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Stochastic models of progression of cancer and their use in controlling cancer-related mortality

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Abstract

We propose to construct a realistic statistical model of lung cancer risk and progression. 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 utilized to define the highest-risk subgroups of the high-risk behavior population (smokers). Calibration and validation of the model will be done by 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.

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 already has spread beyond the limited primary focus. This implies that the extent of intervention needed is lesser and the prognosis improved. This philosophy can be translated into a practical program: (1) Identify a population at high risk for a given cancer. (2) Develop an efficient and inexpensive method of early detection of non-symptomatic tumors. (3) Develop a program of periodic examinations (screening) of the high-risk group using the early detection method. (4) 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 cancers of lung, colon, breast and prostate, the early detection and treatment paradigm works quite poorly. A notable exception is the cancer of uterine cervix, in which a simple early detection method (Pap smears) followed by prompt treatment seems to significantly reduce mortality.

What are the reasons for this failure? As we will see, none of the four steps outlined is easy to implement. Origin 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.

The talk is a review of statistical and health policy problems related to early detection of cancer using mass screening examinations. We discuss a stochastic model (or models) of progression, detection and treatment of cancer, to put our questions into a rigorous setting. Our considerations will be based on the important example of lung cancer, but they are applicable, with appropriate changes, to other cancers.

A stochastic model of lung cancer involves 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. The model should be able to predict mortality reduction caused by early-detection programs, under different scenarios, in presence of competing death causes. As mentioned above, 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). Estimation techniques are needed to obtain distributions of the parameters of the model, using simulation and Bayesian hierarchical modeling.

Although the emphasis is on methodology, 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 published data.

2 Background on lung cancer

Lung cancer remains the largest killer among all cancers in the USA and in the world. It kills more people of both genders than 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 Hydrocarbones (PAH; first of all, in the tobacco smoke) [1], but the genetic predisposition also plays a major role [2]-[4].

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