OPERATIONS RESEARCH MODELS FOR CANCER SCREENING

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INTRODUCTION

In 2008, approximately 1,437,180 Americans were diagnosed with cancer and 565,650 died from it: more than 1500 people a day, making cancer the second leading cause of death in the United States [1]. American men have slightly less than a 1 in 2 lifetime risk of developing cancer; for American women, the risk is a little more than 1 in 3 [1]. Table 1 presents the estimated number of new cases and deaths by selected cancer types in 2008. Figure 1 shows how the incidence and mortality rates of cancer change over time. The economic impact of cancer is also huge. According to the National Institutes of Health, the total cost of cancer care in the United States in 2007 was $219.2 billion, where direct medical costs accounted for $89 billion [1].

Although cancer is a highly fatal disease, as a result of advanced treatment options, most cancers are now curable if detected early. For instance, Surveillance Epidemiology and End Results (SEER) program reports that five-year survival rates for localized (an early stage) and distant (an advanced stage) breast cancer patients are 98% and 23%, respectively [2]. Obviously, a successful screening program would improve the effectiveness of cancer treatment. The five-year relative survival rate for all cancers has improved from 50% in 1975–1977 to 66% in 1996–2003 [1], which can be attributed to the progress in both diagnosing certain cancers at an earlier stage and improvements in treatment the progress [3]. Table 2 lists screening modalities for selected cancer types.

Although screening of a population of asymptomatic individuals can diagnose some early-stage cancers, the vast majority of these individuals receive no benefit since cancer deaths are prevented in only a small fraction of the screened population [5]. In fact, the screened population may be exposed to additional health risks and even death (e.g., perforation during a colonoscopy screening) as a result of screening, such as complications from the screening procedure, from false-positive test results that trigger unnecessary invasive follow-up procedures (e.g., breast biopsy after mammography), and from misdiagnosis and overtreatment of cancers that would have never caused death [5]. Furthermore, population screening is very expensive. Burnside *et al*. [6] estimate that the total costs of just mammography screening for breast cancer and associated work-up of positive findings were between $3–5 billion in 2001. Screening asymptomatic individuals therefore requires a careful analysis of the benefits and risks of screening in both utilitarian and economic terms.

The complexity of selecting a cost-effective cancer screening program creates many challenges that can be addressed using a variety of operations research (OR) tools. There are several review articles that summarize statistical and OR applications in cancer screening. Heidenberger [7] reviews the studies using quantitative approaches that focus on determining which screening strategy should be used for a population or an individual. Stevenson [8] summarizes statistical models considering the problem of planning and evaluation of cancer screening, whereas Pierskalla and Brailer [9] summarize mathematical models for cancer screening including the earliest OR applications. Knudsen *et al*. [5] provide a comprehensive summary of articles that use simulation methodology,the most

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Table 1. Estimated New Cancer Cases and Deaths in the US in 2008 for Selected Cancer Types [1]

Cancer Type	Estimated New Cases	Estimated Deaths
Lung cancer	215,020	161,840
Prostate cancer	186,320	28,660
Breast cancer	184,450	40,930
Colorectal cancer	148,810	49,960
Bladder cancer	68,810	14,100
Skin cancer	67,720	11,200
Leukemia	44,270	21,710
Pancreas cancer	37,680	34,290
Gastric cancer	21,500	10,880
Other cancers	462,600	192,080
Total	1,437,180	565,650

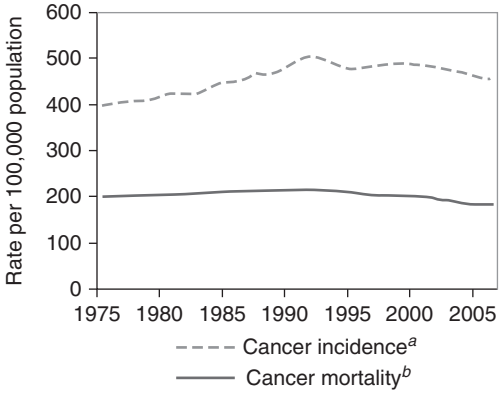

Figure 1. Cancer incidence and mortality rates in the United States between 1975–2006 [2]. Cancer incidence[a] data come from SEER based on nine sites (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta) whereas cancer mortality[b] data come from US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. Both rates are per 100,000 and are age-adjusted to the 2000 US population.

commonly used OR tool in cancer screening. Among all modeling (particularly simulation) studies, research by the Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of National Cancer Institute (NCI)–sponsored investigators, is noteworthy. CISNET investigators use simulation/statistical modeling and common inputs to assess the impact of interventions (e.g., screening and treatment) on current population trends in cancer incidence and mortality. More information about CISNET models is available elsewhere [3,10–12].

This article provides a review of the OR studies considering cancer screening that are either briefly described or not mentioned in previous review articles. We classify relevant literature by cancer type. We start with summarizing cancer screening studies that are not applied to any specific cancer type. We then describe OR models on screening for breast cancer, colorectal cancer, cervical cancer, and other cancer types. We present a list of the articles described in this study in Table 3. Finally, we briefly summarize some issues for future research in cancer screening.

GENERAL MODELS FOR CANCER SCREENING

This section describes general (mostly theoretical) studies that are not applied to any

Table 2. Screening Modalities for Selected Cancer Types [4]

Cancer Type	Screening Modalities
Breast cancer	Clinical breast examination, X-ray mammography, magnetic resonance imaging (MRI), ultrasound computed tomography (CT)
Colorectal cancer	Colonoscopy, fecal occult blood test (FOBT), sigmoidoscopy, virtual colonoscopy, digital rectal examination
Prostate cancer	Digital rectal examination, prostate specific antigen (PSA) blood test
Lung cancer	Chest X-ray, computed tomography (CT) scan
Cervical cancer	Pap smear test, HPV test
Bladder cancer	Microscopic urinalysis, urine dipstick, urine cytology, bladder tumor antigen (BTA), nuclear matrix protein (NMP22) immunoassay
Ovarian cancer	Cancer antigen 125 (CA-125) test, pelvic examination, transvaginal ultrasound

Table 3. Summary of OR Models in Cancer Screening

References	Cancer Type	Objective	Methodology
Prorok [13,14]	General	Provide explicit formulation for the proportion of detected cancer	Stochastic stationary point process
Butler [15]		Maximize expected lifetime	Discrete-time Markov process
Lee and Pierskalla [16]		Minimize aggregate detection delay	General stochastic model
Milioni and Pliska [17]		Minimize screening cost and minimize death probability	Continuous-time semi-Markov process
Houshyar [18]		Minimize the total cost of screening program	General stochastic model
Hanin *et al*. [19]		Minimize the difference between the expected tumor size with and without screening	General stochastic model
Özekici and Pliska [20]	Breast	Minimize total costs	MDP
Parmigiani [21–23]		Minimize expected losses	Non-Markovian stochastic model
Zelen [24] Lee and Zelen [25–27], Lee *et al*. [28]		Maximize total utility	General stochastic model
Tsodikov *et al*. [30]		Minimize the expected delay time for the diagnosis of a recurrent cancer	General stochastic model
Baker [31]		Minimize the cost of screening and lost life-years	General stochastic model
Günes *et al*. [32]		Minimize breast cancer deaths	Queuing model
Maillart *et al*. [33]		Maximize survival probability	POMDP
Ayer *et al*. [34]		Maximize QALYs	POMDP
Ivy [35]		Minimize costs of screening and treatment	POMDP
Chhatwal *et al*. [36]		Maximize QALYs	MDP
Frazier *et al*. [37]	CRC	Find cost-effectiveness of alternative screening programs	Markov process and simulation
Preston and Smith [38]		Minimize the total cost of screening	Continuous-time Markov process and embedded Markov process
Clemen and Lacke [40]		Maximize the number of prevented cancers and minimize the total cost of screening	Simulation
Parmigiani *et al*. [41]		Minimize the probability of becoming infected before the screening examination	Continuous-time stochastic model
Leshno *et al*. [42]		Find cost-effectiveness of alternative screening policies	POMDP
Harper and Jones [43]		Maximize survival and the number of detected CRC	Semi-Markov process and simulation
Yaesoubi and Roberts [44]		Minimize a function of total cost and QALYs (negative term)	Game theoretical model
Erenay and Alagoz [45]		Maximize QALYs and minimize total cost of screening and treatment	POMDP
Myers *et al*. [46]	Cervical	Find cost-effectiveness of alternative screening policies	Markov process

Table 3. (*Continued*)

References	Cancer Type	Objective	Methodology
Goldie *et al*. [47]		Find cost-effectiveness of alternative screening policies	Markov process
Kulasingam *et al*. [48]		Find cost-effectiveness of alternative screening policies	Markov process
Tsodikov and Yakovlev [29]	Lung	Minimize the delay time for cancer detection and minimize total cost	General stochastic model
Pinsky [49]		Provide explicit formulation for the expected number of detected cancers	Convolution model
Tsodikov *et al*. [50]	Prostate	Provide explicit formulation for prostate cancer lead-time and over diagnosis rate	Stochastic model
Kent *et al*. [51]	Bladder	Minimize detection delay	Nonlinear programming
Havrilesky *et al*. [52]	Ovarian	Find cost-effectiveness of alternative screening policies	Markov process
Davies *et al*. [53]	Gastric	Maximize reduction in mortality	Simulation

specific cancer type. In two related articles, Prorok [13,14] introduces a stochastic stationary point process that represents the natural history of a chronic disease such as cancer, under a given screening program. Prorok's stochastic model includes three states: disease-free, preclinical, and clinical states, where the sojourn time for each state is a random variable. The author defines the number of screenings as an exogenous variable to the model. The author also assumes that the time horizon is divided into equal-sized intervals and each screening is assumed to occur in one of these intervals. Prorok provides explicit formulations for the mean lead time, mean forward recurrence time, and proportion of detected cancers by screening for this model. The author performs a numerical analysis using hypothetical parameters.

Butler [15] provides a four-state discrete-time Markov process model to determine the optimal inspection schedule for a system where the inspection itself may cause the failure of the system (e.g., X-ray screening to detect cancer). The author provides an explicit formulation for the inspection schedule that maximizes the expected lifetime of the system and shows in which cases it is optimal not to screen, always to screen, and to screen periodically. The author does not perform any computational analysis.

Lee and Pierskalla [16] develop a general stochastic model that can be used to make a cost-benefit analysis of population screening programs for contagious and noncontagious diseases. The objective of this model is to minimize the aggregate detection delay (or equivalently, minimize the average number of people who have the disease) subject to a budget constraint. The authors convert this stochastic model to a knapsack problem and solve it optimally. They consider both

perfect and imperfect tests, but assume constant screening test accuracy over time. They further assume that the number of susceptible people in the population is constant and the incidence rate is time-stationary. They account for noncompliance to recommended policies. They show that when tests are perfect (i.e., sensitivity and specificity of the tests are 100%), optimal screening policy consists of equally spaced screening intervals.

Milioni and Pliska [17] present a stochastic model to find the optimal inspection schedule for a deteriorating system progressing toward a failure, where the deterioration process is modeled as a continuous-time semi-Markov process. They consider two objectives: minimizing the inspection cost subject to the constraint that the probability of failure is less than a specified value and minimizing the failure probability while the total number of screenings is fixed. They note that their model can be applied to the cancer screening problem. They provide dynamic-programming-based methods to solve the optimal inspection scheduling problem for both objectives.

Houshyar [18] presents a general stochastic model formulation to derive the optimal screening policy for a given disease and population. The objective is to minimize the total cost of a screening program including the costs of screening tests, treatment, and death. The author classifies disease states as occult, clinically surfaced or detected by examination, cured, and death. The author assumes that the screened population is closed and death from cancer is independent of death from other causes. The author concludes that the optimal screening strategy is typically aperiodic and the screening interval is age-dependent.

Hanin *et al*. [19] provide a stochastic model that represents cancer recurrence under a specific screening schedule (or no screening) to evaluate the performance of cancer surveillance programs. They measure the performance of a given screening program by the difference between the expected tumor size with and without screening. They break the tumor progression into three stages: formation of initiated cells, transition from initiated cells to malignant clonogenic cells (cells that have the ability to proliferate to regenerate the tumor), and transition from malignant clonogenic cells to a malignant tumor. They model time in each stage as a random variable and provide examples from different distributions. They present an explicit formulation for screening efficiency and derive the structural properties for an optimal screening schedule. They also present numerical results with hypothetical data. They find that a fixed number of screenings should be uniformly distributed over the decision horizon under exponential tumor growth.

MODELS FOR BREAST CANCER SCREENING

Breast cancer is probably the most commonly studied cancer type in the OR literature. There are several early studies on breast cancer screening such as Zelen and Feinleib [54], Kirch and Klein [55], Blumenson [56], Shwartz [57], Eddy [58], Voelker and Pierskalla [59], van Oortmarssen *et al*. [60], Houshyar and Al-Khayyal [61], which are described in the previous survey articles in detail.

Özekici and Pliska [20] develop an infinite-horizon, undiscounted, delayed Markov decision process (MDP) model that minimizes the total expected cost of inspection, false-positives, corrective actions (treatments), and failures such as deaths. They refer to this model as a delayed MDP because the sojourn time in healthy state is a general nonnegative random variable but once the process leaves healthy states, it behaves like a Markov process. They assume the disease aggression and test accuracies are stationary. They use breast cancer screening problem as an example and show that the optimal policy is not to inspect a person for whom the cost of failure is under $55,000, where the cost of failure is defined as the sum of terminal medical care costs and a dollar value assigned to the possible loss of life.

Parmigiani [21] addresses the question of which age groups and what part of population to screen for breast cancer. The author utilizes a continuous-time non-Markovian stochastic model for disease progression and calculates the optimal policy that minimizes expected losses including financial costs,

side effects, wasted time, stress due to false-negative test results, mortality, morbidity, and cost of treatment. The author presents a set of sufficiency conditions which ensure that screening frequency increases with age. In another paper [22], Parmigiani finds an exact solution to this model when there are only two disease states and the test is imperfect. In a related paper, Parmigiani [23] studies the question of whether to screen or not, given the age and risk factors of the patient and whether to re-examine a recently screened patient.

Zelen [24] develops a continuous-time stochastic model to find the optimal screening policy such that the objective is to maximize a general weighted utility function. The author considers age-specific incidence while keeping all other parameters stationary. The author concludes that if the incidence is stationary and the sensitivity of the test is perfect, then the screening intervals should be equally spaced. As a result, the author suggests that women over 50 should have an annual mammography screening.

In a series of papers, Lee and Zelen [25–27] and Lee *et al*. [28] extend the model of Zelen [24] to address various problems in cancer screening such as the optimal time to initiate screening. Lee and Zelen [25] consider the problem of finding the best periodic screening schedule for the early detection of a given disease. They develop a three-state stochastic model based on the model of Zelen [24] and determine the best screening schedule using two approaches. The first approach imposes a limit to the probability of being in a preclinical state whereas the second approach maximizes the ratio of expected number of patients diagnosed by the screening test over the expected number of cancer patients. They assume patients have different disease development risks and the time in preclinical state is exponentially distributed. They then illustrate the performance of their proposed screening schedules on breast cancer. In a related paper, Lee and Zelen [27] develop a stochastic model for predicting the mortality for specific screening policies for breast cancer. They consider age-specific incidence and sensitivity. They use Breast Cancer Surveillance Consortium (BCSC) data and conclude that initiating screening at age 40 instead of age 50 would lead to a small reduction in mortality.

Tsodikov *et al*. [30] consider breast cancer recurrence under a specific screening schedule. They build a stochastic model for the recurrence of a posttreatment cancer by assuming that the initial number of clonogenic cells follows Poisson distribution and the time until tumor recurrence from each clonogenic cell is identically distributed. They explicitly model cancer recurrence time and apply the optimization framework provided by an earlier article by Tsodikov and Yakovlev [29] to determine the optimal discrete-time cancer screening schedule that minimizes the expected delay time for the diagnosis of a recurrent cancer. They also perform a numerical analysis using BCSC data.

Baker [31] builds a stochastic model to evaluate the cost of screening and the cost of life-years lost due to breast cancer. The author measures costs such as screening costs in terms of months of life. Baker assumes one month of life is worth eight screenings. The author also assumes that ductal carcinoma *in situ* (DCIS) tumors, a noninvasive breast disease, are not harmful and thus can be ignored. The author evaluates a set of policies and concludes that the optimal screening policy should start at age 48, end at age 61.5, and should occur approximately every 2.5 years.

Günes *et al*. [32] develop a queueing model to investigate the impacts of various dynamic factors in mammography screening that are in interaction such as mammography reading volume and quality, access to screening, and delays in service. Their queueing model represents patients as the customers and radiologists as the servers, where the service capacity is limited. They also develop a simulation model. They minimize breast cancer deaths, while keeping system cost as a constraint. They find that improving the dissemination without an increase in the quality of the screening tests would result in excessive waste of resources.

Maillart *et al*. [33] develop a partially observable Markov chain model to investigate the relative value and frequency of

mammography screening for premenopausal women versus postmenopausal women. Their objective is to maximize the survival probability of a given patient. Using sample path enumeration, they evaluate 1223 policies, where each policy consists of two different screening intervals. They consider age-specific disease aggression and imperfect tests (both false-positive and false-negative test results). They show that screening should start at early ages and continue relatively late in life regardless of the screening intervals adopted.

Ayer *et al*. [34] develop a finite-horizon partially observable Markov decision process (POMDP) model to determine the optimal mammography screening strategy for an individual patient. The objective of this POMDP model is to find the optimal personalized screening policy that maximizes the total expected quality-adjusted life-years (QALYs) of a woman during her lifetime. They optimally solve this POMDP model using real data. They consider age-dependent disease progression and test accuracies as well as the possibility of self-detection. They show that the individualized personalized screening schedules outperform the existing guidelines with respect to the total expected QALYs, while significantly decreasing the number of mammograms. They further demonstrate that the mammography screening threshold risk increases with age. They also derive several structural properties of their POMDP model, including the sufficiency conditions that ensure the existence of a threshold cancer risk over which it is optimal to mammogram.

Ivy [35] builds a POMDP model that determines a cost-optimal screening and treatment policy from the payer's perspective while accounting for the patient's utility. The author assumes that both the likelihood of death from other causes and test accuracy are age-independent. The author discretizes the state space of the POMDP model, converts it into an MDP model, and solves this MDP using data from the literature. Ivy then presents the policy trade-off curves based on probabilities of *in situ* and invasive cancer while balancing payer cost and patient utility.

Chhatwal *et al*. [36,62] develop a finite-horizon MDP model to optimize breast-biopsy decisions based on mammography findings and demographic risk factors for women undergoing mammography. They compute the optimal biopsy decisions as a function of the probability of cancer while maximizing the total expected QALYs of a woman. They perform a structural analysis of the MDP model and prove several structured policies such as the optimal policy is a control-limit type for all ages (there exists a threshold probability of cancer such that it is always optimal to biopsy over that threshold) and the optimal control limit is nondecreasing with age. They use clinical data to solve the MDP model optimally and show that as women get older, the biopsy should be made less aggressively since women in older age groups benefit less from aggressive biopsying due to limited life expectancies.

Models for Colorectal Cancer Screening

The earlier studies on colorectal cancer (CRC) screening such as the studies by Eddy [63] and Eddy *et al*. [64] are described in previous review articles. Frazier *et al*. [37] compare the cost-effectiveness of several CRC screening policies suggested by several expert panels. They model the progression of CRC using a Markov process and develop a Markov-process-based simulation model to evaluate the performance of a given screening policy. They use data from literature and SEER database to simulate the US population by gender and age, and evaluate the performance of each screening policy. They perform extensive sensitivity analyses and report the best screening policies for each of these cases. They suggest the use of annual fecal occult blood test (FOBT) plus five-year sigmoidoscopy for CRC screening.

Preston [38] uses a continuous-time Markov process, an extension of the model described by Preston and Smith [39], to evaluate the performance of periodic screenings for a specific disease and a screening test with a particular sensitivity and specificity. The author models disease progression as an embedded Markov process with five system states. The author assumes that

the screening interval is constant (i.e., only periodic screenings are considered) and incorporates the total cost of cancer screening into the model. Preston also uses a parametric critical test value, a threshold that determines whether the test result is negative or positive. The author shows that the optimal combination of screening interval and critical test value minimizing the total expected cost of screening can be obtained by a nonlinear optimization model. The author presents numerical results for CRC screening when the only available screening modality is FOBT.

Clemen and Lacke [40] develop a simulation model by adding stochastic variables such as cancer dwelling time to an earlier deterministic model of Wagner *et al*. [65] and compare 30 different CRC screening policies. They use expert opinion and statistical methods to estimate the input parameters of the simulation model. They consider two criteria to compare various screening policies: number of prevented cancers and expected cost per saved life year. Their results show that undergoing colonoscopy every three years is the best screening policy.

Parmigiani *et al*. [41] develop a stochastic model to find the optimal timing of colonoscopy in a continuous-time setting in which individuals are examined only once in their lifetime. They derive a closed-form solution for the optimal timing of screening by maximizing a utility function which is equivalent to minimizing the probability of becoming infected before the screening examination. Therefore, they find the optimal time of screening by taking the derivative of this probability function. They assume that the sensitivity of the screening test is the same for all ages. They find that the optimal time for screening is at age 75 if the patient undergoes screening just once during his/her lifetime.

Leshno *et al*. [42] make a cost-effectiveness analysis for CRC screening for an individual with average risk of developing CRC. They build a POMDP model to represent the progression of CRC for a given screening strategy and use it to evaluate the performance of a set of common CRC screening strategies. They use data from the literature to estimate the input parameters and perform an extensive numerical analysis, which suggests that the use of colonoscopy every ten years and the use of annual FOBT plus five-year sigmoidoscopy are the most cost-effective two strategies.

Harper and Jones [43] consider the problem of determining the best screening policy for an average patient using semi-Markov process and simulation models. They develop a five-state semi-Markov process model using general transition time distributions. They show how to calculate the probability of early polyp and cancer detection given that the time between two consecutive screenings is constant. The authors do not provide any numerical results for the semi-Markov process model; instead, they present a detailed simulation model where disease progression is modeled as a semi-Markov process. The state space of the simulation model consists of conventional cancer states (clean, polyp, cancer) and metastatic CRC state. They utilize clinical data from European health institutions to evaluate and compare six different screening policies with respect to several criteria such as mean survival time from CRC diagnosis, percentage of detected polyps, cancers, etc.

Yaesoubi and Roberts [44] develop a sequential game theory model with perfect information to analyze the decisions of an insurance company for covering CRC screenings. The insurer decides which screening alternatives to cover, how much the insurance premium would increase to cover CRC screenings, and how much the insurees would have to pay to cover recommended screenings. The insurer's objective is to minimize a weighted average of the total screening/treatment cost and total QALYs of all of the patients (a negative term). In return, the insurees choose the screening alternative that maximizes a utility function of screening cost and their total QALYs. The authors assume that the decisions are made every 10 years. They also assume that patients have perfect information about the progression of the CRC and are able to estimate their total expected QALYs. They use a simulation model and clinical data to estimate the progression of CRC under

certain screening alternatives. The details of this simulation model are explained in another related paper by Roberts *et al*. [72]. Yaesoubi and Roberts assume that the patients belong to the two risk groups (low and high risk) and they consider only two screening alternatives: FOBT and colonoscopy. Their numerical results show that covering CRC screening, especially for low risk patients, is not economically attractive for the insurer unless the insurer's valuation of QALY is very high.

Erenay and Alagoz [45] develop a finite-horizon POMDP model that can be used to obtain a patient-specific optimal lifetime screening policy. They use two optimization criteria: total expected QALYs of the patient and total cost of screening and treatment. They consider the effect of age, gender, and personal CRC history on CRC progression. They model patients with both low and high risk of developing polyps, the precursor of CRC, separately. They also account for the secondary occurrence of CRC, which enables the model to determine the optimal screening policy for CRC surveillance. They perform a numerical analysis by using data from SEER database, clinical databases, and literature.

Models for Cervical Cancer Screening

The earlier studies on cervical cancer screening such as Lincoln and Weiss [66], Eddy [67], Habbema *et al*. [68], and Boyd *et al*. [69] were described in previous survey articles in detail. Myers *et al*. [46] develop a Markov model that represents the natural history of the human papillomavirus (HPV), the primary cause of cervical cancer, and cervical cancer under a specific Pap smear screening. They use the Markov model to analyze the effects of different screening interval choices on cervical cancer incidence for a cohort population. They vary starting age for screening to evaluate the performance of screening policies using Pap smear test with 1-to-5-year intervals and compare them to no screening. They show that as the screening intervals decrease, the performance of the screening improves. However, the benefit of more frequent screening reduces for women over a threshold age. They also note that the performance difference is insignificant if the screening starts at a very early age such as 15–25.

There are several other studies that analyze the effect of HPV screening and prevention techniques on cervical cancer prevention, by using Markov models. Goldie *et al*. [47] evaluate the cost-effectiveness of the HPV DNA test in addition to conventional cytology tests scheduled according to the national guidelines. Kulasingam *et al*. [48] consider whether adding HPV vaccination to the cervical cancer screening policy suggested by national guidelines as compared to screening alone is cost-effective or not. Their numerical results show that both DNA test with conventional screening and vaccination with conventional screening are, cost-effective when compared to conventional screening alone.

Models for Screening Other Cancers

Tsodikov and Yakovlev [29] consider the problem of optimizing cancer screening schedule for a given patient and apply their theoretical findings to lung cancer screening. They classify the health states as disease-free, infected, and heavily infected. They perform an analytical study by developing a stochastic model that optimally schedules cancer screenings over a given decision horizon for given data. They first assume that the number of total screenings is fixed and minimize the total expected delay time to diagnose the cancer. They then relax this assumption and minimize the total cost of cancer screening by assigning a unit cost for delay time to cancer detection. They further assume that there is no symptomatic diagnosis and cancer diagnosis probability after screening increases with time within the same health state. They derive several structural properties of the optimal screening schedule such as the existence of an optimal periodic screening schedule when the total number of screenings is fixed.

Pinsky [49] develops a natural history model for a specific disease and measures the performance of a screening policy for a target population. The author develops a five-state convolution model by relaxing the Markovian assumption in Chen *et al*.'s [70] five-state Markov process model. Pinsky demonstrates the computation of the expected number of

screen-detected preclinical and clinical disease states given a specific screening program and provides closed-form solutions for various components of the model such as sojourn time and over-diagnosis rate. The author uses data from literature and Mayo Lung Cancer Screening Trial (MLCST) [71] and performs a numerical analysis for lung cancer, which shows that the model's results fit well to the MLCST. The author also investigates how screening interval affects the model's outputs. For example, the author shows that lead times are not affected by changes in screening interval whereas the proportion of the cohort ever diagnosed with late-stage lung cancer is very sensitive to the screening intervals.

Tsodikov *et al*. [50] use a three-stage stochastic model to represent prostate cancer progression under a PSA screening program. They explicitly formulate certain characteristics of the prostate cancer progression including mean lead time, prostate cancer incidence under a given screening program, and over-diagnosis rate for each patient type and representative population. They then use SEER data to perform a numerical analysis and estimate these characteristics for prostate cancer.

Kent *et al*. [51] develop a nonlinear optimization model to determine the optimal time for the bladder cancer screening from the physician's perspective. They optimize the expected detection delay while minimizing the probability that the cancer spreads to other parts of the body. They assume that only a limited number of screenings is available and recurrence of tumors follows a Poisson process. They further assume that the screening tests are perfect. They conclude that their proposed screening policy would save three weeks of delay in detection when compared to clinical practice.

Havrilesky *et al*. [52] build a Markov-process-based simulation model to estimate the cost-effectiveness of various screening strategies for ovarian cancer. They use age-specific incidence and mortality rates from SEER data. Their outcome measures include mortality reduction, number of false-positive tests, positive predictive value, years of life saved, lifetime economic costs, and incremental cost-effectiveness ratio. They conclude that annual screening is cost-effective and cost-effectiveness of screening is most sensitive to test frequency, specificity, and cost.

Davies *et al*. [53] build a discrete-time simulation model to measure the performance of a screening program against *Helicobacter pylori* infection, the primary cause for gastric cancer, in England and Wales, where individuals under age 50 would be screened only once. They use data from the literature and the simulation model to estimate the reduction in mortality due to the screening program and the cost of the program. They report sensitivity analyses for five parameters with high uncertainty.

FUTURE RESEARCH IN CANCER SCREENING

Cancer screening is very controversial with many open research questions such as when to start and end screening? How often should a target population undergo a particular screening modality? Is the use of dynamic screening interval/policy a better strategy than the current screening recommendations using static screening strategies? How can a more personalized screening policy based on individual risk factors be implemented? What would be the effects of requiring some patients to use more expensive but more sensitive screening modalities? Is it cost-effective to use a new screening technology over an existing one? What are the mortality and morbidity benefits of a particular screening program?

Because of its importance, there is a growing interest among operations researchers in studying the cancer screening problem. As Maillart *et al*. [33] note, there are two approaches taken in quantitative cancer screening models. On one extreme, which is taken by most studies in the literature, empirical, cost-effectiveness simulation models based on clinical trials and clinical data are used. A simulation model can be used to find the best strategy that maximizes an objective by testing all reasonable screening strategies and comparing their outcomes. This is feasible only when the number of reasonable screening policies is very small.

However, the number of possible screening policies (due to open questions such as when to start and end screening, what should be the optimal screening interval for different risk groups, which screening technology should be used for which type of patients) increases dramatically and hence the computation of all cost-effective strategies becomes intractable.

At the other extreme, analytical models are utilized, which have several modeling limitations. For instance, most of these studies do not perform extensive numerical analyses using reliable real clinical data. In particular, while several researchers solve their analytical models using data from the literature, some of the data sources include unreliable/inaccurate estimations, which may affect the policy recommendations made by these studies. The validation of the data used in these studies is typically missing whereas it is of crucial importance. Furthermore, the existing studies make several unrealistic assumptions by ignoring important factors affecting the screening decisions. For instance, many studies consider only fixed screening intervals (i.e., the screening interval does not depend on the results of the previous screening tests) whereas the screening policy should consider the results of the previous tests in making further screening recommendations.

Moreover, several studies do not explicitly model precursor states, which is very critical in modeling diseases (such as CRC) that have a precursor clinical state (such as polyps in CRC) which progresses to cancer with time. That is, certain cancer types may not be represented properly with these models. Because removing such precursors affects further cancer development, any realistic model should consider them explicitly. Most researchers assume constant screening test accuracy, that is, the accuracy of the screening tests does not depend on age. Similarly, several studies assume that the disease aggression does not change with age although there is strong evidence that the progression of the diseases is highly age-dependent.

In addition to these common limitations of the existing studies, some of the other limiting assumptions in these models include the following: the number of the susceptible people in the population is constant and the incidence rate is time-stationary; the time in preclinical state is exponentially distributed; the risk of cancer is the same for all population; the number of available screening tests is equal to one; screening tests are perfect; tumor recurrence follows a Poisson process; self-diagnosis of diseases (such as breast cancer) is not possible; the disease mortality does not change with age.

Although the validation of OR models constitutes a barrier for their policy implementation, mathematical modeling is an essential tool for planning and improving cancer screening due to the complexity of the cancer screening problem. Future research in cancer screening may need to combine the two approaches described earlier. Furthermore, there is also a strong need to develop models without making any unrealistic assumptions, such as the ones listed earlier. Another important issue in cancer screening studies is to conduct numerical analyses using reliable data. Fortunately, there are many statistical modeling approaches in the literature that study disease progression and treatment decisions more rigorously. Combining the OR methods with statistical tools that analyze real clinical data more rigorously is another promising area of research. Considering huge economic cost of and lives lost due to cancer, more research is needed to design better screening programs, the most cost-effective means for controlling this disease.

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