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STOCHASTIC MODELS OF PROGRESSION OF CANCER AND THEIR USE IN CONTROLLING CANCER-RELATED MORTALITY

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A construction of a realistic statistical model of lung cancer risk and progression is proposed. The essential elements of the model are genetic and behavioral determinants of susceptibility, progression of the disease from precursor lesions through early (localized) tumors to disseminated disease, detection by various modalities, and medical intervention. Using model estimates as a foundation, mortality reduction caused by early-detection and intervention programs can be predicted under different scenarios. Genetic indicators of susceptibility to lung cancer should be used to define the highest-risk subgroups of the high-risk behavior population (smokers). The calibration and validation of the model requires applying our techniques to a variety of data sets available, including public registry data of the SEER type, data from the NCI lung cancer chest X-ray screening studies, and the recent ELCAP CT-scan screening study.

Keywords: lung cancer, genetic susceptibility, environmental exposure, tumor growth, statistical modeling, simulation

1. Introduction

One of the strategies of defeating cancer is to detect it early. The philosophy is simple: the earlier the cancer is detected, the smaller the chance that it has already spread beyond the limited primary focus. This implies that the extent of intervention needed is smaller and the prognosis is improved. This philosophy can be translated into a practical program: (a) identify a population at high risk for a given cancer, (b) develop an efficient and inexpensive method of early detection of non-symptomatic tumors, (c) develop a program of periodic examinations (screening) of the high-risk group using the early detection method, (d) treat the early cancer cases detected in this way. This will reduce mortality from the target cancer (Fig. 1).

Unfortunately, in most common cancers, such as the cancers of lung, colon, breast and prostate, the early detection and treatment paradigm raises lots of concerns (Bonneux, 2002; du Bois, 2002; Miettinen *et al.*, 2002; Olsen and Gotzsche, 2001; Werth, 2002) though it is only lung cancer that screening is not recommended for (Smith *et al.*, 2002). A notable exception is the cancer of uterine cervix, in which a simple early detection method (Pap smears) followed by a prompt treatment seems to significantly reduce mortality (Petterson, 1991).

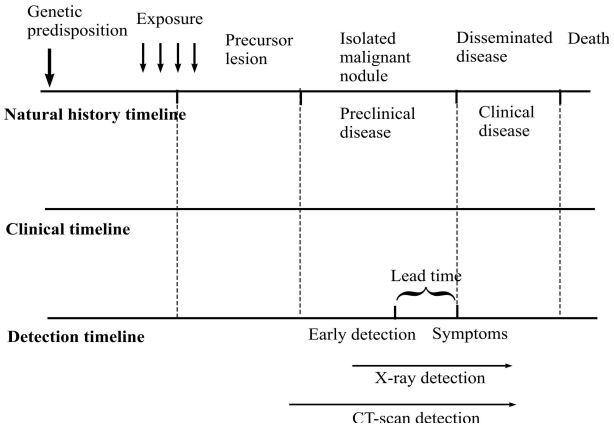

Fig. 1. Schematic depiction of sequences of events and time intervals in an individual's lifetime, relevant for modeling of lung cancer risk, progression, and detection and treatment.

What are the reasons for the failure of the paradigm? As we will see, none of the four outlined steps is easy to implement. The origins and progression of cancer are stochastic and dynamic in nature and so is detection and, to some extent, treatment. Ignoring these features leads to incorrect estimates and predictions and, in some cases, to incorrect policy recommendations.

A comprehensive stochastic model of lung cancer should involve genetic and behavioral determinants of susceptibility, the progression of the disease from precursor lesions through early localized tumors to disseminated disease, detection by various modalities, and medical intervention. The model should be able to predict mortality reduction caused by early detection programs, under different scenarios, in presence of competing death causes. It will be important to utilize the genetic indicators of susceptibility to lung cancer to define the highest-risk subgroups of the high-risk behavior population (smokers).

The purpose of this paper is to identify the problems related to early detection and treatment of lung cancer and to describe a stochastic model which makes it possible to address these problems, i.e., to reconcile the results of screening trials with other existing statistics of lung cancer. The model is presented on the background of previous works on the subject. Arguably, it is more complete and better tested compared with these previous attempts. In its present version, the model includes neither explicit mechanisms of tumor growth, nor individualized genetic susceptibility. These will be introduced in the future. We will show the performance of the model on a range of data sets available to us, such as data from the NCI lung cancer chest X-ray screening studies, the recent ELCAP computed tomography (CT-scan) screening study and some other published data (Kakinuma *et al.*, 1999; Yankelevitz *et al.*, 1999; 2000). Our deliberations will be based on the important example of lung cancer, but they are applicable, with appropriate changes, to other cancers.

2. Background on Lung Cancer. High Risk Groups

Lung cancer remains the largest killer among all cancers in the USA and in the world. It kills more people of both genders than the cancers of breast, colon and prostate combined, and more women than breast cancer. An overwhelming majority of cases is related to exposure to Polycyclic Aromatic Hydrocarbons (PAH), such as benzo[a]pyrene, first of all, in the tobacco smoke (Goldman *et al.*, 2001), but genetic predisposition also plays a major role (Amos *et al.*, 1999; Auer *et al.*, 1999; Wu *et al.*, 1998).

Two major factors make lung cancer difficult to fight. One of them is that a majority of cases are detected only when they are quite advanced. Attempts at early detection using chest X-ray and sputum cytology screening of high-risk individuals produced controversial and ambiguous results (Flehinger *et al.*, 1988; 1993; Marcus *et al.*, 2000; Strauss, 2002). Another factor is that the high-risk population (cigarette smokers) has largely evaded the attempts at further stratification with respect to their risk of contracting the disease.

There has been a recent progress in lung cancer detection techniques. Computed tomography (CT) allows the visualization of very small nodules in the lungs and therefore it has the potential to detect malignant tumors when they still are in an early stage. It detects mainly peripheral tumors, a large proportion of which is adenocarcinomas that recently became the most common type of lung cancer, and bronchoalveolar carcinomas (Henschke *et al.*, 2002). The results of preliminary studies in the United States (Henschke and Yankelevitz, 2000; Yankelevitz *et al.*, 1999; 2000), Japan (Kaneko *et al.*, 2000; Sone *et al.*, 2001) and Western Europe (Hillerdal *et al.*, 2001; van Klaveren *et al.*, 2001) have been published and they point at an increased detection rate of potential early malignancies. The probability that these will develop into progressing lung cancers is not known, particularly that of some of the lesions (e.g. the so-called "ground glass opacities", or GGO) which frequently lack well-defined nodule components (Hasegawa *et al.*, 2000).

Another area of progress concerns the genetic factors predisposing individuals to developing lung cancer. There exist a lot of data, concerning mostly the families of lung cancer patients (Amos *et al.*, 1999). Molecular epidemiological studies have shown a poor DNA repair capacity, as measured by assays that provide its overall estimate, to be a risk factor for developing lung cancer (Hsu *et al.*, 1991; Wei *et al.*, 2000). Genetic factors involved in the metabolism of carcinogens have also been suggested to contribute to lung cancer susceptibility (Strong and Amos, 1996). These associations can help to identify individuals (smokers) at a high risk to develop lung cancer.

3. Screening for Lung Cancer: Ideas and Difficulties

As has already been mentioned, the idea underlying mass-screening programs for early detection of cancer is that a sensitive detection technique (chest X-ray, CT-scan or biomarkers) allows diagnosing lung cancer at an early stage, when it is still curable (Fig. 1). If the early-stage detection is followed by an appropriate treatment, then mass screening can result in a reduction of population mortality attributed to lung cancer. However, there exist several caveats, which have to be considered to understand how difficult a practical implementation of this principle can be.

- *Identifying high-risk population.* For the screening program to be cost efficient, the yield of cases should be relatively high. In a clinical trial setting, if the population being screened is overly inclusive (e.g., all smokers), the high yield of cases in the program, and, as a result, a big difference between the screened and control groups, will not be observed. This may

reduce our ability to decide if the observed mortality reduction is significant, and it will definitely inflate the cost of the program. This may be illustrated by the results of our preliminary modeling. As it shows, annual CT screening of all smokers for 20 years can reduce mortality by 36%. If, within the same group, only one quarter of it comprising high-risk individuals defined as having elevated BPDE sensitivity and reduced DRC is screened, the mortality reduction is 19%. The screening of only highly BPDE sensitive people (regardless of their DRC) is somewhat less effective as it reduces mortality by only 17%, but further modeling to consider the costs associated with screening only parts of the population is warranted.

- *Screening biases.*

  (i) The *lead-time* bias means that in the screened group survival may be better than in the control group, even if screening is no benefit to the patients. This simply results from the fact that the disease is detected earlier and thus the time between the diagnosis and death (survival time) is longer in the screened group even in the case when the death itself is not postponed (Fig. 1). Thus, the survival benefit observed in a screening program might be misleading.

  (ii) The *length bias* (or its extreme form—*overdiagnosis bias*) results from the fact that screening is more likely to detect longer lasting and therefore possibly more indolent cases (Fig. 2). This bias can inflate cure rates, as well as survival, of screen-detected cases by including indolent cases that would never surface in the absence of screening (Gates, 2001).

- Another difficulty may arise if the biology of lung cancer causes it to progress (metastasize) already when the primary nodule is very small. This will make the whole philosophy of early detection invalid and the early detection itself a futile exercise as the removal of a small primary will not improve curability (Patz *et al.*, 2000). However, recent data from CT screening programs (Henschke *et al.*, 2002) as well as the MLP data (Flehinger *et al.*, 1992) show that this is not the case as early diagnosed lung tumors have high curability rates while the tumors that are not resected kill the patients in 80% (Sobue *et al.*, 1992) to 90% (Flehinger *et al.*, 1992) cases.

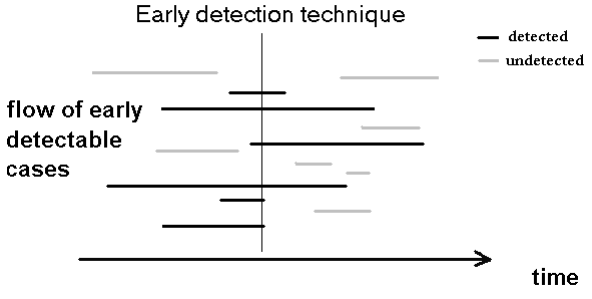

Fig. 2. Illustration of the length bias. Cases detected on a screen with perfect sensitivity in general remain at the early stage for longer, which implies they may be less aggressive.

4. Randomized Clinical Trials (RCT)

RCT is a comparison of lung cancer mortalities in a study in which high-risk subjects are randomly assigned to two groups, screened and control. After a predetermined time, the numbers of deaths from lung cancer in both groups are compared. This design removes the impact of lead-time and length biases. However, it is sensitive to the non-compliance of screened individuals and the contamination of controls by voluntary screening. Also, if the yield of cases is low and/or the reduction of mortality is real but smaller than expected, or if it occurs after a time longer than expected, the design may yield inconclusive results (Gorlova *et al.*, 2001; Strauss, 2000). Several major RCTs of lung cancer screening were carried out using chest X-ray and sputum cytology as detection tools. None of them demonstrated a reduction in mortality from lung cancer. Increases in the number of early-stage lung cancers in the screening group were observed (and these cases enjoyed a much improved survival), but they were attributed to the lead-time and overdiagnosis biases (Marcus *et al.*, 2000). These findings resulted in recommendations by the American Cancer Society and National Cancer Institute against annual chest X-ray examinations of smokers' lungs and in generally adverse attitudes towards the potential of screening for lung cancer (Wagner and Ruckdeschel, 1995). Even in view of the recent application of CT-scan as a screening tool, the medical community remains cautious, as evidenced by a number of recent publications (Grann and Neugut, 2003; Marcus, 2001; Marcus *et al.*, 2000; Patz *et al.*, 2001). Mahadevia *et al.* (2003) performed a computer simulation-based analysis of the cost-effectiveness of screening programs to conclude that the high costs associated with screening, along with harms from unnecessary invasive testing and uncertainty of benefits, make helical CT screening of smokers not advisable.

To resolve the concerns, a new randomized controlled clinical trial, the National Lung Screening Trial, started in September 2002 (see `http://www.cancer.gov/NLST`).

5. Models of Lung Cancer Natural History and Detection Developed by Others

Attempts to model the natural history of lung cancer are not numerous. Walter and Day (1983) developed a model that provides estimates of lead-time and sensitivity of screening, using data on the observed prevalence of disease at a screen and incidence between screens. The model has been applied to the data from a Chechoslovak lung trial (Walter *et al.*, 1992). The authors concluded that the detectable stage of lung cancer before the symptoms appear is as short as 7–8 months, while the detection sensitivity is close to 100%. The mortality reduction due to screening, as concluded by the authors, should be very small. The authors assumed a constant detection probability over time, not allowing for a greater likelihood of detection for tumors screened later in their preclinical detectable stage. This preclinical entirely detectable stage would correspond to the advanced asymptomatic stage in the model proposed by Flehinger and Kimmel (1987). In their model it is also detected with 100% probability but has zero probability of cure and is preceded by an early stage with non-zero curability but not easily detectable (see below). However, the mean duration of that stage was estimated as 2 years by Flehinger and Kimmel (1987) vs. 0.7 years by Walter *et al*. (1992), which may be attributed to the use of a different detection tool (small-picture X-ray in the Chechoslovak study, vs. full-size X-ray in the NCI studies).

Bartoszynski *et al.* (2001) suggested to model cancer detection as a quantal response variable, relating the chance of detecting a tumor to its size. A different model, involving tumor-size dependence of the rate of metastasis, was proposed by Kimmel and Flehinger (1991).

A simulation model where the natural history of lung cancer was modeled as a Markov process from cancer free state to death was developed by Yamaguchi *et al.* (1991; 1994) to predict the potential impact of primary (reduction in smoking initiation and smoking cessation) and secondary (screening) prevention on mortality from lung cancer. They evaluated the mortality reduction due to screening as very low (11%).

Strauss with co-authors (1993; 1997; 2002) used regression analysis applying it to the MLP data to show that the survival benefit in the screened group is not attributable to a lead time bias or a length bias or to overdiagnosis, and that the tumor resection was the only significant multivariate predictor of survival.

Yankelevitz *et al.* (2003) evaluated growth rates of tumors found in Memorial Sloan-Kettering, John Hopkins, and Mayo lung trials using an exponential law of growth and imposing a sensitivity threshold on those observations invisible in retrospect. As the authors concluded, most tumors demonstrated a typical malignant growth rate, which makes a high degree of overdiagnosis very unlikely.

In the subsequent sections of the paper, we will describe in greater detail a stochastic model which includes most of the features of the models listed above. It provides predictions of the number of deaths from lung cancer, in the presence or absence of screening, under diverse scenarios.

6. A Stochastic Model of Lung Cancer

The mathematical model of the natural history of lung cancer in a periodically screened population was previously described (Flehinger and Kimmel, 1987; Flehinger *et al.*, 1988). Here we present the assumptions that capture the essential properties of the progression dynamics of lung cancer.

1. In the high-risk population selected for screening, a subgroup of participants is susceptible to non-small cell lung cancer. The probability that a person belongs to this group is ρ.

2. In the absence of screening and treatment, non-small cell lung cancer after its onset progresses through 2 stages—early and advanced—followed by the death from cancer.

3. For a person in the susceptible subgroup, the age of the onset of the early stage, τ_0, is a random variable with a trapezoidal distribution.

4. The durations of the early and advanced stages, τ_1 and τ_2, are independent exponential random variables with means μ_1 and μ_2, respectively.

5. The screening program consists of examinations at fixed intervals intended to detect the cancer.

6. Those participants whose lung cancers are detected and treated at the baseline screening (prevalence cases) may optionally be removed from the study and control groups.

7. Given the presence of early cancer, the first examination after the onset of the disease detects early cancer with probability p. If no detection occurs, each subsequent examination detects the early cancer with probability λp. Since a small tumor missed on one examination because of its location in the chest is likely to escape detection again 4 months later, λ was assumed to be less than 1. Detection on successive examinations is independent. It is assumed that advanced cancers are surely detected after the stage transition.

8. When cancer is detected, screening is aborted and the patient is treated. The probability of curing early-stage lung cancer is equal to c; there is no possibility of curing advanced-stage lung cancer. The cure is defined pragmatically in terms of the survival of patients after detection: if patients are cured, their ages at death are the same as if they had never had cancer; if they are not cured, their ages at death are the same as if their cancer had not been detected through screening.
9. Distribution of ages at enrollment and death from competing causes are estimated from the data.

The model is among the simplest imaginable. It can be run using simulation, but a range of analytic techniques was also developed. It explains the reasons for the failure to observe a reduction of mortality in X-ray-based screening programs. The main reason is the poor performance of chest X-rays as a screening tool, which provides only a limited mortality benefit from screening. Other reasons include the lack of sufficient time to observe a benefit from screening in the trial, as well as a high level of non-adherence in the screened group and of contamination in the control group. The model provides predictions of an improved efficacy of screening techniques such as the CT-scan.

The model shows that the duration of screening in an RCT is very important (Fig. 3), particularly when the effect of screening is around 15% as presumed for chest radiography, and thus much less than that for CT.

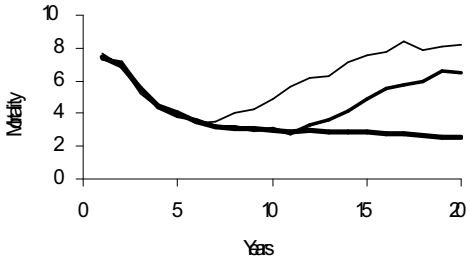

Fig. 3. Annual number of lung cancer deaths under annual CT screening and follow up. Screening performed for 5 years (the thin line), for 10 years (the thicker line), and for 20 years (the thickest line). Vertical axis: Number of lung cancer deaths per year per 5,000 screened individuals. Numbers of deaths approximately comparable to those expected in the ACRIN study.

7. Modeling Stochastic Transitions in Lung Cancer

A more refined model of cancer progression should include several mechanisms, which recently became estimable due to an influx of new data:

- *Genetic determinants of carcinogenesis.* Lung cancer is caused by the accumulation of DNA defects caused by exposition to PAH metabolites. PAH are metabolized by a cascade of reactions facilitated by enzymes (Fig. 4), expressed differently in different individuals. Considering the genetic sensitivity to mutagens (such as PAH) and DNA repair capacity will help isolate the highest-risk subpopulation, as well as estimate the individual susceptibility to lung cancer.
- *Models of tumor-size dependent metastases.* Stochastic modeling allows integrating data from different sources (CT-scan and X-ray screening programs and clinical-case registries) representing samples of tumors of different stages. Therefore it is possible to estimate the probabilities of lymph node and distant organ metastases for tumors of different sizes (cell type, molecular features, and so forth). Techniques, using the E-M algorithm, have already been developed (Kimmel and Flehinger, 1991).
- *Models of tumor growth.* Repeated measurements of small tumors obtained from CT-scans will allow the estimation of variability in the rate and pattern of the growth of early lung cancer (Yankelevitz *et al.*, 2000). These estimates can be obtained using maximum likelihood and imputation methods, whenever measurements are missing or biased.

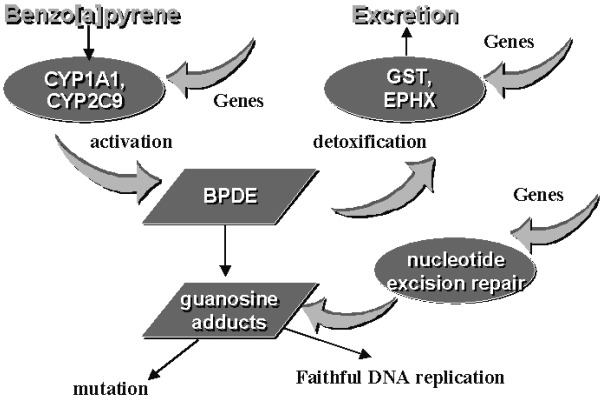

Fig. 4. Metabolism of benzo[a]pyrene.

It should be understood that the average growth rate observed within a sample depends on the way the sample was ascertained. It has already been mentioned that screen-detected cases represent a fraction of slower growing tumors due to a length bias, compared to all tumors. If the sensitivity of a screening tool is low, the bias is even stronger (Fig. 5). Within screen-detected cases, those visible in retrospect are expected to be slower than an average screen-detected case (Fig. 6(a)). Cases dealt with

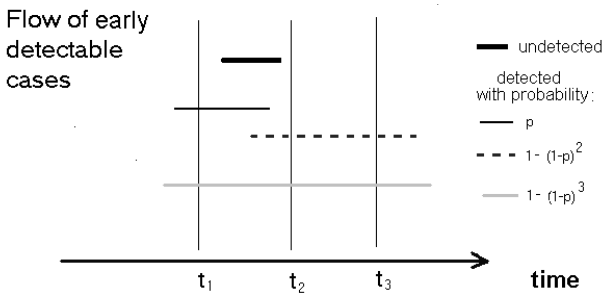

Fig. 5. Length bias in case of low sensitive screening modality; p – probability to detect an early lesion per one screen; t_1, t_2, t_3 – times of screening examinations. Longer-lasting cases have a higher probability of detection.

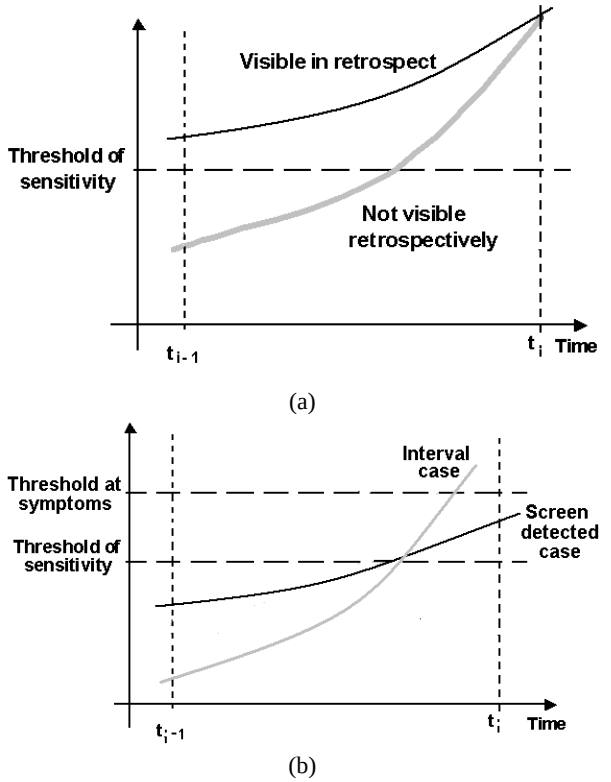

Fig. 6. Comparison of growth rates of various types of cases detected in a screening study: cases visible vs. invisible in retrospect (a); screen-detected vs. interval cases (b).

in prospective studies will be less biased in terms of the growth rate than the cases visible in retrospect because of a higher frequency of screening as it is unethical not to closely follow up any detected lesion. Interval cases (cases detected between screens) represent faster growing tumors as they have small size at one screen and thus remain undetected, but they reach a big size that causes symptoms, which leads to clinical detection before the next screen (Fig. 6(b)). The so-called nonsolid nodules (previously called "ground-glass opacities", cf. Henschke *et al.*, 2002) show a slower growth than solid tumors (Aoki *et al.*, 2000). To summarize, estimates obtained based on measurements from different studies vary widely, which is not surprising in view of different ways of samples' ascertainment.

To estimate the tumor growth rate, we apply a maximum likelihood approach if two size measurements of a tumor at two different time points are available. We assume the exponential law of growth (this is a standard assumption for macroscopic but still small tumors), so that

$$s(t) = s_0 \exp(rt),$$

where s is the size (volume in our case), t is the time and r is the parameter characterizing growth rate. We suppose that r is a lognormally distributed random variable. Consequently, $\ln r$ is distributed normally with parameters (ρ, τ^2). We develop a procedure to estimate these parameters by maximum likelihood to show that

$$\hat{\rho} = \frac{1}{n}\sum_{i=1}^{n} \ln\left(\frac{l_{2i} - l_{1i}}{\Delta t_i}\right)$$

and

$$\hat{\tau} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left[\ln\left(\frac{l_{2i} - l_{1i}}{\Delta t_i}\right) - \hat{\rho}\right]^2}.$$

If two measurements are available for some tumors and only one measurement for others (which means that no tumor was seen in retrospect for those cases), then a simulation approach was used. The idea of the latter was to reconstruct the missing measurement as being below the detection threshold. The threshold is considered a lognormal random variable, the distribution of which can be, with some approximation, estimated from data (Table 1). Note that the threshold for the screen detection and for the retrospective examinations should be different, the latter being smaller.

Table 1. Estimated parameters for the distribution of the sensitivity threshold.

Detection		Retrospective examination	
Mean	90% quantile	Mean	90% quantile
12	43	6.6	23.65

The simulation procedure was as follows. First, the maximum likelihood estimates for ρ and τ^2 were obtained based only on cases with 2 measurements, as described above. These estimates were then used as the initial values for the parameters to generate a lognormal random variable r (growth rate). Then the threshold value was generated from the lognormal distribution with the

Table 2. Results of estimation of the growth parameters based on tumor size data.

Data set	Number of tumors with 2 measurements	Number of tumors with 1 measurement	Estimated doubling time	Estimated ρ	S.d. of ρ	Estimated τ
Yankelevitz *et al.* (2000)	5		90.78	−4.875	0.183	0.410
Yankelevitz *et al.* (1999)	9		70.35	−4.62	0.0935	0.281
Kakinuma *et al.* (1999)	6		315.60	−6.121	0.227	0.556
MSKCC stage 1	36		166.41	−5.481	0.11	0.657
MSKCC stage 1 corrected[a]	36	9	148.83	−5.368	0.125	0.720
MSKCC stage 3	10		186.32	−5.594	0.25	0.791
MSKCC stage 3 corrected[a]	10	12	103.54	−4.998	0.250	0.992
MSKCC interval cases	5		132.89	−5.256	0.359	0.802
MSKCC interval cases corrected[a]	5	20	67.43	−4.565	0.260	1.022

corresponding parameters (Table 1). Based on the equation of exponential growth, the generated value of r, a known tumor size at detection and the time interval between detection (t_2) and previous examination (t_1) with the negative result, a tumor size s_1 at the time of the previous examination (t_1) was calculated. If the size happened to be greater than the threshold, r was generated anew until the tumor at t_1 became less than the threshold. The procedure was performed for every case for which only one measurement was available. As a result, "missing" tumor sizes at t_1 were restored for 1-measurement cases. For this partially simulated data set, maximum likelihood estimates for ρ and τ^2 were recalculated. The procedure was repeated 30 times and then the final estimates were obtained by averaging over all iterations. The procedure was verified by simulating data for a range of initial parameters ρ and τ^2 and several sets of detection threshold distributions. For convenience, the tumor volume doubling time T_d (in days) was used along with the growth rate. The relationship between these two parameters is as follows:

$$T_d = \ln(2)/\exp(\hat{\rho}).$$

The distribution of the doubling times was compared to the actual distribution of log growth rates, which was known from simulation. The comparison was based on a numerical approximation of the following index:

$$I = \int_0^1 \left|F^{-1}(u) - F_{\mathrm{sim}}^{-1}(u)\right| \mathrm{d}u / T_{d,\mathrm{median}},$$

where $F^{-1}(u)$ and $F_{\mathrm{sim}}^{-1}(u)$ are the inverse cumulative distribution functions of the estimated doubling times and of the simulated doubling times, respectively, divided by the median doubling time in the simulations. The index can be interpreted as a standardized mean of absolute differences between the estimated and simulated doubling times. Without getting into details, the relative error index I rarely exceeds 15–20%.

We then applied our procedures to several data sets that originated from different studies. The estimates obtained based on measurements from different studies vary widely (Table 2), which is not surprising because samples were selected in different ways, and the results agree well with the expectations.

8. Conclusions

The integration of detailed estimates of stochastic transitions into the progression network of lung cancer with screening detection and subsequent treatment will make it possible to predict the efficacy of different detection programs. It will also allow optimizing the selection of individuals to be included in mass screening. It is the only method that allows accomplishing these tasks in the presence of a continuous change in detection and treatment techniques as well as in presence of varying exposure to carcinogens (fluctuating with behavioral factors such as smoking) and a differing genetic make-up of people at risk.

[a]Estimates were corrected for the missing sizes of the tumors invisible in retrospect using the simulation approach.

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