Quantifying the duration of the preclinical detectable phase in cancer

screening: a systematic review

Sandra ME Geurts PhD^{1*}, Anne MWM Aarts MSc^{2*}, André LM Verbeek PhD², Tony HH Chen PhD³,

Mireille JM Broeders PhD^{2,4}, Stephen W Duffy MSc⁵

*Shared first authorship

¹ Department of Medical Oncology, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands

² Radboud Institute for Health Sciences, Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

³ Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan

⁴ Dutch Expert Centre for Screening, Nijmegen, the Netherlands

⁵ Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Corresponding author

Sandra M.E. Geurts, PhD

sandra.geurts@mumc.nl

Department of Internal ~~M~~medicine

Division of ~~M~~medical ~~O~~ncology

Academic Hospital Maastricht

P. Debyelaan 25

6229 HX Maastricht

The Netherlands

Running title

Preclinical detectable phase of cancer

Epub ahead of print

Abstract

Objectives: ~~To~~ The aim of this study was to provide an overview of published mathematical estimation approaches to quantify the duration of the preclinical detectable phase using data from cancer screening programs.

Methods: A systematic search ~~in~~ of PubMed and Embase was conducted for original studies presenting mathematical approaches using screening data. The studies were categorized by mathematical approach, data source, and assumptions made. Furthermore, estimates of the duration of the preclinical detectable phase of breast and colorectal cancer were reported per study population.

Results: From 689 publications, 34 estimation methods were included. Five distinct types of mathematical estimation approaches were identified: ~~prevalence to incidence ratio~~ prevalence-to-incidence ratio (n=8), maximum likelihood estimation (n=16), expectation-maximization algorithm (n=1), regression of observed on expected (n=6) and Bayesian Markov-~~C~~Chain Monte Carlo estimation (n=5). Fourteen studies used data ~~of~~ from a both screened and ~~an~~ unscreened populations, whereas ~~nineteen~~ 19 studies included only information from a screened population. Estimates of the duration of the preclinical detectable phase varied between ~~two~~ 2 and ~~seven~~ 7 years for breast cancer ~~within~~ the HIP study (annual mammography and clinical breast examinations in women aged 40-64 years) and ~~two~~ 2 and ~~five~~ 5 years for colorectal cancer ~~within~~ the Calvados study (~~a one~~ guaiac fecal occult blood test in men and women aged 45-74 years).

Conclusions: Different types of mathematical approaches lead to different estimates of the ~~duration~~ of preclinical detectable phase duration. We advise researchers to use the method that matches the data available, and to use multiple methods for estimation when possible, ~~as~~ since no method is perfect.

Introduction

Cancer screening programs aim to detect cancer precursors or cancers at an early stage, in order to prevent cancer death by timely treatment. Treatment for cancer precursors or cancers in their preclinical phase is generally more effective than treatment upon clinical symptoms [1]. The duration of the preclinical detectable phase, also referred to as the sojourn time, can be considered the window of opportunity for screening to detect a cancer early. This duration is correlated with the sensitivity of the screening test and the underlying cancer incidence. A screening test that can detect very early stages of cancer is associated with a longer preclinical detectable phase duration than a test that detects more a higher number of cancers but at a more advanced cancers stage. As such, both the preclinical detectable phase duration and the sensitivity of the screening test are central to the determination of the screening interval [1].

Quantifying the duration of the preclinical detectable phase duration is challenging because it is not directly observable. We know when an individual cancer is diagnosed, but we do not know for how long prior to diagnosis it was in the preclinical detectable phase. The preclinical detectable phase duration can be seen as a function of tumor growth, often expressed as volume doubling time [2, 3]. However, Volume-volume doubling times are, however, difficult to estimate since once a cancer is diagnosed it is excised or otherwise treated, and observation of its natural growth cannot be observed thereafter. Therefore, a number of mathematical approaches have been developed for the estimation of to estimate the duration of the preclinical detectable phase duration based on data from cancer screening programs, including rates of detection of cancer at first and subsequent screens and the incidence rates of interval cancers [4-11].

Since an overview of these approaches and their underpinnings is not available, we have conducted a systematic review that can help researchers choose the mathematical approach that best suits their data. As there is no preferred mathematical estimation approach for the preclinical detectable phase duration *a priori*, we attempted ed to investigate the impact of the mathematical approach used on the actual estimate by studying its application to breast and colorectal cancer screening program data.

메모 포함[C1]: Please confirm that this clarification of "more but more advanced cancers" accurately reflects your intended meaning.

Specificity is another important attribute of a screening test, but since this is readily estimable from empirical false-positive data, without complex modelling, we focused here on the duration of the preclinical detectable phase and the sensitivity.

Epub ahead of print

Materials and Methods

Literature search and study selection

We performed a systematic search to identify studies that described a new or adapted mathematical models designed to estimate the duration of the preclinical detectable phase ~~duration~~ in cancer screening. The search strategy was composed of ~~three 3~~ parts: 1) cancer, 2) screening, 3) preclinical detectable phase, sojourn time, or lead time (Table S1) ~~—~~ and was performed in PubMed and Embase on February 8, 2018. Only primary studies in English or Dutch were included. Methods measuring tumor volume doubling time and using microsimulations were excluded. Finally, the references of the included studies were searched for relevant missing articles.

Data extraction

For each study, ~~two 2~~ researchers (AA and SG) extracted details on the mathematical approach, data source, cancer type, and model assumptions with arbitration by a third researcher (SWD) where needed. Next, the studies were grouped by the mathematical estimation approach and classified per data source (screened and/or unscreened population). Per study, the following attributes were collected: screening rounds (first and/or subsequent), data used for estimation (~~screen-detected~~ screen-detected and/or interval cancers), the underlying incidence of cancer, assumed distribution(s) of the preclinical detectable phase duration and/or lead time, confidence intervals or standard error, and test sensitivity. The underlying incidence of diagnosed cancer is sometimes considered to be equal to the rate of transition from the no-disease state to preclinical cancer [12], although in the presence of overdiagnosis, this assumption is problematic. When ~~there is data~~ are available on people not invited to the screening program, the underlying incidence can be observed from this comparison group. Otherwise the underlying incidence either needs to be estimated within the model, observed from registry data, or not included. Test sensitivity ~~is was either~~ assumed to be

100%, estimated within the mathematical model₇ or observed from [the](#) literature, or not included ~~et~~ [at all](#).

Information was sought on whether the assumed model of natural history allowed tumors to regress (i.e., allowed [the possibility of](#) ~~for~~ a decrease in the size, extent₄ or even presence of cancer) and whether the model corrected for length bias and/or overdiagnosis. Definitions of the screening terms used are summarized in Table 1.

Applications in breast and colorectal cancer screening

To investigate the effects of the different approaches on preclinical detectable phase estimates, we compared estimates of the preclinical detectable phase duration for breast and colorectal cancer between studies with different mathematical approaches, but based on the same data [set](#) (screening test, [population and](#) age range). From the included studies, screening program details including data used, age range₂ and test sensitivity were collected.

Results

From 689 publications ~~resulting identified in from~~ the search, 33 were included in this review, describing 34 methods (Figure S1). From these, ~~five~~ 5 distinct mathematical approaches to estimate the preclinical detectable phase duration were identified: ~~prevalence-to-incidence-ratio-prevalence-to-incidence ratio~~ [6, 13-19], maximum likelihood estimation- [7, 12, 18, 20-32], expectation-maximization algorithm- [33], regression of observed on expected- [8, 11, 34-37], and Bayesian Markov-Chain Monte Carlo estimation- [18, 30, 38-40] (Table 2). Fourteen methods required data on a screened and an unscreened population- [6, 7, 13-17, 20, 21, 23, 33-35, 39], whereas ~~nineteen~~ 19 obtained estimates using only information from a screened population- [8, 11, 12, 18, 19, 22, 24-32, 36-38, 40]. The ~~five~~ 5 mathematical estimation approaches are described below; details concerning the model assumptions in the individual studies per type of mathematical approach are reported in Table 3 and S2. The algebraic development of the ~~five~~ 5 mathematical approaches, with examples, ~~is~~ are described in Supplementary Text 1.

1. Prevalence-to-incidence ratio

The ~~prevalence-to-incidence-ratio-prevalence-to-incidence ratio~~ is the simplest way to estimate the preclinical detectable phase duration and was applied in ~~eight~~ 8 of the included studies [6, 13-19]. This model is based on the well-established relationship, where ~~in~~ disease prevalence is equal to the product of the incidence of the disease and the average disease duration (in this case, preclinical disease duration)- [41]. The attraction of this approach is its simplicity, as the estimation can be carried out with closed form algebra. A disadvantage is that in its simplest form it assumes 100% sensitivity, although it can be corrected by dividing by a sensitivity probability derived from other sources. Furthermore, this approach assumes that the incidence of preclinical cancers is the same as the incidence of clinical cancers at the moment of observation. In the presence of overdiagnosis, this assumption is inaccurate, but if overdiagnosis is not substantial, it may be a useful approximation.

2. Maximum likelihood estimation

Using a formal likelihood expression, the duration of the preclinical detectable phase ~~duration may~~ can be estimated based on the observed prevalence of cancer at screening examinations (i.e., ~~screen-detected~~screen-detected cancers), subsequent screens, and the incidence of cancer in the interval between screening examinations (i.e., interval cancers) in relation to the underlying incidence [7, 20]. In other words, researchers ask— what preclinical detectable phase duration is most likely to explain the observed detection rates and incidence rates of interval cancer found in the screening data? This method was applied in 16 of the included studies [7, 12, 18, 20-32]. In this mathematical approach, it is usually assumed that before screening is initiated, the incidence rate of cancer in the population remains constant and that it will remain constant in the absence of screening. Thus, to take account of varying parameters by age, this approach is often performed stratified by age group. This is usually involves simply performing theseparate estimations separate for several five- or ten10-year age groups. However, more complex approaches are available. For example, Shen and Zelen [27] and Wu et al. [30] proposed models incorporating the possibility that cancers which would have arisen symptomatically in one age group are diagnosed in a younger age group, due to screening. Hsieh et al. [29] used a parametric model with progression parameters common to all age groups, but with underlying preclinical incidence varying with age. Cong et al. et al [31] fit two2 models: one1 in which the sensitivity hasd a linear dependence on age and one1 in which the mean sojourn time hasd such a dependence.

~~At t~~The first screening examination detects a certain number of cancers ~~are detected which that~~ have not yet surfaced clinically. As time passes after the first screening examination, new cancers will develop to become interval cancers, or, in the case of a second examination, will be ~~screen-~~screen-~~detected~~screen-detected. The incidence of interval cancers in the interval between ~~two-2~~ screening examinations will comprise ~~of~~ individuals who had false-negative screening results and newly

diagnosed cases. This process will repeat itself during periodic screening examinations. When the screening is stopped, the incidence will gradually return to the incidence before the introduction of a cancer screening program [7, 20]. With assumed distributions of the relevant observations, a formal statistical likelihood is derived and maximized to estimate the parameters of the preclinical incidence rate, average preclinical detectable phase duration, and test sensitivity [20].

3. Expectation-maximization algorithm

Etzioni et al. are the only group to that described an expectation-maximization algorithm as a tool for obtaining maximum likelihood estimates of the preclinical detectable phase duration, test sensitivity, and the time of cancer onset [33]. The relationships between these variables are described in the same way as in the maximum likelihood estimation models. An expectation-maximization algorithm is an iterative method to maximize likelihood estimates of the parameters of interest in statistical models, where the model depends on unobserved latent variables. Its advantage is that it simplifies the analytical work that is needed to obtain maximum likelihood estimates from a rather complicated underlying model.

4. Regression of observed on expected

Regression of observed on expected, which is a variant of the method of moments, was applied in six of the included studies [8, 11, 34-37]. The method of moments is a method of estimating method of population parameters in which population moments (e.g., expected values of the variables observed) are expressed as a function of the parameter of interest. Estimates are derived by assuming that the population moments are equal to those observed in the data. This method can sometimes be performed by closed form algebra, and is thus analytically more simple than for instance methods such as maximum likelihood estimation. In regression of observed on expected, the estimation of parameters is performed by letting the observed numbers (for example, the number of screen-detected screen-detected or interval cancers) equal the expected numbers derived

from the underlying assumed model (see Supplement 2) plus an error term, using non-linear regression [34, 37]. These expected numbers are formulae ~~that which~~ include the duration of the preclinical detectable phase duration, and may also include sensitivity.

5. Bayesian Markov-Chain Monte Carlo simulation

Bayesian Markov-Chain Monte Carlo simulation methods for estimating the parameters of the preclinical detectable phase duration were applied in ~~five~~ 5 included studies [18, 30, 38-40]. The posterior joint distribution (usually composed of ~~three~~ 3 parameters, ~~the~~ the preclinical incidence rate, the average preclinical detectable phase duration, and test sensitivity) is formed by the prior distributions of the parameters and the likelihood function based on the observed data [42]. The marginal posterior distribution for the parameter of primary interest, ~~(i.e., the average duration of the preclinical detectable phase) duration~~, can, in theory, be estimated by integrating out other parameters. However, as the marginal posterior distribution is often intractable, Bayesian Markov-Chain Monte Carlo simulation (using a sampling algorithm such as the Gibbs sampler), rather than numerical integration, can be used to estimate the parameters. This can be done because after a substantial number of repeated conditional samples, the posterior distribution of the parameter of interest conditional on the other parameters and the data will approximate its marginal distribution.

Applications in breast and colorectal cancer screening

For breast cancer screening, we found ~~thirteen~~ 13 studies reporting ~~fourteen~~ 14 estimates of the preclinical detectable phase duration, all using data from the Health Insurance Plan trial, which offered mammography and clinical breast examination ~~s~~ as ~~the~~ a screening test [6-8, 12-14, 20, 23, 27, 30, 31, 33]. Using the prevalence-to-incidence ratio method, the estimates of the preclinical detectable phase duration at age 40-64 years were 1.3-1.8 years; test sensitivity was assumed to be 100% (Figure 1 and Table S3). The results of the other mathematical estimation approaches (maximum likelihood estimation, Bayesian Markov-Chain Monte Carlo simulation, regression of

observed on expected, and expectation-maximization algorithm) applied to the same data ~~were~~ yielded a preclinical detectable phase duration of 1.2-3.0 years and a test sensitivity ranging from 59% to 90%. Thus, the prevalence-to-incidence method ~~obtained generally led to~~ lower estimates than ~~were obtained using~~ the other methods, ~~generally~~.

For colorectal cancer screening, we identified ~~two-2~~ studies reporting ~~five-5~~ different estimates of the preclinical detectable phase duration in a guaiac fecal occult blood test screening program in a population aged 45-74 years, all using data from the Calvados study in France (Figure 2 and Table S5) [18, 28, 32]. Using the prevalence-to-incidence ratio method, the preclinical detectable phase duration and test sensitivity were estimated to be ~~two-2~~ years and 75%, respectively. The results of the maximum likelihood estimation and the Bayesian Markov-chain Monte Carlo simulation were a preclinical detectable phase duration of around ~~five-5~~ years and a test sensitivity of 50% [18, 28].

~~Prevalence~~The prevalence-to-incidence estimates of the average preclinical detectable phase duration were lower than those of the Bayesian Markov-chain Monte Carlo simulation and maximum likelihood estimation.

Other estimates of preclinical detectable phase duration from studies on breast and colorectal cancer screening programs applied to different screening programs are given in Tables S3-6. Please be awareIt should be kept in mind that estimates can only be compared between methods if the methods were used on with the same data.

Discussion

To our knowledge, this is the first systematic review providing a comprehensive overview of mathematical approaches to estimate the duration of the preclinical detectable phase ~~duration~~ using prevalence and incidence data alongside screening frequency data, and optionally interval cancer data. We identified 34 approaches ~~which that~~ could be classified into ~~five~~ 5 distinct mathematical estimation approaches to estimate the duration of the preclinical detectable phase ~~duration~~. When using the same data source, estimates of the preclinical detectable phase duration varied ~~between~~ among the mathematical approaches. Most (n=16, 47%) methods used maximum likelihood estimation. Estimation approaches based on the ~~prevalence to incidence ratio prevalence to incidence ratio~~ generally ~~lead to yielded~~ shorter estimates of the preclinical detectable phase duration than the other approaches. As the actual duration of the preclinical detectable phase ~~duration~~ is unknown, it is complicated to determine which mathematical method is superior.

~~The A~~ comparison of the estimates of the preclinical detectable phase durations in breast and colorectal cancer screening sheds light on the differences ~~brought by~~ resulting from the mathematical approach, assumptions, and data input (summarized in Table 4). ~~The Prevalence-to-incidence ratio models generally yielded the shortest durations of the~~ preclinical detectable phase, ~~durations estimated with prevalence to incidence ratio models were found to be the shortest,~~ sometimes but not always because 100% sensitivity was assumed. In these models, sensitivity estimates are nearly 100%, suggesting some estimation instability with this oldest method, despite its simplicity. Estimates of the preclinical detectable phase durations were longest in models including the regression of observed on expected. A potential explanation could be that these models did not generally take overdiagnosis into account. In addition, the data source is likely to influence ~~the~~ estimated estimations of the preclinical detectable phase duration. The ~~prevalence to incidence ratio prevalence to incidence ratio~~ uses only data from the prevalence screen, and tends to estimate

shorter preclinical detectable phase durations. Estimates ~~which that~~ used only the first screen averaged 1.5 years, whereas estimates using subsequent screens and/or interval cancers averaged 2.5 years (Table S3). Even when restricted to a single trial, the Health Insurance Plan study of Greater New York-, the averages were 1.6 and 2.0 years, respectively.

Another observation is that ~~two-2~~ studies in the maximum likelihood estimation group based their ~~estimates of the~~ preclinical detectable phase duration ~~estimate~~ only on interval cancers, estimating longer preclinical detectable phase durations. This is unexpected, since one would expect estimation from ~~screen-detected~~~~screen-detected~~ cancers to be affected by length bias or overdiagnosis, ~~and~~ therefore ~~leading to an overestimate-overestimation of~~ the preclinical detectable phase duration, whereas interval cancers would, if anything, be expected to have shorter preclinical detectable phase durations than ~~screen-detected~~~~screen-detected~~ cancers.

We further found, ~~not-un~~surprisingly, that shorter ~~durations of the~~ preclinical detectable phase ~~durations~~ were observed when test sensitivity was assumed to be 100%. This is consistent with the fact that a high detection rate can be modelled as either high test sensitivity or a long ~~duration of the~~ preclinical detectable phase ~~duration~~. Whether the underlying incidence was estimated or observed seemed to have no impact on ~~the estimations of the estimated~~ preclinical detectable phase duration. It also appeared that models that estimated “nuisance-~~nuisance~~” parameters such as the underlying incidence and test sensitivity were more in line with prior knowledge of already analyzed cancer screening programs ~~compared with~~ than models ~~which that~~ constrained some of these parameters from external sources. This might be because the former models better reflect biological complexity or population-specific effects than ~~the~~ models with more parameters constrained in advance.

Can we conclude which estimates are best? Not with 100% certainty, but certain remarks can be made. ~~First,~~No method is perfect. The major advantage of the prevalence-to-incidence ratio prevalence-to-incidence ratio methods is its simplicity, and while its major disadvantages are- the necessity for a number of assumptions and the lack of sound theoretical properties to allow reliable measures of uncertainty. The major advantage of the formal statistical methods such as maximum

likelihood estimation and Bayesian Markov-Chain Monte Carlo simulation is that both give the opportunity to include related parameters (e.g., incidence, and test sensitivity) in the model, and yield estimates which-that take into account the fact that these parameters are also unknown and are estimated with a measure of uncertainty. They~~The disadvantages are the increased complexity and the need for specialized statistics or statistical computing expertise. However, they~~ also allow the calculation of theoretically valid confidence intervals or credibility intervals on the average preclinical detectable phase PCDP duration itself, thus giving more reliable estimates of the uncertainty on this parameter or-of primary interest. Consequently, we suggest that these are preferable to prevalence to incidence ratio-prevalence-to-incidence ratio models.

The preclinical detectable phase duration can be used for both the both to design ~~of~~ cancer screening programs (e.g., the Swedish breast cancer [43] and the Australian bowel cancer [44] screening programs) and the evaluation of existing programs [45, 46]. This review also provides information concerning which data is needed on the data needed for the estimation of the to estimate the duration of the preclinical detectable phase duration and can help researchers to anticipate this issue when developing cancer screening programs.

Most mathematical approaches included in this review were developed for and applied to breast cancer screening. The current literature is thus less focused on other cancer screening programs such as colorectal and cervical cancer. The latter two-2 cancer types, more often than breast cancer, face involve the possibility of non-progressive preclinical (and premalignant) states [47]. Only a small number of the included studies took tumor non-progression into account, indicating the need to define the scope of the investigation to develop methods addressing the overdiagnosis of cancer and regression of precancerous lesions, and making it applicable for all cancer types.

Conclusion

The preclinical detectable phase duration can be estimated by several mathematical estimation approaches ~~which that~~ may lead to different estimates. It seems that the simple approaches of ~~the prevalence-to-incidence ratio~~ prevalence-to-incidence ratio and regression of observed on expected numbers of cancers have deficiencies ~~which that are not shared by the~~ more formal statistical approaches, such as maximum likelihood estimation, expectation-maximization algorithm estimation, and Bayesian Markov-Chain Monte Carlo simulation ~~do not have~~. However, we still advise researchers to use multiple estimation approaches, as none of the models is perfect. As in the physical sciences, when one cannot measure something perfectly, a sound approach is to measure it several times by different methods.

Acknowledgments

We want to thank librarian Alice Tillema for her help with creating the search strategy.

References

- 1.Cole P, Morrison AS. Basic issues in population screening for cancer. *Journal of the National Cancer Institute* 1980;64:1263-1272.
- 2.Lundgren B. Observations on growth rate of breast carcinomas and its possible implications for lead time. *Cancer* 1977;40:1722-1725.
- 3.Otten JD, van Schoor G, Peer PG, den Heeten GJ, Holland R, Broeders MJ, et al. Growth rate of invasive ductal carcinomas from a screened 50-74-year-old population. *J Med Screen* 2018;25:40-46.
- 4.Bae JM. Methodological issues for determining intervals of subsequent cancer screening. *Epidemiol Health* 2014;36:e2014010.
- 5.Stevenson CE. Statistical models for cancer screening. *Stat Methods Med Res* 1995;4:18-32.
- 6.Zelen M, Feinleib M. On the theory of screening for chronic diseases. *Biometrika* 1969;56:601-614.
- 7.Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. *Biometrics* 1984;40:1-14.
- 8.Paci E, Duffy SW. Modelling the analysis of breast cancer screening programmes: Sensitivity, lead time and predictive value in the Florence District Programme (1975-1986). *International Journal of Epidemiology* 1991;20:852-858.
- 9.Chen JS, Prorok PC. Lead time estimation in a controlled screening program. *American Journal of Epidemiology* 1983;118:740-751.
- 10.van Oortmarssen GJ, Habbema JD, Lubbe JT, van der Maas PJ. A model-based analysis of the HIP project for breast cancer screening. *Int J Cancer* 1990;46:207-213.
- 11.Duffy SW, Chen HH, Tabar L, Day NE. Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. *Statistics in Medicine* 1995;14:1531-1543.
- 12.Jiang H, Walter SD, Brown PE, Chiarelli AM. Estimation of screening sensitivity and sojourn time from an organized screening program. *Cancer Epidemiol* 2016;44:178-185.
- 13.Hutchison GB, Shapiro S. Lead time gained by diagnostic screening for breast cancer. *Journal of the National Cancer Institute* 1968;41:665-681.
- 14.Shapiro S, Goldberg JD, Hutchison GB. Lead time in breast cancer detection and implications for periodicity of screening. *American Journal of Epidemiology* 1974;100:357-366.
- 15.Albert A, Gertman PM, Louis TA. Screening for the early detection of cancer. I. The temporal natural history of a progressive disease state. *Mathematical Biosciences* 1978;40:1-59.
- 16.Albert A. Screening for the early detection of cancer II. The impact of screening on the natural history of the disease. *Mathematical Biosciences* 1978;40
- 17.Louis TA, Albert A, Heghinian S. Screening for the early detection of cancer. III. Estimation of disease natural history. *Mathematical Biosciences* 1978;40:111-144.
- 18.Launoy G, Smith TC, Duffy SW, Bouvier V. Colorectal cancer mass-screening: Estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. *International Journal of Cancer* 1997;73:220-224.
- 19.Brenner H, Altenhofen L, Katalinic A, Lansdorp-Vogelaar I, Hoffmeister M. Sojourn time of preclinical colorectal cancer by sex and age: Estimates from the german national screening colonoscopy database. *American Journal of Epidemiology* 2011;174:1140-1146.
- 20.Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. *American Journal of Epidemiology* 1983;118:865-886.
- 21.Alexander FE. Estimation of sojourn time distributions and false negative rates in screening programmes which use two modalities. *Statistics in Medicine* 1989;8:743-755.
- 22.Pinsky PF. An Early- and Late-Stage Convolution Model for Disease Natural History. *Biometrics* 2004;60:191-198.
- 23.Shen Y, Zelen M. Robust modeling in screening studies: Estimation of sensitivity and preclinical sojourn time distribution. *Biostatistics* 2005;6:604-614.

24. Brookmeyer R, Day NE, Moss S. Case-control studies for estimation of the natural history of preclinical disease from screening data. *Statistics in Medicine* 1986;5:127-138.
25. Brookmeyer R, Day NE. Two-stage models for the analysis of cancer screening data. *Biometrics* 1987;43:657-669.
26. Straatman H, Peer PGM, Verbeek ALM. Estimating lead time and sensitivity in a screening program without estimating the incidence in the screened group. *Biometrics* 1997;53:217-229.
27. Shen Y, Zelen M. Parametric estimation procedures for screening programmes: Stable and nonstable disease models for multimodality case finding. *Biometrika* 1999;86:503-515.
28. Pinsky PF. Estimation and prediction for cancer screening models using deconvolution and smoothing. *Biometrics* 2001;57:389-395.
29. Hsieh HJ, Chen TH, Chang SH. Assessing chronic disease progression using non-homogeneous exponential regression Markov models: an illustration using a selective breast cancer screening in Taiwan. *Stat Med* 2002;21:3369-3382.
30. Wu D, Rosner GL, Broemeling L. MLE and Bayesian inference of age-dependent sensitivity and transition probability in periodic screening. *Biometrics* 2005;61:1056-1063.
31. Cong XJ, Shen Y, Miller AB. Estimation of age-specific sensitivity and sojourn time in breast cancer screening studies. *Statistics in Medicine* 2005;24:3123-3138.
32. Shen Y, Dong W, Gulati R, Ryser MD, Etzioni R. Estimating the frequency of indolent breast cancer in screening trials. *Stat Methods Med Res* 2019;28:1261-1271.
33. Etzioni R, Shen Y. Estimating asymptomatic duration in cancer: the AIDS connection. *Stat Med* 1997;16:627-644.
34. Chen HH, Duffy SW, Tabar L. A Markov chain method to estimate the tumour progression rate from preclinical to clinical phase, sensitivity and positive predictive value for mammography in breast cancer screening. *Statistician* 1996;45:307-317.
35. Chen HH, Duffy SW, Tabar L, Day NE. Markov chain models for progression of breast cancer. Part I: tumour attributes and the preclinical screen-detectable phase. *J Epidemiol Biostat* 1997;2:9-23.
36. Duffy SW, Day NE, Tabar L, Chen HH, Smith TC. Markov models of breast tumor progression: some age-specific results. *Journal of the National Cancer Institute* 1997; Monographs.:93-97.
37. Chen TH, Kuo HS, Yen MF, Lai MS, Tabar L, Duffy SW. Estimation of sojourn time in chronic disease screening without data on interval cases. *Biometrics* 2000;56:167-172.
38. Shen S, Han SX, Petousis P, Weiss RE, Meng F, Bui AA, et al. A Bayesian model for estimating multi-state disease progression. *Comput Biol Med* 2017;81:111-120.
39. Myles JP, Nixon RM, Duffy SW, Tabar L, Boggis C, Evans G, et al. Bayesian evaluation of breast cancer screening using data from two studies. *Stat Med* 2003;22:1661-1674.
40. Kim S, Jang H, Wu D, Abrams J. A Bayesian nonlinear mixed-effects disease progression model. *J Biom Biostat* 2015;6:271.
41. Freeman J, Hutchison GB. Prevalence, incidence and duration. *Am J Epidemiol* 1980;112:707-723.
42. Borgelt C KR. *Graphical Models: Methods for Data Analysis and Mining*. Chichester: Wiley; 2002
43. Socialstyrelsen. Screening för bröstcancer. Rekommendation och bedömningsunderlag. Available from: <https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-screeningprogram/2014-2-32.pdf>.
44. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber A, Habbema JD. A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. *Cancer* 2009;115:2410-2419.
45. Aarts AMWM, Duffy SW, Geurts SME, Vulkan DP, Otten JDM, Hsu CY, et al. Test sensitivity of mammography and mean sojourn time over 40 years of breast cancer screening in Nijmegen (The Netherlands). *J Med Screen* 2019;26:147-153.
46. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. *Med J Aust* 2014;201:456-461.
47. Segnan N, Minozzi S, Armaroli P, Cinquini M, Bellisario C, Gonzalez-Lorenzo M, et al. Epidemiologic evidence of slow growing, nonprogressive or regressive breast cancer: A systematic review. *Int J Cancer* 2016;139:554-573.

Epub ahead of print

Table 1 Definitions used in this manuscript

Term	Definition	Ref.
The p Preclinical detectable phase duration	The time interval between the start of the preclinical detectable phase and the time when the cancer manifests itself -clinically (in the absence of screening). The starting point of the preclinical detectable phase depends upon characteristics of the screening test, notably its sensitivity.	[26]
Sensitivity	The proportion of people with a positive screening test among those who have a cancer in the preclinical detectable phase. Note that the s Sensitivity is usually considered to be a constant throughout the preclinical detectable phase, but this is likely to be only approximately true. Intuitively, sensitivity would be lower for smaller tumors earlier in the preclinical detectable phase and higher for larger tumors later in the preclinical detectable phase.	[1]
Lead time	The duration by which the diagnosis of a cancer is moved forward in time due to detection during a screening examination rather than being detected clinically. In other words, the preclinical detectable phase duration is the “potential time-time” a diagnosis of a cancer is moved forward, while lead time is the actual time. Under the assumption of an exponential preclinical detectable phase distribution, the mean preclinical detectable phase duration can also be an estimate of the expected lead time for an individual cancer.	[20]
Screen-detected cancers	Cancers diagnosed by a screening examination, while-whereas interval cancers were-are clinically diagnosed in-between screening examinations.	[12]
Length time bias	Length bias occurs because slow-ly growing tumors with a favorable prognosis have a longer preclinical detectable phase, and are thus more frequently detected at screening than rapidly growing tumors with an unfavorable prognosis.	[1]
Overdiagnosis	The diagnosis of cancer at screening that would never have caused any symptoms or problems during an individual's lifetime.	[48]

Table 2. Overview of the included studies that described d mathematical estimation approaches to estimate the duration of the preclinical detectable phase ~~duration~~ grouped by type of mathematical model and study design. Author, year (cancer type used as an example).

Mathematical approach to estimation	Data source	
	Screened and unscreened [†] populations	Screened population
Prevalence--to--incidence ratio	Hutchinson 1968 (breast) [13] Zelen 1969 (breast) [6] Shapiro 1974 (breast) [14] Albert I-III 1978 (cervix) [15-17]	Launoy 1997* (colorectal) [18] Brenner 2011 (colorectal) [19]
Maximum likelihood estimation	Walter 1983 (breast) [20] Day 1984 (breast) [7] Alexander 1989 (breast) [21] Shen 2005 (breast) [23]	Brookmeyer 1986 ^c (cervix) [24] Brookmeyer 1987 ^c (cervix) [25] Launoy 1997* (colorectal) [18] Straatman 1997 (breast) [26] Shen 1999 (breast) [27] Pinsky 2001 (colorectal) [28] Hsieh 2002 (breast) [29] Pinsky 2004 (lung) [22] Wu 2005* (breast) [30] Cong 2005 (breast) [31] Jiang 2016 (breast) [12] Shen 2019 (breast) [32]
Expectation-maximization algorithm	Etzioni 1997 (breast) [33]	
Regression of observed on expected	Chen 1996 (breast) [34] Chen 1997 (breast) [35]	Paci 1991 (breast) [8] Duffy 1995 (breast) [11] Duffy 1997 (breast) [36] Chen 2000 (breast) [37]
Bayesian Markov--cChain Monte Carlo simulation	Myles 2003 (breast) [39]	Launoy 1997* (colorectal) [18] Wu 2005* (breast) [30] Kim 2015 (breast, lung) [40] Shen 2017 (lung) [38]

[†] The unscreened population is considered as a control group, and may include the control arm of a randomized controlled trial or a historical control group from the time period before screening.

* Studies that describe multiple mathematical approaches to estimate the preclinical detectable phase duration.

^c Study The study design of these articles was case-control.

Table 3. Model assumptions of the included papers by mathematical approach.

Article	Model assumptions							
Author, year	Screening round (first and/or subsequent)	Screening data used for estimation (screen-detected and/or interval cancers)	Underlying incidence of cancer (estimated within the model, observed from the control group, observed from registry data or not included)	Assumed distribution(s) of the preclinical detectable phase duration	Lead time modeled (yes, no) and its assumed distribution	Confidence interval or standard error around estimate (yes, no)	Test sensitivity (estimated within the model, assumed 100%, observed from the literature, or not included)	Tumor regression modeled (yes, no), estimates corrected for length time bias and/or overdiagnosis
Prevalence to incidence ratio								
Hutchinson, 1968 [13]	First	Screen-detected cancer data	Observed from control from <u>the control</u> group	Constant	Yes, constant	No	Assumed 100%	No, no
Zelen, 1969 [6]	First	Screen-detected cancer data	Observed from control from <u>the control</u> group	Exponential	Yes, exponential	No	Assumed 100%	Yes, length time correction
Shapiro, 1974 [14]	First	Screen-detected and interval cancer data	Observed from control from <u>the control</u> group (corrected for self-selection)	Exponential	No, NA	No	Assumed 100%	No, no
Albert I-III, 1978 [15-17]	First	Screen-detected cancer data	Observed from control from <u>the control</u> group	Exponential, gamma	Yes, exponential	No	Not included	Yes, length time and overdiagnosis correction
Launoy, 1997* [18]	First	Screen-detected and interval cancer	Observed from registry data	Not reported	No, NA	Yes	Estimated within the model	No, no
Brenner, 2011 [19]	First	Screen-detected cancer data	Observed from registry data	Exponential	No, NA	Yes	Assumed 100%	No, no
Maximum likelihood estimation								
Walter, 1983 [20]	First and subsequent	Screen-detected and interval cancer data	Observed from control from <u>the control</u> group	Exponential, log-normal, step function	Yes, NA	Yes	Estimated within the model	No, length time correction

Day, 1984 [7]	First and subsequent	Screen-detected and interval cancer data	Observed from control <u>from the control</u> group	Exponential	Yes, exponential	Yes	Estimated within the model	No, length time correction
Brookmeyer, 1986 [24]	First and subsequent	Screen-detected and interval cancer data	Not included (cancelled <u>canceled</u> out the model)	Exponential, piecewise exponential, Weibull, log-normal	No, NA	Yes	Estimated within the model	No, no
Brookmeyer, 1987 [25]	First and subsequent	Screen-detected and interval cancer data	Not included (cancelled out the model)	Exponential	No, NA	Yes	Estimated within the model	Yes, overdiagnosis correction
Alexander, 1989 [21]	First and subsequent	Screen-detected and interval cancer data	Observed from control <u>from the control</u> group (corrected for self-selection)	Exponential	Yes, exponential	No	Estimated within the model	No, no
Launoy, 1997* [18]	First	Screen-detected and interval cancer data	Observed from registry data	Not reported	No, NA	Yes	Estimated within the model	No, no
Straatman, 1997 [26]	First and subsequent	Screen-detected cancer data	Estimated within the model	Exponential	Yes, exponential	No	Estimated within the model	No, no
Shen, 1999 [27]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Estimated within the model	No, no
Pinsky, 2001 [28]	First	Screen-detected and interval cancer data	Observed from registry data	Exponential, gamma & Weibull	Yes, not reported	Yes	Estimated within the model	No, length time and overdiagnosis correction
Hsieh, 2002 [29]	First and subsequent	Screen-detected cancer data	Estimated within the model	Weibull and piecewise exponential	No, NA	Yes	Assumed 100%	No, no
Pinsky, 2004 [22]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential, Weibull	Yes, not reported	Yes	Estimated within the model	No, overdiagnosis correction

Shen, 2005 [23]	First and subsequent	Screen-detected and interval cancer data	Observed from <u>the</u> control group	Piecewise-constant	No, NA	No	Estimated within the model	No, no
Wu, 2005* [30]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Log-logistic	No, NA	No	Estimated within the model	No, no
Cong, 2005 [31]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Estimated within the model	No, no
Jiang, 2016 [12]	First and subsequent	Screen-detected and interval cancer data	Not included (assumed constant)	Exponential	No, NA	Yes	Estimated within the model	No, no
Shen, 2019 [32]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Observed from literature	Yes, no
Expectation-maximization algorithm								
Etzioni, 1997 [33]	First and subsequent	Screen-detected and interval cancer data	Observed from control <u>from the control</u> group	NA	No, NA	No	Estimated within the model	No, no
Regression of observed on expected								
Paci, 1991 [8]	First and subsequent	Interval cancer data	Estimated within the model	Exponential	Yes, exponential	Yes	Estimated within the model	No, no
Duffy, 1995 [11]	First and subsequent	Interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Assumed 100%	No, no
Chen, 1996 [34]	First and subsequent	Screen-detected and interval cancer data	Observed from control <u>from the control</u> group	Exponential	No, NA	Yes	Estimated within the model	No, no
Chen, 1997 [35]	First and subsequent	Screen-detected and interval cancer data	Observed from control <u>from the control</u> group	Exponential	No, NA	Yes	Assumed 100% or observed from <u>the</u> literature	No, no

Duffy, 1997 [36]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Estimated within the model	No, no
Chen, 2000 [37]	First and subsequent	Screen-detected cancer data	Estimated within the model	Not reported	No, NA	Yes	Assumed 100% or estimated within the model	No, no
Bayesian Markov Chain Monte Carlo simulation								
Launoy, 1997* [18]	First	Screen-detected and interval cancer data	Observed from registry data	Not reported	No, NA	Yes	Estimated within the model	No, no
Myles, 2003 [39]	First and subsequent	Screen-detected and interval cancer data	Observed from control from the control group	Poisson	No, NA	Yes	Estimated within the model	No, no
Wu, 2005* [30]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Non-parametric	No, NA	Yes	Estimated within the model	No, no
Kim, 2015 [40]	First and subsequent	Screen-detected interval cancer data	Estimated within the model	Log-logistic	No, NA	Yes	Estimated within the model	No, no
Shen, 2017 [38]	First and subsequent	Screen-detected and interval cancer data	Estimated within the model	Exponential	No, NA	Yes	Assumed 100% or estimated within the model	Yes, overdiagnosis correction

* Articles that described multiple methods to estimate the preclinical detectable phase duration

Table 4 Summary of the method-specific findings

Type of mathematical estimation approach	Prevalence- to -incidence ratio models tends to give shorter <u>estimates</u> , and regression of observed on expected <u>tends to give</u> longer <u>estimates of the</u> preclinical detectable phase durations and higher test sensitivities when compared with the <u>than</u> other mathematical estimation approaches.
Data used	The use of only prevalence screening data tends to give shorter <u>estimates</u> , whereas the use of only interval cancer data tends to give longer <u>estimates of the</u> preclinical detectable phase durations than using both.
Test sensitivity	Shorter <u>durations of the</u> preclinical detectable phase durations are observed if 100% test sensitivity is assumed (these studies were <u>pre</u> dominated by the Health Insurance Plan study data with a younger population and 1960's film technology mammography) than when test sensitivity was estimated within the model.
Underlying incidence	No impact on the preclinical detectable phase duration.

Figure 2. The relation between the average preclinical detectable phase duration and test sensitivity for colorectal cancer screening using guaiac fecal occult blood test (first screen) in men and women aged 45-74 years (i.e. Calvados study, France, 4 estimates from 2 studies) by mathematical estimation type.

Figure 1. The relation between the average preclinical detectable phase duration and test sensitivity for annual screening for breast cancer comprising mammography and clinical breast examination in women aged 40-64 years (i.e. Health Insurance Plan study, USA, 14 estimates from 13 studies) by mathematical estimation type.