (20) we find that x and x_3 satisfy the equation

$$\begin{cases} \dot{x}(s) = & -(\mu_I + \mu_P)\, x + \mu_I + \mu_P x_3, \qquad x(0) = 1, \\ \dot{x}_3(s) = & -\mu_C x_3, \qquad x_3(0) = 1. \end{cases} \tag{22}$$

If the transition rates are constant, we solve the first equation in (22) for x_3 and use the expression

and its derivative in the second equation to solve for x to obtain the input-output equation,

$$\begin{cases} \ddot{x} + \dot{x}\left[\mu_I + \mu_P + \mu_C\right] + x\left[\mu_C(\mu_I + \mu_P)\right] - \left[\mu_C \mu_I\right] = 0, \\ x(0) = 1, \qquad \dot{x}(0) = 0, \end{cases} \tag{23}$$

where the left-hand side is a monic polynomial in $\ddot{x}$, $\dot{x}$, x and 1.

Screening. Screening observes, with screening sensitivity β, whether the system is in either the preclinical indolent or the preclinical progressive state. Therefore, screening measures

$$\begin{aligned} w(t) &:= \beta\ \mathbb{P}(Y_2(t) + Y_3(t) = 1 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1) \\ &= \beta\ \left(1 - \mathbb{P}(Y_2(t) + Y_3(t) = 0 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1)\right). \end{aligned}$$

We find that

$$\begin{aligned} &\mathbb{P}(Y_2(t) + Y_3(t) = 0 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1) \\ &= \sum_{(i_1,k,l,i_4)} \mathbb{P}(Y_1(t) = i_1, Y_2(t) = k, Y_3(t) = l, Y_4(t) = i_4 | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1) 1^{i_4} 0^k 0^l 1^{i_4} \\ &= \mathbb{E}\left(1^{Y_1(t)} 0^{Y_2(t)} 0^{Y_3(t)} 1^{Y_4(t)} | Y_1(0) = 1, Y_i(0) = 0, \forall i > 1\right) \\ &= \Phi_1(1, 0, 0, 1; 0, t). \end{aligned}$$

We define now $z(s) = \Phi_1(1, 0, 0, 1; t - s, t)$ and accordingly $z_k(s) = \Phi_k(1, 0, 0, 1; t - s, t)$, for $k = 1, 2, 3$. It follows that $w(t) = \beta\,(1 - z(t))$. Substituting $z(s)$ and $z_k(s)$ into the backward Kolmogorov equation (20) we obtain

$$\begin{cases} \dot{z} = & -(\mu_I + \mu_P) z + \mu_P z_3, \quad z(0) = 1, \\ \dot{z}_3 = & \mu_c(1 - z_3), \quad z_3(0) = 0 \\ w = & \beta(1 - z), \quad w(0) = 0. \end{cases} \tag{24}$$

From here, we derive the input-output equation for w as a monic polynomial in the observable variable w and its derivatives,

$$\begin{cases} \ddot{w} + \dot{w}\left[\mu_I + \mu_P + \mu_C\right] + w\left[\mu_C(\mu_I + \mu_P)\right] - \left[\beta \mu_C \mu_I\right] = 0, \\ w(0) = 0, \quad \dot{w}(0) = \beta(\mu_I + \mu_P). \end{cases} \tag{25}$$

Conclusion. Under full observation of the trajectory of clinical incidence, $\{x(t) : t \geq 0\}$, Theorem 0.1 asserts that the coefficients of the ODE are uniquely determined, and hence the uniquely

identifiable parameter combinations are

$$\mu_I + \mu_P + \mu_C, \qquad \mu_C(\mu_I + \mu_P), \qquad \mu_C\mu_I. \tag{26}$$

Therefore, based on our assumption that $\mu_I + \mu_P < \mu_C$, all three parameters occurring in (27) are uniquely identifiable. In the case of a interval-censored observation, $\{x(t) : t \in [t_1, t_2]\}$, we can exploit properties of second-order linear ODEs to show that measuring the interval-censored trajectory still leads to uniquely identifiable parameters. It remains to identify β, which we can do based on information from screening, see input-output equation (25). Because we have already identified μ_I, μ_P, μ_C from clinical incidence information, inspection of the explicit solution to (25) reveals that a single measurement of $w(t_1)$ at $t_1 > 0$ is sufficient to determine β. In conclusion, all four parameters are globally identifiable. □

Remark 0.4. *Regarding screening, see input-output equation* (25)*, we note that based on the observation of the full trajectory including the initial condition, Theorem 0.1 states that the following parameter combinations are globally identifiable:*

$$\mu_I + \mu_P + \mu_C, \qquad \mu_C(\mu_I + \mu_P), \qquad \beta\mu_C\mu_I, \qquad \beta(\mu_I + \mu_P). \tag{27}$$

It is straight-forward to verify that the mapping from $(\mu_I, \mu_C, \mu_P, \beta)$ to the above combinations is one-to-one given that $\mu_I + \mu_P < \mu_C$.

Web Table 1

Screening round	No. of women	Screen-detected cases	Interval-detected cases
1	19711	142	15
2	17669	66	10
3	17347	43	9
4	17193	54	9
5	9876	28	5

CNBSS-2. Grouped data from the Canadian Breast Cancer Screening Study-2 [3]. "No. of women" is the number of women who attended all screening rounds up to and including the current round.

Web Table 2

ψ	$\hat{\lambda}$	95% CI	$\hat{w}$	95% CI	$\hat{\beta}$	95% CI	χ^2	P-value
0.00	0.30	0.10-0.47	0.0031	0.0023-0.0036	0.81	0.44- NA	6.20	0.7984
0.05	0.30	0.09-0.48	0.0029	0.0023-0.0034	0.75	0.41-0.96	7.03	0.7226
0.10	0.28	0.09-0.48	0.0028	0.0023-0.0032	0.69	0.40-0.90	7.74	0.6546
0.20	0.26	0.11-0.48	0.0026	0.0022-0.0030	0.59	0.39-0.79	8.23	0.6061
0.40	0.34	0.16-0.62	0.0024	0.0022-0.0027	0.51	0.38-0.64	8.39	0.5905

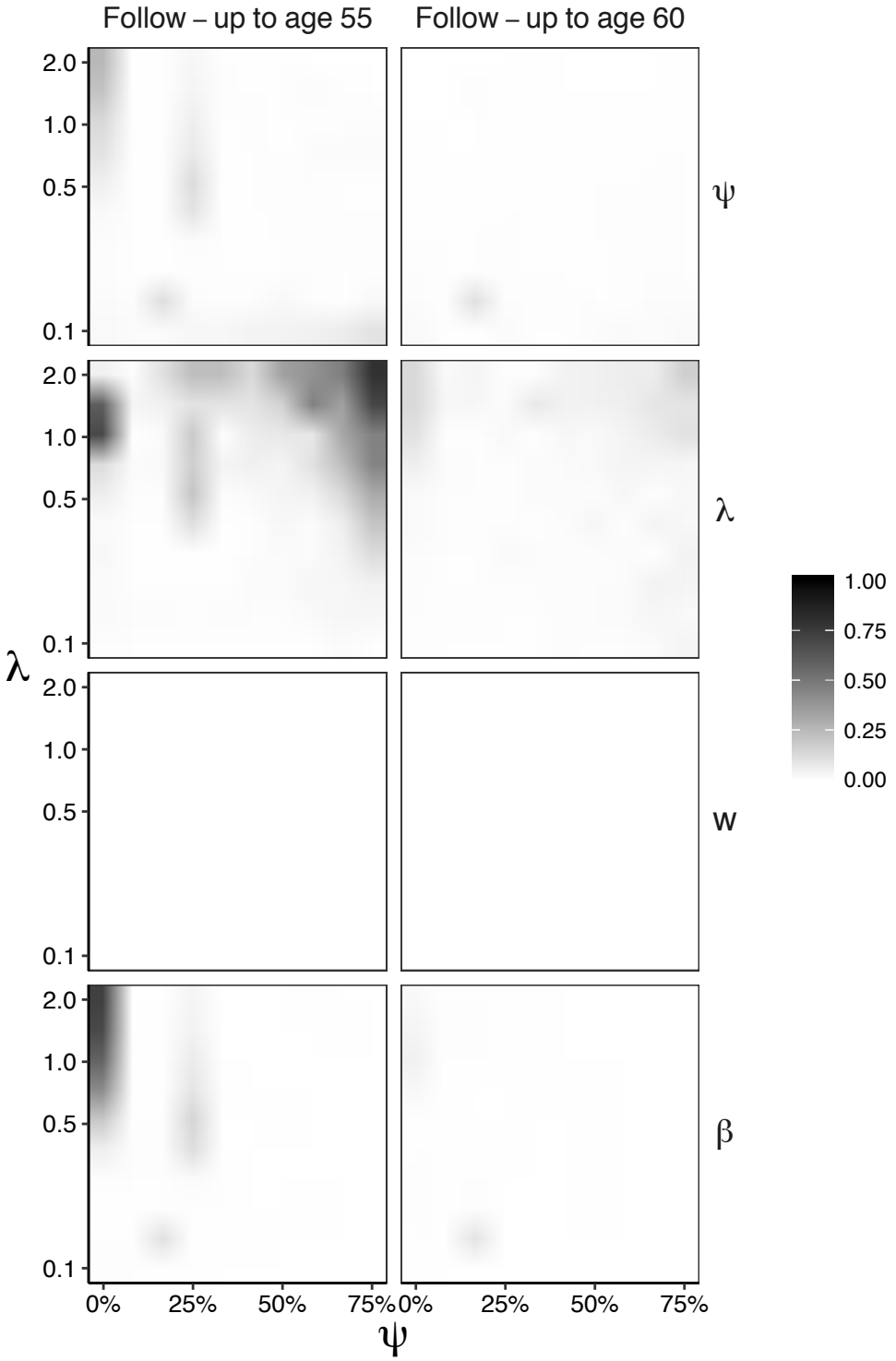
CNBSS-2: Parameter estimation and goodness of fit for constrained mixture model. The mixture model with fixed fraction of indolent cancers ψ is fit to the CNBSS-2 data (see Web Table 1). Onset of preclinical disease is assumed to be negligible before age $\Delta_0 = 45$ years.

Web Table 3

Δ_0	$\hat{\psi}$	95% CI	$\hat{\lambda}$	95% CI	$\hat{w}$	95% CI	$\hat{\beta}$	95% CI	χ^2	P-value
35	0.30	NA-0.56	0.25	0.05- NA	0.0019	0.0016-0.0040	0.40	0.29- NA	12.10	0.2782
40	0.32	NA-0.64	0.26	0.06- NA	0.0021	0.0018-0.0039	0.44	0.32- NA	10.92	0.3634
45	0.00	NA-0.57	0.30	0.10-0.69	0.0031	0.0023-0.0036	0.81	0.42- NA	6.20	0.7984
50	0.00	NA-0.74	0.23	0.12- NA	0.0032	0.0029-0.0036	0.76	0.58-0.96	2.20	0.9946

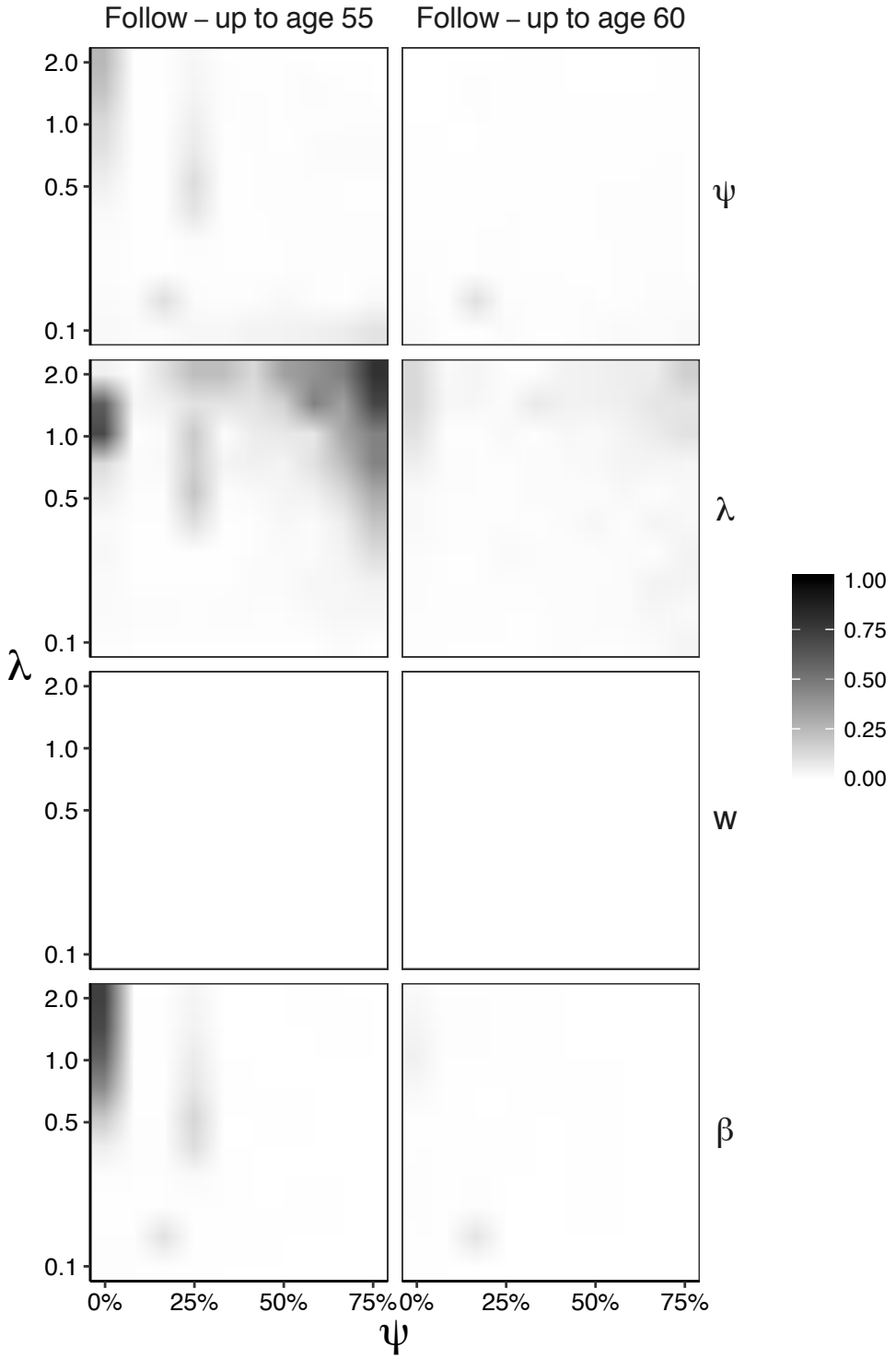
CNBSS-2: Parameter estimation and goodness of fit for varying onset ages. The mixture model is fit to the CNBSS-2 data (see Web Table 1) for varying ages of first possible onset of preclinical disease.

Web Figure 1



Sensitivity of bias to follow up. Absolute bias for all four model parameters assuming 50,000 women were screened annually at ages 50–54 years with follow-up to age 55 years (left column) and age 60 years (right column). Screening test sensitivity was set to $\beta = 80\%$.

Web Figure 2



Sensitivity of the standard error to follow up. Standard errors for all four model parameters assuming 50,000 women were screened annually at ages 50–54 years with follow-up to age 55 years (left column) and age 60 years (right column). Screening test sensitivity was set to $\beta = 80\%$.

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