A Potential Error in Evaluating Cancer Screening: A Comparison of 2 Approaches for Modeling Underlying Disease Progression

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Background. *Evaluating cancer screening often requires modeling the underlying disease process and not observed disease, particularly in the absence of direct evidence linking screening to a survival benefit.* ***Methods.*** *To illustrate a potential error in modeling disease progression among healthy persons with a history of a precancerous lesion, we constructed 2 models with 4 basic health states (disease free, presence of a precancerous lesion, presence of cancer, dead), calibrated to predict the same 10-year cancer incidence. We assumed a homogeneous cohort enters each model free of disease, the probability of developing a precancerous lesion was greater for patients with a history of a prior lesion, and the screening test was perfect and riskless. In one model, we assigned a higher transition probability from a precancerous lesion to cancer in those with a history of a previously removed lesion; in the other, we assumed it was equal to those with no history.* ***Results.*** *Using the 1st model, life expectancy without screening was 2.4 months longer than with screening. This error did not occur using the 2nd model, in which the transition from precancerous lesions to cancer was not conditional on a history of a lesion. This modeling error's magnitude was examined under a variety of assumptions.* ***Conclusions.*** *We have identified an important error to avoid when modeling the underlying disease process in evaluating screening programs for cancers associated with precancerous states.* ***Key words:*** *model errors; cancer screening; Markov models.* ***(Med Decis Making 2003;23:232–241)***

Randomized, controlled trials provide the most valid estimate of cancer-screening efficacy in that they adjust for both known and unknown confounding variables.[1] However, the randomized controlled trial, despite its strengths, also has several economic and practical difficulties.[2] First, the magnitude of the typical population health gain achieved by a cancer-screening program is small because only a small proportion of the population is at risk for the disease and able to realize a screening benefit.[3] In cases in which screening detects early precursor lesions, such as dysplasia in the cervix or adenomatous polyps in the colon, several decades of observation might be necessary from the time of initiating a screening program to when an effect on cancer incidence would be measurable. Thus, clinical trials to evaluate a cancer-screening program require large sample sizes and long followup times. Second, a randomized, controlled trial of screening is not always considered an acceptable alternative if screening already is widely accepted as a standard of care. Because both clinical decisions for individuals and broader public policy decisions must proceed before all uncertainties are resolved, decision-analytic models are in-

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creasingly being used as tools to evaluate the benefits of preventive interventions such as cancer-screening programs, for which the availability of direct data linking screening to a population survival benefit is limited.

The goal of most cancer-screening interventions is to detect cancer at an earlier and presumably more treatable stage of disease. Another goal, achievable only with screening for certain types of cancers (e.g., cervical cancer or colorectal cancer), is the detection and removal of precancerous conditions (e.g., cervical lesions, adenomatous polyps of the colon or rectum). Typically, in the absence of direct evidence linking screening to a survival benefit, evaluating cancer screening requires modeling the underlying disease process instead of the observed disease. Such models can also be used to simulate the interruption of natural history by the detection and removal of the precancerous entity.

The data available to derive the estimates for the transition probabilities in these models are often from heterogeneous populations, but we do not always know the underlying or distinguishing risk factors that characterize the heterogeneity. In the absence of detailed information on the nature of the heterogeneity, we assume a homogeneous population when these data are incorporated into Markov models. We have identified an error that may be made when modeling the underlying disease process in decision-analytic models for evaluating cancer-screening programs. This analysis was motivated by our prior work in the areas of cervical cancer, anal cancer, and colorectal cancer screening.[4–7]

METHODS

We first describe a general framework for structuring and parameterizing a model of the natural history of a cancer that is characterized as having detectable, asymptomatic, and treatable precancerous health states. For example, in the case of colorectal cancer, the precancerous states would represent the presence of adenomatous polyps. In the case of cervical cancer, the precancerous states would represent the presence of cervical squamous intraepithelial lesions. Although the terminology, biology, natural history, and specific treatments will vary among different types of cancer, we use a generic structure for our model and refer to all precancerous entities as "precancerous lesions" for simplicity. We present a simplified version of this general model to focus our investigation on the disease progression among persons who are disease free after the removal of a precancerous lesion.

Natural History Model

The general format of a natural history model consists of health states defined to reflect the general categories of absence of disease, presence of a precancerous lesion, and presence of invasive cancer. Health states reflecting a precancerous lesion may be further stratified to reflect the grade, histology, or size of the lesions. Health states reflecting invasive cancer are generally stratified to distinguish the stage of cancer and whether it is detected (and therefore treated) or not. In our simplified model, we assume that there is only 1 precancerous state and 1 invasive cancer state. A homogeneous cohort enters the model free of disease. Individuals face a monthly probability of developing a precancerous lesion, and those with established precancerous lesions face a monthly risk for developing invasive cancer.

Complete information on all transition probabilities required for a natural history model of cancer is never available. In particular, the following probabilities can be difficult to obtain: (1) the probability of progressing from a precancerous lesion to invasive cancer, (2) the probabilities reflecting progression from earlier to later stages of cancer, and (3) the probabilities of stage-specific symptom detection. For example, to conduct a study to assess the annual probability of progression from an identified precancerous lesion to invasive cancer would be unethical, particularly for higher risk lesions. On the other hand, information is generally available on the incidence of diagnosed invasive cancer in an unscreened or partially screened population using cancer registries. In such a situation, after incorporating the data that are directly available, one may derive the progression rate of a precancerous lesion to cancer, cancer stage sojourn times, and symptom detection rates by calibrating the model to the observed incidence and stage distribution of diagnosed invasive cancer.[8,9]

Screening Model

If a screening program is in place, then there is a chance that an individual with a precancerous lesion would be detected during a screening month on the basis of the sensitivity of the screening test for detecting precancerous lesions. In the case of a true-positive screening test result, the individual is treated and has the precancerous lesion removed. The individual then returns to a disease-free health state. A 2nd and unique disease-free health state is created for individuals with

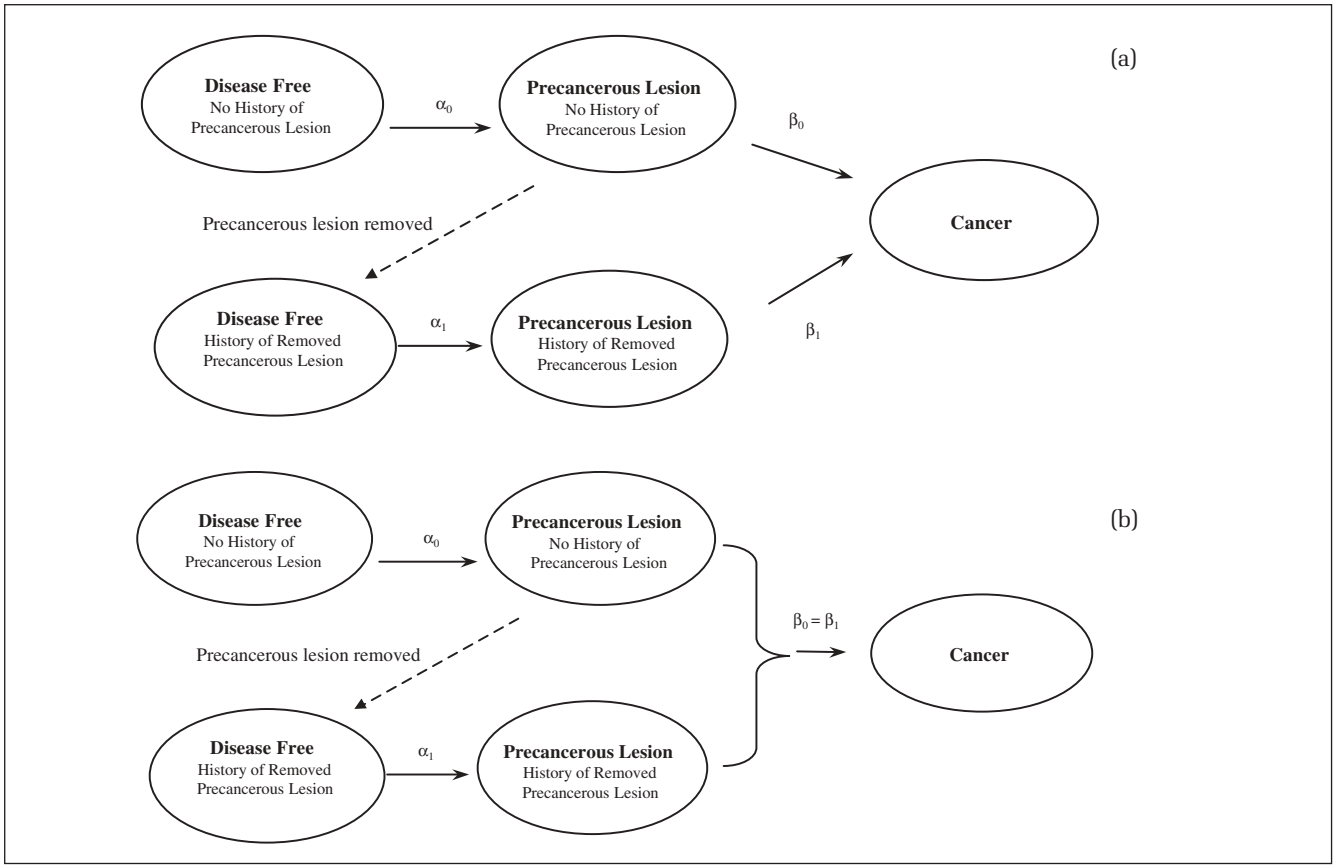

Figure 1 The 2 simple screening models have 3 basic live health states: (1) disease free, (2) presence of a precancerous lesion, and (3) presence of cancer. In MODEL 1 (a) and MODEL 2 (b), we assumed that the probability of developing a precancerous lesion was greater among individuals with a history of a previously removed precancerous lesion (α_1) compared to persons without a prior abnormality (α_0). In MODEL 1 (a), we also assumed that the transition from a precancerous lesion to invasive cancer was greater for persons with a history of a removed precancerous lesion than for persons without such a history ($\beta_1 > \beta_0$). In contrast, in MODEL 2 (b), we assumed that the transition from a precancerous lesion to invasive cancer for persons with a history of a removed precancerous lesion was equal to the transition for persons without such a history ($\beta_1 = \beta_0$). The dead state is not shown.

a history of a treated precancerous lesion in part because there are data to support that individuals with a history of a previously removed precancerous lesion are at a higher risk for developing an additional precancerous lesion and subsequent invasive cancer than those without a prior precancerous lesion. Further, this additional disease-free health state is required to permit the evaluation of screening strategies that assign different screening and diagnostic algorithms to patients with a previously removed precancerous lesion. Thus, despite the seemingly homogeneous group of patients who enter the model, as individuals transition to different health states, some degree of heterogeneity is created, and challenging decisions will need to be made regarding parameterization of the model.

To illustrate the impact of a potential error that may be made when modeling disease progression among disease-free persons with a history of a precancerous lesion, we constructed 2 simple screening models with 4 basic health states: (1) disease free, (2) presence of a precancerous lesion, (3) presence of cancer, and (4) dead (Fig. 1). In both models, we assumed that the probability of developing a precancerous lesion was greater among individuals with a history of a prior precancerous lesion (α_1) compared to persons without a prior abnormality (α_0). In the 1st model (herein referred to as MODEL 1), we also assumed that the transition from a precancerous lesion to invasive cancer was greater for persons with a history of a precancerous lesion (β_1) than for persons without such a history (β_0). (Fig. 1a) In contrast, in the 2nd model (herein referred to as MODEL 2), we assumed that the transition from a precancerous lesion to invasive cancer for persons with a history of a precancerous lesion was equal to the

Table 1 Model Variables

Variable	MODEL 1 ($\alpha_0 < \alpha_1$, $\beta_0 < \beta_1$)	MODEL 2A ($\alpha_0 < \alpha_1$, $\beta_0 = \beta_1$)	MODEL 2B ($\alpha_0 < \alpha_1$, $\beta_0 = \beta_1$)
Parameters for MODEL 1, MODEL 2A, and MODEL 2B			
Individuals without a history of a precancerous lesion			
Probability of developing a precancerous lesion (α_0)	0.0013	0.0013	0.00075
Probability of progressing from a precancerous lesion to cancer (β_0)	0.003	0.003	0.006
Individuals with a history of a removed precancerous lesion			
Probability of developing a precancerous lesion (α_1)	0.065	0.065	0.065
Probability of progressing from a precancerous lesion to cancer (β_1)	0.006	0.003	0.006
Parameters used in all models			
Probability of death from cancer	0.035	0.035	0.035
Probability of death from all causes	0.004	0.004	0.004

Note: α_0 = probability of developing a precancerous lesion; α_1 = probability of developing a precancerous lesion among individuals with a history of a prior precancerous lesion; β_0 = probability of progressing from a precancerous lesion to cancer; β_1 = probability of progressing from a precancerous lesion to cancer in persons with a history of a precancerous lesion. Parameter estimates shown are monthly probabilities.

transition for persons without such a history ($\beta_1 = \beta_0$). (Fig. 1b) For purposes of presentation, we defined the relative risk for progression from a precancerous lesion to cancer in persons with a history of a previously removed lesion compared to persons without such a history (β_1/β_0) as the "progression ratio." For our example, we considered the screening benefit associated only with the removal of a precancerous lesion, not with the early detection of cancer. We therefore were able to restrict these models to 1 cancer state each, with a cancer-specific mortality that was independent of cancer stage and detection status.

For MODEL 1, we assigned values to α_0 and α_1 and the progression ratio (i.e., β_1/β_0) on the basis of data we have previously used to model anal neoplasia and anal cancer in gay men.[6] We applied these transition probabilities to a hypothetical cohort of 30-year-old men and assumed that progression to cancer among men with a history of a precancerous lesion was twice that of men without such a history. We then derived β_0 by calibrating the model to a 10-year cancer incidence of 0.0175. We evaluated 2 MODEL 2 scenarios (MODEL 2A and MODEL 2B) and required both models, in the absence of screening, to predict the same 10-year cancer incidence as MODEL 1. For MODEL 2A, we used the same natural history estimates as MODEL 1 (α_0 and β_0) but forced the progression to cancer estimates to be independent of the history of prior precancerous lesions ($\beta_0 = \beta_1$). To derive an additional set of parameters for MODEL 2B, we assigned the value used for β_1 in MODEL 1 to both β_0 and β_1. We then calibrated MODEL 2B by adjusting the probability governing progression from no disease to precancerous lesions (α_0) such that the model predicted the same 10-year cancer incidence as MODEL 1 in the absence of screening. The values used for all models are shown in Table 1.

The benefit of screening was measured in terms of life-expectancy gains. Because we were not modeling any risk associated with screening and assumed that the screening test was perfect (sensitivity 100% and specificity 100%), we expected screening to have a positive life-expectancy benefit. We purposefully assumed a perfect test without any associated risk to highlight the effect and implications of our choices of transition probabilities.

Of note, the transition probabilities were not conditional on the results of the screening test, whether positive or negative; they were conditional on the underlying true state of disease. Thus, the "screen-positive" patients do not have a higher risk for cancer in our model by virtue of having had screening tests. Rather, patients with a precancerous lesion who are treated successfully have a different risk for cancer than those who never had a lesion in the first place.

Estimates of progression ratios (i.e., β_1/β_0) in practice are likely to be > 1 because of the heterogeneity of the population. However, to incorporate an estimate > 1 into a decision-analytic model without formally accounting for population heterogeneity violates the assumption of health-state homogeneity and will thus cause an error in model results.[10] We define this error in terms of an absolute progression bias and a relative progression bias:

Absolute progression bias: $\Delta LE_2 - \Delta LE_1$
Relative progression bias: $(\Delta LE_2 - \Delta LE_1)/\Delta LE_2$

ΔLE_2 refers to the change in life expectancy associated with a screening program with MODEL 2A or MODEL

Table 2 Results

Model	10-y Cancer Incidence	Life Expectancy (y)	Screening Benefit (mo)
MODEL 1 ($\alpha_0 < \alpha_1$, $\beta_0 < \beta_1$)			
No screening	0.018	18.86	
Screening every 3 y		18.66	–2.4[a]
MODEL 2A ($\alpha_0 < \alpha_1$, $\beta_0 = \beta_1$)			
No screening	0.018	18.86	
Screening every 3 y		19.19	3.9[a]
MODEL 2B ($\alpha_0 < \alpha_1$, $\beta_0 = \beta_1$)			
No screening	0.018	19.14	
Screening every 3 y		19.36	2.7[a]

Note: α_0 = probability of developing a precancerous lesion; α_1 = probability of developing a precancerous lesion among individuals with a history of a previously removed precancerous lesion; β_0 = probability of progressing from a precancerous lesion to cancer; β_1 = probability of progressing from a precancerous lesion to cancer in persons with a history of a previously removed precancerous lesion.

a. ΔLE_2 refers to the change in life expectancy associated with a screening program with MODEL 2A or MODEL 2B, and ΔLE_1 refers to the change in life expectancy with MODEL 1. The absolute progression bias ($[\Delta LE_2 - \Delta LE_1]$) observed with MODEL 1 relative to MODEL 2A is 6.3 months, and the relative bias ($[\Delta LE_2 - \Delta LE_1]/\Delta LE_2$) is 1.6. The absolute progression bias observed with MODEL 1 relative to MODEL 2B is 5.1 months, and the relative bias is 1.9.

2B, and ΔLE_1 refers to the change in life expectancy with MODEL 1.

We repeated these analyses using previously developed models of cervical cancer screening and colorectal cancer screening. For each of these models, we estimated the magnitude of the progression bias under the assumptions outlined for MODEL 1 and MODEL 2.

RESULTS

The results using the 2 simple models are shown in Table 2. Using MODEL 1 ($\alpha_0 < \alpha_1$, $\beta_0 < \beta_1$), the projected life expectancy with no screening was 18.86 years and with screening every 3 years was 18.66 years. This implies a negative screening benefit (–2.4 months) for a test that is perfect and riskless. Using MODEL 2A ($\alpha_0 < \alpha_1$, $\beta_0 = \beta_1$), the projected life-expectancy benefit with screening was positive (+3.9 months). The absolute progression bias was therefore quantified as 6.3 months, and the relative progression bias was 1.6. (A relative bias of 1 indicates no life-expectancy benefit with MODEL 1; a relative bias > 1 indicates a negative life-expectancy benefit with MODEL 1.)

We examined the magnitude of this modeling error under a variety of assumptions and conducted a series of sensitivity analyses to determine how the bias behaved when key parameters were varied in the models. First, we quantified the error using an alternative set of parameters that were derived using different assumptions while calibrating to the same 10-year cancer incidence. Using this alternative set of parameters (MODEL 2B), we found that the life-expectancy benefit with screening every 3 years was 2.7 months. This result implied a somewhat smaller absolute bias from MODEL 2A (5.1 months) but a larger relative bias (1.9).

Figure 2 shows the life-expectancy benefit associated with screening every 3 years projected by MODEL 1, MODEL 2A, and MODEL 2B, as the monthly probability of developing a precancerous lesion in persons with a history of a treated precancerous lesion (α_1) is varied from 0.0013 (the value of α_0) to 0.1000. (base case 0.065). Holding all other probabilities constant, we found that the magnitude of the absolute progression bias increased as α_1 increased. For example, when the value of α_1 was 0.1000, the absolute bias was 6.5 and 5.6 months with MODEL 2A and MODEL 2B, respectively. The extreme counterintuitive result (i.e., a negative life-expectancy benefit) occurred with values of $\alpha_1 > 0.038$.

A 2-way sensitivity analysis was conducted in which we varied the screening frequency and the progression ratio (i.e., β_1/β_0). Figure 3 shows the impact on the relative progression bias using MODEL 2A. Regardless of the screening frequency, when the progression ratio was 1, the bias was 0 because in this situation, the models are actually the same. As the progression ratio increased from 1 to 4, the relative progression bias increased as well. We found that the magnitude of the relative progression bias was moderately affected by changes in the screening frequency at all relative risks > 1. The bias was smaller with more frequent screening (e.g., annual screening) compared to less frequent screening.

The counterintuitive result of a lower life expectancy with screening compared to no screening (i.e., a negative life-expectancy benefit) is an extreme example of the potential effect of the modeling error made in parameterizing MODEL 1. We assessed the degree to which this phenomenon would persist if the probabilities of progression from a precancerous lesion to cancer were varied simultaneously in individuals with and without a history of a previously removed precancerous lesion. Figure 4a shows the impact of varying these 2 probabilities (β_0 and β_1) in the setting of screenings every 5 years, Figure 4b shows the impact in the setting of screenings every 3 years (base case), and Figure 4c shows the impact in the setting of screenings every year. The shaded area represents the zone in which the expected value of no screening was higher than the ex-

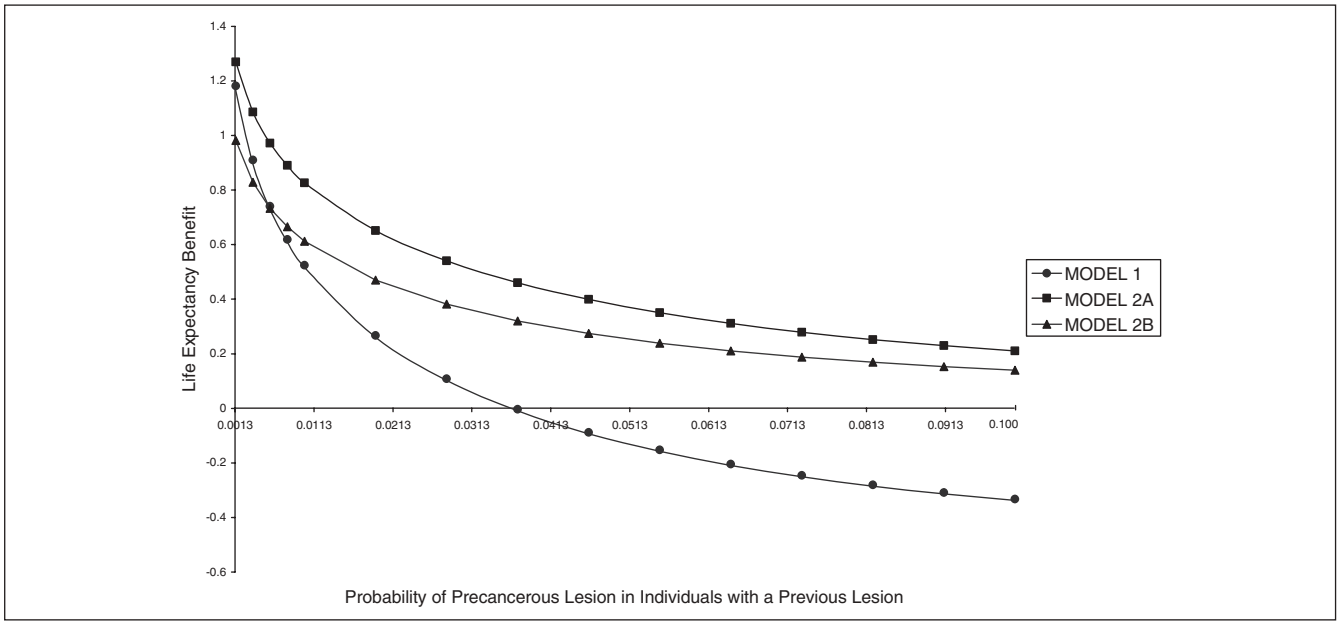

Figure 2 The life-expectancy benefit associated with screening every 3 years projected by MODEL 1, MODEL 2A, and MODEL 2B, as the monthly probability of developing a precancerous lesion in persons with a history of a removed precancerous lesion (α_1) is varied.

pected value of screening. This area decreased as the screening frequency increased.

In both of the analyses reflected in Figures 3 and 4, the impact of screening frequency on this type of modeling error was consistent (i.e., the bias was attenuated with frequent screening). When screening intervals were far apart, there was more time for progression to occur between disease states in both persons with a history of a lesion and those without such a history. Thus, the magnitude of the error increased accordingly. In contrast, consider the extreme example of screening every 3 months. In a designated screening month, a patient with a detected precancerous lesion would be treated and return to the state reflecting the history of that treatment. The person would face a higher risk for developing a precancerous lesion for only 2 Markov cycles before being screened again. There would not be enough time for him to develop a precancerous lesion and then dwell in that health state long enough to face the higher probability of progression from a precancerous lesion to cancer, as is the case in MODEL 1. In other words, the frequent screening for and removal of precancerous lesions minimizes this hypothetical person's exposure to the higher progression rate (β_1).

We repeated these analyses using 2 previously developed models of cancer screening. Figure 5 shows the relationship between the progression ratio (β_1/β_0) and the life expectancy with 4 colorectal cancer screening strategies: no screening, annual fecal occult blood

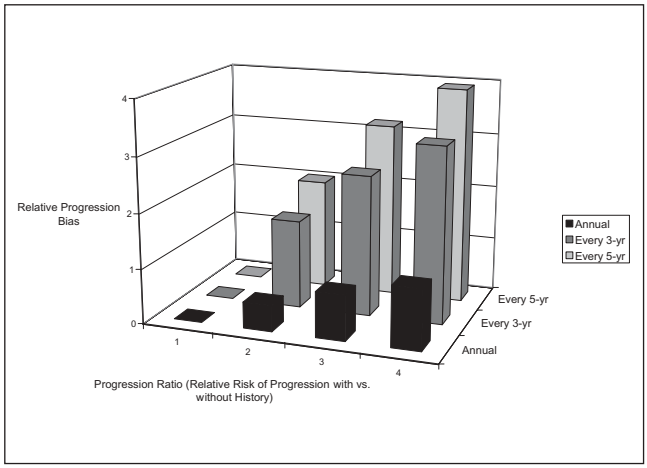

Figure 3 Two-way sensitivity analysis varying both the screening frequency and the progression ratio (relative risk of progression from a precancerous lesion to cancer in persons with a history of a removed lesion compared to persons without such a history, or β_1/β_0).

testing (FOBT), sigmoidoscopy every 5 years, and annual FOBT plus sigmoidoscopy every 5 years. On the basis of our analyses using our simple models, we would expect the strategy with the least frequent screening intervals to be associated with the greatest error and progression bias. As expected and as shown in Figure 5, sigmoidoscopy every 5 years was most affected by the progression ratio, and annual FOBT was

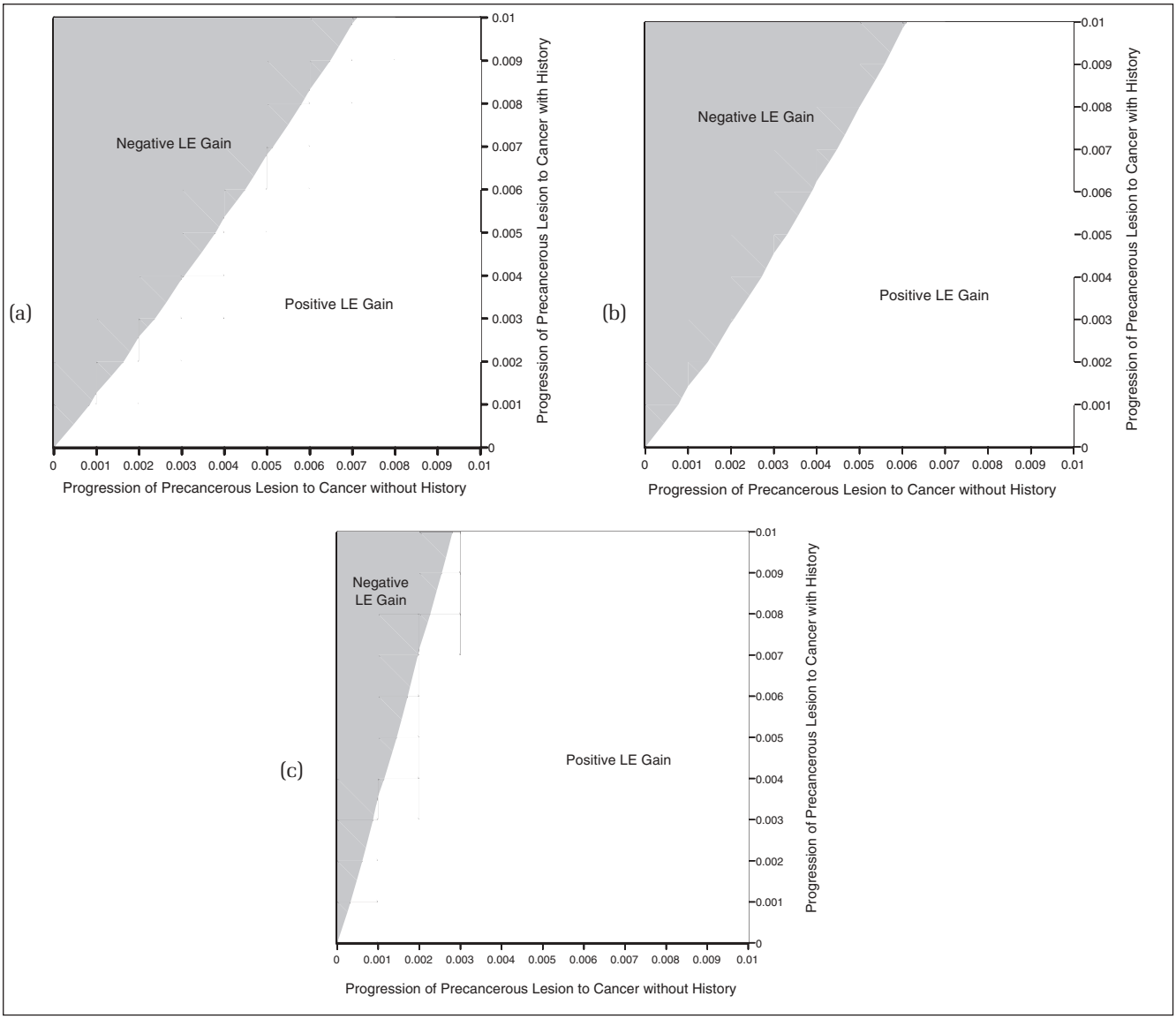

Figure 4 Sensitivity analysis varying the probabilities of progression from a precancerous lesion to cancer in individuals with and without a history of a removed precancerous lesion (β_0 and β_1, respectively). (a) Impact of varying β_0 and β_1 in the setting of screenings every 5 years, (b) impact in the setting of screenings every 3 years (base case), (c) impact in the setting of screenings every year. The shaded area represents the zone in which the counterintuitive result of a negative life-expectancy (LE) benefit is obtained (i.e., the expected value of no screening is higher than the expected value of screening)—as the screening frequency is increased, this zone becomes smaller.

least affected. The addition of sigmoidoscopy every 5 years to annual FOBT was more affected by the progression ratio than the strategy of FOBT alone because sigmoidoscopy has a greater ability to diagnose and remove precancerous polyps compared to FOBT. This illustrates the interaction between screening interval and test sensitivity for the detection of precancerous lesions on the progression bias effect. Figure 6 shows the relationship between the progression ratio and the life expectancy with 3 cervical cancer screening strategies: no screening, screening every 5 years, and screening with Pap smears every 3 years. The counterintuitive result, in which the expected value for screening is lower than for no screening, occurred at lower progression ra-

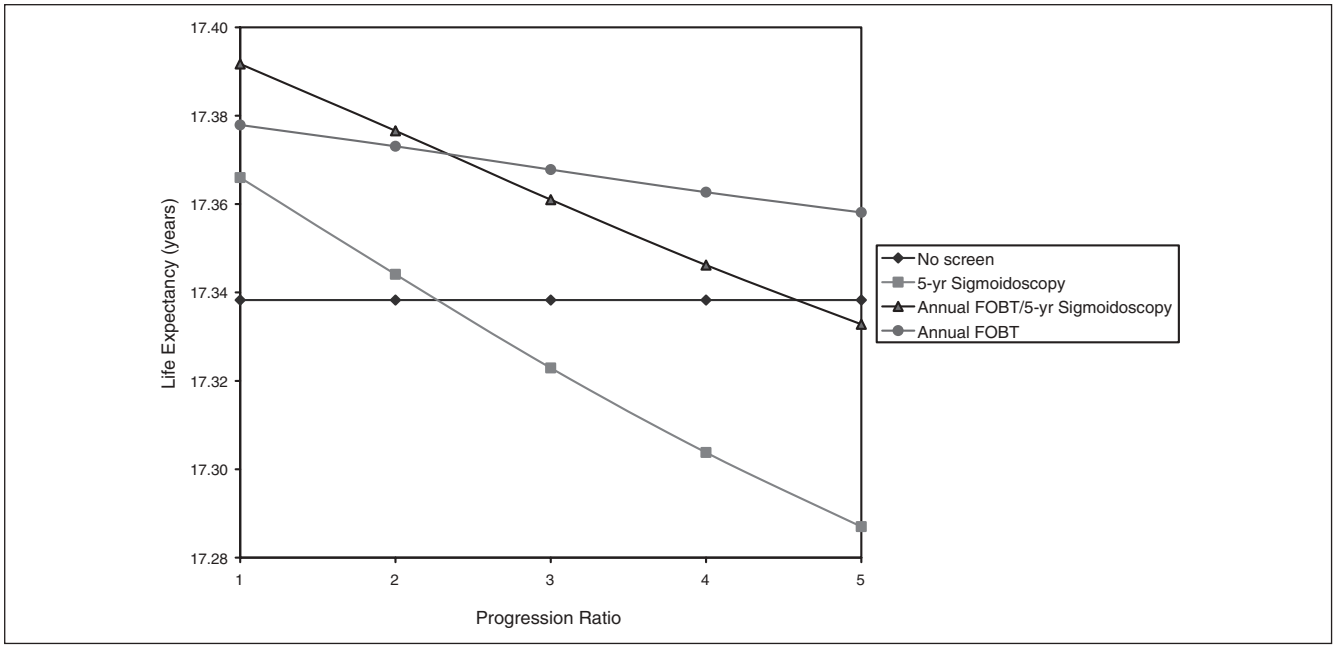

Figure 5 Colorectal cancer screening: relationship between the progression ratio (β_1/β_0) (which reflects the magnitude of the modeling error) and life expectancy with 4 strategies: no screening, annual fecal occult blood testing (FOBT), sigmoidoscopy every 5 years, and annual FOBT plus sigmoidoscopy every 5 years.

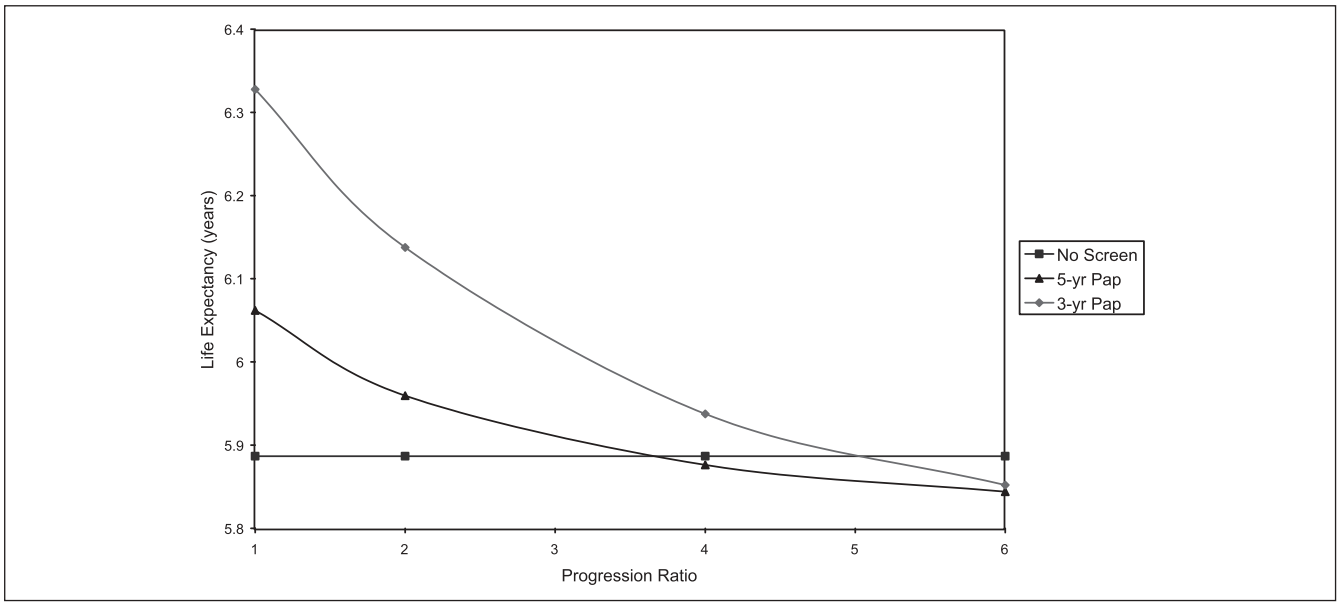

Figure 6 Cervical cancer screening in HIV-infected women. Relationship between the progression ratio (β_1/β_0) (which reflects the magnitude of the modeling error) and life expectancy with 3 strategies: no screening, screening every 5 years, and screening with Pap smears every 3 years.

tios in the strategies with infrequent screening intervals. For example, with screening every 5 years, this counterintuitive result occurred when the progression ratio was > 3.8. With screening every 3 years, this counterintuitive result did not occur until the progression ratio was > 5.

DISCUSSION

There has never been a randomized controlled trial of cervical cancer screening, although it is referred to as one of our most successful cancer screening interven-

tions.[11] The acceptance of cervical cancer screening as the standard of care precludes a trial of this intervention from occurring. For colorectal cancer screening, only FOBT has been evaluated in a clinical trial setting. The effectiveness of other colorectal cancer screening modalities (e.g., flexible sigmoidoscopy, double contrast barium enema) has been based on data from other types of observational studies.[12] Thus, we do not have the advantage of adequate, direct evidence of screening effectiveness on which to base policy recommendations. Mathematical models can be a useful way to evaluate alternative strategies by extending the knowledge from empirical studies to a broader array of clinical situations.[13–16] Analysts who evaluate cancer screening strategies are often forced to model the underlying disease process instead of the observed disease, particularly in the absence of direct evidence linking screening to a survival benefit. Modeling the underlying disease process is also desirable because it appropriately adjusts for lead and length time biases.

Particularly with the evaluation of preventive interventions, the gains in life expectancy will be small because of the effect of averaging across a population, most members of which would never contract the disease.[2] With effect sizes this small, mistakes that cause even small differences in expected values may, in certain situations, lead to critical errors in an analysis. Because the evaluation of policy decisions with regard to cancer screening often rely on the results of a model, and because the magnitude of the life-expectancy benefits obtained with cancer screening is relatively small, it is crucial to identify potential mistakes that result from choices in the model structure and its parameters. We have identified an important error to avoid when modeling the underlying disease process in the evaluation of screening programs for cancers that are associated with precancerous states.

In the absence of specific and detailed information on the heterogeneity of risk within a population, we assume a homogeneous population when we incorporate data into Markov models. A plausible assumption is that the risk for cancer is higher in individuals with a history of a previously treated precancerous lesion; however, there are multiple ways parameters may be combined in natural history models such that this increased risk is represented. We constructed a simple model to demonstrate a potential error that may occur when assigning parameters to represent this increased risk. In this model, we assumed that the transition probabilities among persons with a history of a treated precancerous lesion were increased for both the incidence and the progression of a precancerous lesion (MODEL 1). The results of this purposefully simple and transparent model showed that the life expectancy with no screening was greater than that with screening, an obviously erroneous result. We constructed a companion model to demonstrate how to avoid this error in which we assumed that the transition from precancerous lesions to cancer was equal to that of patients with no prior history (MODEL 2). When we forced the progression rate of a precancerous lesion to cancer to be the same in individuals both with and without a history of a previously treated lesion, we did not observe the counterintuitive result. Regardless of the actual transition rate for developing a precancerous lesion, the flawed MODEL 1 consistently underestimated the screening benefit compared to MODEL 2, provided both models were calibrated using the same observed long-term outcome data (e.g., 10-year cancer incidence).

Why does this error occur? The data available to derive the estimates for the transition probabilities are from a heterogeneous population, but we do not always know the underlying or distinguishing risk factors that characterize the heterogeneity. Because of this heterogeneity, it is understandable how we might observe the probability governing the rate of progression of a precancerous lesion to cancer to be greater in those with a history of a previously treated precancerous lesion detected with screening programs. A greater under-standing of the underlying risk factors would allow us to directly model the heterogeneity whereby within each risk stratum, the probability of progressing from a precancerous lesion with a history of a precancerous lesion would be equal to the corresponding probability without a prior precancerous lesion. In the absence of this additional information on the nature of the heterogeneity, we assume a homogeneous population when we incorporate these data into Markov models.

This is an important potential mistake that may occur when modeling the underlying disease process in cost-effectiveness analyses for cancer screening, and it alerts us to use caution when using data from heterogeneous populations for models that assume homogeneity. Because decision-analytic models are increasingly being used as tools to evaluate the benefits of preventive interventions, it is important for analysts to be aware of hidden pitfalls when modeling the underlying disease process.

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