Estimating Age-Specific Mean Sojourn Time of Breast Cancer and Sensitivity of Mammographic Screening by Breast Density among Korean Women

Eunji Choi
National Cancer Center
Mina Suh
National Cancer Center
So-Youn Jung
National Cancer Center
Kyu-Won Jung
National Cancer Center
Sohee Park
Yonsei University
Jae Kwan Jun
National Cancer Center
Kui Son Choi (kschoi@ncc.re.kr)
National Cancer Center https://orcid.org/0000-0001-5336-3874

Research article

Keywords: breast density, breast neoplasms, mammography, natural history, mean sojourn time, screening sensitivity.

Posted Date: February 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-238539/v1

Abstract

Background: High breast cancer incidence among women in forties are specific to Asian, implicating dense breast. This study examined the natural history of breast cancer progression among Korean women according to the levels of breast density.

Methods: We applied a three-state Markov model to fit the natural history of breast cancer to data in the Korean National Cancer Screening Program. Diagnosis of breast cancer was ascertained by linkage to the Korean Central Cancer Registry. Disease progression rates (i.e., transition rates from healthy to preclinical state, and from preclinical to clinical state) were estimated across levels of breast density determined by the Breast Imaging, Reporting and Data System (BI-RADS). Preclinical incidence of breast cancer, mean sojourn time (MST) and mammographic screening sensitivity were simultaneously generated in the model.

Results: Overall prevalence of dense breast among Korean women was 53.9%, which declined with age. Transition rate from healthy to preclinical state, indicating the preclinical incidence of breast cancer, was estimated to be higher among women aged 40-49 years (0.0019, 95% CI; 0.0017-0.0021) and women aged 50-59 years (0.0020, 95% CI; 0.0017-0.0022), than older women aged 60-69 years (0.0014, 95% CI; 0.0012-0.0017). Transition rate from preclinical to clinical state was also fastest among younger age groups, which directly translated to the shortest MSTs, estimated as 1.98 (95% CI; 1.67-2.33), 2.49 (95% CI; 1.92-3.22) and 3.07 (95% CI; 2.11-4.46) years for women in forties, fifties and sixties, respectively. The sensitivity of the mammographic screening was higher among older women (0.70, 95% CI; 0.62-0.77) than women in fifties (0.65, 95% CI; 0.62-0.77) and women in forties (0.61, 95% CI; 0.54-0.61). Having dense breasts increased the likelihood of the preclinical cancer risk (1.96 to 2.35 times) and decreased the duration of MST (1.53 to 2.02 times).

Conclusions: Korean women showed 1.5 to 2 times higher prevalence of dense breast tissues, compared to Western women. This study estimated Korean-specific parameters for the natural history of breast cancer that would be utilized for establishing optimal screening strategies in countries with higher dense breast prevalence.

Introduction

Breast cancer poses a major public health problem for women worldwide. Different patterns of incidence and mortality of breast cancer across countries have been explained by availability or accessibility of treatment or early detection program [1]. Previous studies demonstrated that the racial/ethnic differences are attributable in part to prevalence and effect of dense breast. Dense breast, referring over 50% composition of fibroglandular tissue in breast, is well-established risk factor of breast cancer [2-4]. In addition, dense breast plays a role of masking factor in screening and increases interval cancer rates [3]. The mechanisms of dense breast effect are closely interacting with age and menopausal status. Dense breast causes higher incidence of breast cancer and lower mammographic sensitivity among younger women, but the density gradually decreases as women age after menopause.

Mammographic screening is effective method to reduce breast cancer mortality, thus implemented regionally or nationally in many countries [5, 6]. However, the recommendation guidelines in terms of screening intervals or starting- and stopping-ages of screening eligibility are slightly different between Western and Asian countries. While the guidelines from Western countries were not targeted at women aged younger than 50 years [5, 6], Asian guidelines specify earlier starting ages in 40 or 45 years due to a higher proportion of younger women with breast cancer [7-9]. These observations of higher breast cancer incidence among younger women constantly implicate the effect of dense breast.

Although the Korean National Cancer Screening Program (KNCSP) for breast cancer was launched in 2002 to provide biennial mammographic screening for women aged 40 years and older [1], the screening frequencies and timing was not based on Korean-specific evidence. The optimal timing and frequencies need to be quantified by examining natural history of breast cancer. Moreover, examination of dense breast effect on breast cancer progression will provide helpful information on disease incidence and mammographic screening sensitivity under the implementation of KNCSP.

This study aimed to estimate natural history of breast cancer specific for Korean women by utilizing nationwide screening databases from the KNCSP. Also, we examined the effect of having dense breast on breast cancer risk as well as the sojourn time of preclinical breast cancer. In addition, we provided the recent information of prevalence dense breasts among Korea women based on the Breast Imaging, Reporting and Data System (BI-RADS). This study will enhance our understanding of natural history of breast cancer among women in countries with higher prevalence of dense breast and suggest the evidence for optimizing screening strategies.

Methods

A Three-State Markov Model

Given that the progression of breast cancer from disease-free to preclinical or clinical state is not directly observable, various modeling approaches have been developed [10-13]. Markov-based models present its strength in simulating breast cancer progression by utilizing data directly from trials or organized screening programs [14, 15]. In a screening setting, “disease-free/healthy state” is interpreted as state with non-detectable cancer, “preclinical state” with screen-detected cancer, and “clinical state” with interval cancer. The actual record of the screening results for a woman, whether showing negative, screen-detected cancer or interval cancer, determines the transition from one state to another. Although the transition from preclinical state (screen-detected cancer) to clinical state (interval cancer) is not observable in the screening database, but estimable by a likelihood function constructed by transition rates from healthy to preclinical state, and from healthy to clinical state [16, 17].

Therefore, we applied a three-state unidirectional progressive Markov model to fit healthy, preclinical and clinical state of breast cancer for individual women, by which three natural history parameters were simultaneously estimated: 1) transition rates, 2) mean sojourn time (MST) and 3) mammographic screening sensitivity. In figure 1, the λ1 and λ2 represent the transition rates from healthy to preclinical state, and from preclinical to clinical state, respectively. The λ1 describes the instantaneous rate at which a tumor progresses from healthy to preclinical state, reflecting the incidence level of breast cancer among a population. The λ2 refers the rate of preclinical tumor transitioning to clinical tumor, and the inversion of λ2 is MST, during which screening tests can make an earlier diagnosis of asymptomatic disease before symptom presentation. Another important parameter is sensitivity of the screening tests because false-positives or false-negatives are inevitable in a real-world screening program, and misclassification of false-negative results of preclinical cancer ultimately underestimates transition rate parameter in the model. Furthermore, sensitivity has a direct relationship with the MST, because improved test sensitivity creates a longer MST due to the higher probability of detecting disease in the preclinical state. Sensitivity also can be deteriorated due to various factors, such as high breast density, that defer the starting point when screening can detect the disease [18]. Therefore, we simultaneously estimated the sensitivity of mammographic screening tests by specifying a probability of false-negative results (one minus sensitivity) in the modeling procedure [17].

Study Population

Since 2002, the KNCSP for breast cancer has provided biennial mammographic screening for all Korean women aged 40 years and older, and the BI-RADS information has been collected since 2009. To establish our baseline analytic population, we included cancer-free women who underwent KNCSP for breast cancer, for the first time in 2009. Women with incomplete screening results and BI-RADS were excluded, given the importance of the factors in modeling and small missing rates (<2%). In addition, we obtained data only from tertiary hospitals (27.7% of total hospitals) where the quality-controlled screening data are available. The final study cohort comprised 290,448 women. Among them, 149,665 women attended second round of breast cancer screening in 2011, and 91,269 of the women attended all of the three rounds of biennial screening from 2009 to 2013.

By using unique 13-digit resident IDs, the Korean Central Cancer Registry (KCCR) was linked for the baseline study population in the KNCSP to ascertain cancer diagnosis. From the KCCR, we obtained information on primary breast cancer, 10th Revision [ICD-10] codes (C50.0-C50.9, D05.0-D05.9), and date of diagnosis. Women who had screened positive and were diagnosed with breast cancer within one year from the screening attendance were considered as “screen-detected” cases (cancers detected in the preclinical state).

When cancer screening is first implemented in a country, detection rates are higher, than the rates in the following screening rounds, due to the detection of cases that were prevalent before the practice of screening started. So, breast cancers diagnosed within three weeks after women’s first screening in 2009 were excluded to eliminate the prevalent cases, satisfying the Markov assumption of a cancer-free cohort at the start of analysis. A three-week exclusion period resulted in similar detection rates in the first screening round to the following (second and subsequent) screening rounds [14].

Statistical Analysis

An analytical dataset was constructed using the full history of screening results and cancer diagnosis for each of the women. For each event of screening attendance or cancer diagnosis, women’s records were cumulated from the cohort enrollment on January 1, 2009 to the time of the event observation. Lastly, all records were sorted chronologically for each woman to fit the Markov model through the *msm* package in R [17]. Women aged 70 years and older were excluded in the modeling procedure due to small number of cases.

We investigated the effect of the BI-RADS on transition rates (λ1 and λ2) using a proportional hazards model. The BI-RADS system classifies breast tissues by percentage of fibroglandular densities at four levels: (1) predominantly fatty breast (0%–25% dense), (2) scattered fibroglandular densities (25%–50% dense), (3) heterogeneously dense (50%–75% dense), and (4) extremely dense (75%–100% dense). If having denser tissue increased the rate of transition from healthy to preclinical state, it was considered as higher density causally increasing breast cancer risk; if having denser breast made faster the rate of transition from preclinical state to clinical state, ultimately shortening the MST, then it was considered to have a masking effect in mammographic screening by lowering mammographic sensitivity [19]. All results were presented by women’s 10-year age groups.

Results

Breast density composition

Prevalence of dense breast among Korean women who participated in the KNCSP in 2009 were shown in Table 1. About half of Korean women (53.9%) had dense breast. Prevalence of dense breast were 72.4%, 45.9%, 21.7% and 9.2% for women in forties, fifties, sixties and seventies, respectively. Table 1 showed the number of interval cancers and screen-detected cancer according to women’s age groups and status of breast density, with the ratio from interval cancer to screen-detected cancer (I/S). In total, the I/S ratio was higher among women with dense breasts (0.64) compared to women with non-dense breasts (0.46). However, the higher I/S ratio was not detected among women aged 40-49 years, which might be caused by high recall rates reported among the corresponding age group (Table 1).

Cases of screen-detected and interval cancers in the KNCSP screening rounds

Cases detected in the three rounds of screenings were summarized in Table 2. At first screening round (prevalence screen), 337 and 219 invasive cancers were diagnosed as screen-detected and interval cancers. From in situ cancers, 71 and 26 screen-detected and clinical cancer were diagnosed. At second round (first incident screening round), 193 and 114 invasive breast cancer, and 37 and 16 in situ breast cancers were screen-detected and interval cancers,

respectively. 120 and 63 invasive breast cancer, and 24 and 13 in situ breast cancers were screen-detected and interval cancers, respectively, at second incident screen. When examined by age groups, women aged 40-49 years indicated the highest number of breast cancers detectable at screening or within screening-intervals in all screening rounds. Women aged 70 years and older demonstrated the lowest incidence of breast cancer.

Estimated parameters

The rate of transition from healthy to preclinical state, λ1, was 0.0018 (95% CI; 0.0017-0.0019) for total women aged 40-69 years (Table 3). Compared with women in sixties, younger women in forties and fifties demonstrated higher rate transitioning from healthy to preclinical state, estimated to be 0.0019 (95% CI; 0.0017-0.0021) and 0.0020 (95% CI; 0.0017-0.0022), respectively. As the λ1 reflects the incidence level of breast cancer among a population, our results also align with the fact that younger women aged 45-54 years have the highest breast cancer incidence in Korea [20].

In Table 3, the MST, the inverse of λ2, was 2.39 years (95% CI, 2.09 to 2.74) among total women. Higher transition rate from preclinical to clinical state (λ2) among younger women generated shorter MST, 1.98 (95% CI ,1.67 to 2.34), 2.49 (95% CI, 1.93 to 3.23) and 3.07 (95% C, 2.11 to 4.47) years for women aged 40-49, 50-59 and 60-69 years.

The sensitivity of the mammographic screening was estimated to be 0.67 (95% CI, 0.62 to 0.72) for total women, and to be higher among older women, shown as 0.70 (95% CI, 0.62 to 0.77), 0.65 (95% CI, 0.59 to 0.77) and 0.61 (95% CI, 0.54 to 0.61) for women in sixties, fifties and forties, respectively (Table 3).

Hazard of breast density on transition rates

Overall, having 2 to 4 levels of BI-RADS was significantly associated with 1.96 to 2.35-fold accelerated transition from healthy to preclinical state, compared with women with level 1 BI-RADS (Table 3). In addition, women with heterogeneously dense tissue (level 3) and extremely dense tissue (level 4) showed 2.02- and 1.94-times higher hazard on transition to clinical cancer, compared to women with level 1 of BI-RADS. These observations are translated into the significantly shorter MSTs among women with heterogeneously dense breast (1.92 years, 95% CI, 1.64 to 2.27) and extremely dense breast (2.01 years, 95% CI, 1.62 to 2.50). Compared to the current biennial screening protocol from the KNCSP, women with predominantly fatty (Level 1) and scattered fibroglandular tissues (Level 2) have longer-than-2-year MSTs with 3.89 years (95% CI, 2.60 to 5.80) and 2.54 (95% CI, 2.05 to 3.15), respectively.

According to women's age groups, consistent results were shown that having higher levels of BI-RADS was associated with significantly greater risk of transition from healthy to preclinical state. However, transition from preclinical to clinical cancer was not significantly different by breast density levels among women aged 40-49 and 50-59 years, thus showing overlapped confidence intervals in MSTs across four BI-RADS levels, indicating that breast density as a masking factor did not significantly reduce mammographic screening sensitivity (Table 3). Moreover, the MSTs across all BI-RADS levels among women aged 40 to 59 years included 2-year threshold that the current KNCSP provides mammographic screening.

Women aged 60-69 years with extremely dense breast (Level 4) had significantly higher hazard of transitioning to clinical state, compared to those with predominantly fatty breast (Level 1). The MSTs among women in sixties with non-dense breasts were 4.23 years (95% CI, 2.39 to 7.46) and 2.88 years (95% CI, 2.02 to 4.11), respectively for Level 1 and Level 2, which are longer than the current 2-year KNCSP protocol.

The values of MSTs for women with extremely dense breast tissue were estimated as 2.17 (95% CI, 1.67 to 2.82), 1.71 (95% CI, 1.10 to 2.67) and 1.34 years (95% CI, 0.64 to 2.80) for women in their 40s, 50s and 60s, but the MSTs for older women were modeled by the small number of cancer cases and showed the widest range of confidence intervals (Table 3).

Discussion

We estimated the natural history parameters of the progression trajectory of breast cancer by using the nationwide cancer screening databases in the KNCSP. Overall, women aged 40-69 years had 2.39 years on average during which preclinical breast cancer develops into symptomatic cancer. Women aged 40-59 years had higher breast cancer risk and faster clinical presentation of breast cancer with shorter MSTs, compared to women in sixties. Furthermore, prevalence of dense breasts was higher among Korean women (53.9%), compared to Western women (24-43%) [19, 21]. Women with dense breasts had increased risk of preclinical cancer onset, suggesting dense breasts as a risk factor of breast cancer in our natural history modeling. The hazard of having dense breasts on transition to clinical cancer was not significant in the stratified analysis by women's 10-year age groups, indicating dense breast as masking factor did not substantially reduce mammographic screening sensitivity.

Natural history modeling for breast cancer has been conducted in various Western countries and presenting specific MSTs by each country [14, 22-26]. A few studies presented the MST values for women aged under 50 years, ranging from 1.71 to 2.46 years [24-26]. The MSTs from previous studies were slightly longer than our estimation, but the results from HIP trials are similar to our estimation at around 1.71 years [25]. However, the analyses of HIP trials were problematic in that they manipulated continuous variables into categorical variables. Chen et al. estimated the MST for Taiwanese women by using Markov models without interval cancer information, providing 1.99-year MST for women aged 35 to 80 years [27]. Their MST seemed to be shorter than our estimates, because they only included high risk women for breast cancer. Compared with the MSTs from other observational studies for women aged 50 to 69 years from the Netherlands, Finland, Norway, and Canada, ranging from 2.02 to 7.00 years [18, 28-30], our results were far shorter, possibly due to different prevalence of dense breasts.

Several modeling methods have been utilized to quantify sojourn time. The parametric method is one of the simpler models for estimating MSTs, utilizing only breast cancer prevalence and incidence data [11, 12]. The parametric methods derive incidence and prevalence data of the disease with assumption of a specific distribution of sojourn time to estimate the MST. However, the method has been criticized due to its too constrained and underestimated screening intervals, occurred by the use of incidence data only [18]. In Korea, Lee et al. adopted a derivative method from the parametric model to obtain the optimal screening intervals directly, suggesting 1.2–1.6, 1.0–1.6 and 1.8–1.9 years for women aged 40 to 49, 50 to 59, and 60 years and older, respectively [31]. Because the parametric method used only incidence data in the estimation procedure, the estimated MSTs were shorter than those in our results from the Markov models. Furthermore, they utilized breast cancer incidence data from the 2002 KCCR, whereas our study applied KCCR data from 2009 through 2014, creating the discrepancies between the estimated MSTs.

To our knowledge, the present study is the first attempt as of Korea and Asian countries to use individualized data in the nationwide screening databases to fit natural history of breast cancer together with the risk of breast density, based on the Markov model. Information of breast density was collected through screening results by radiologists which increased the accuracy of the information. Our analyses were based on the “real-world” data from organized screening programs for the entire population of Korean women. Our study presents the evidence for policy suggestions regarding screening intervals in the KNCSP for breast cancer. The current biennial mammographic screening protocol might be too frequent than desired, especially for women in sixties with non-dense breasts.

Out study is not without limitations. Changes in breast density levels were not allowed in our model, although breast density is generally lowered as women age. We condensed our data with only tertiary hospitals to obtain stable estimates. In the analyses of entire data in the KNCSP databases (data not shown), having dense breast extended the duration of MSTs among women in forties, which is counterintuitive because the effect of dense breast reduces mammographic sensitivity and thus shortens the sojourn time of preclinical state. We might find the reasons from extremely higher recall rates for younger women with dense breast tissue from several screening centers. Although results from tertiary hospitals are generally accepted as high-quality data, not all tertiary hospitals in Korea are well-controlled for the screening quality [32]. If the quality of screening could be maintained at ideal levels, the values of MSTs would be more consistent and longer, thereby leading to improved efficiency of implementation achieved through fewer but more accurate screenings.

This study presents Korean-women-specific estimates of the natural history parameters for breast cancer, by using “real-world” nationwide data in the KNCSP. The current biennial screening practice might need to continue for women aged 40 to 59 years as well as women in sixties with dense breast tissue. For older women with non-dense breasts, a prolonged interval could be recommended, creating more convenience for participants and less waste of resources, while still providing effective early detection of new cancer cases. This study first suggests the natural history parameters of breast cancer for women in countries with high prevalence of dense breasts.

Abbreviations

BI-RADS: Breast Imaging, Reporting and Data System; MST: mean sojourn time; KNCPS: the Korean National Cancer Screening Program; KCCR: the Korean Central Cancer Registry.

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of the National Cancer Center, Korea (Institutional Review Board no. NCCNCS08129). We collected data regularly from the National Health Insurance Service, and the need for informed consent for this specific study was waived as the KNCSP database is quite large. With permission from the Ministry of Health and Welfare, the investigators used data maintained and de-identified by the National Health Insurance Service.

Consent for publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing interests

The authors made no disclosures.

Funding

This study was supported by a Grant-in-Aid for Cancer Research and Control from the National Cancer Center of Korea (1910231-1). The funders had no role in the study design, analysis, interpretation, and preparation of the manuscript. All researchers retained complete independence in the conduct of this study.

Author's Contributions

EC drafted the manuscript, and all authors contributed to review and revision and approved the final manuscript. EC, MS, SP, JKJ and KSC participated in the conceptualization of the study. EC, SYJ, KWJ, SP, JKJ and KSC participated in the development of the methodology. EC performed statistical analysis. KSC supervised the study.

References

1. Choi E, Lee YY, Yoon HJ, Lee S, Suh M, Park B, et al. Relationship between Cancer Worry and Stages of Adoption for Breast Cancer Screening among Korean Women. PLoS One. 2015;10(7):e0132351.
2. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.
3. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356(3):227-36.
4. Park B, Cho HM, Lee EH, Song S, Suh M, Choi KS, et al. Does breast density measured through population-based screening independently increase breast cancer risk in Asian females? Clin Epidemiol. 2018;10:61-70.
5. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-96.
6. The benefits and harms of breast cancer screening: an independent review. Lancet. 2012;380(9855):1778-86.
7. Hamashima C, Hamashima CC, Hattori M, Honjo S, Kasahara Y, Katayama T, et al. The Japanese Guidelines for Breast Cancer Screening. Jpn J Clin Oncol. 2016;46(5):482-92.
8. Huang Y, Tong Z, Chen K, Wang Y, Liu P, Gu L, et al. Interpretation of breast cancer screening guideline for Chinese women. Cancer Biol Med. 2019;16(4):825-35.
9. Yen AM, Tsau HS, Fann JC, Chen SL, Chiu SY, Lee YC, et al. Population-Based Breast Cancer Screening With Risk-Based and Universal Mammography Screening Compared With Clinical Breast Examination: A Propensity Score Analysis of 1429890 Taiwanese Women. JAMA Oncol. 2016;2(7):915-21.
10. ZELEN M, FEINLEIB M. On the theory of screening for chronic diseases. Biometrika. 1969;56(3):601-14.
11. Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. Biometrics. 1984;40(1):1-14.
12. 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). Int J Epidemiol. 1991;20(4):852-8.
13. 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. Stat Med. 1995;14(14):1531-43.
14. Taghipour S, Banjevic D, Miller AB, Montgomery N, Jardine AK, Harvey BJ. Parameter estimates for invasive breast cancer progression in the Canadian National Breast Screening Study. Br J Cancer. 2013;108(3):542-8.
15. Tan KH, Simonella L, Wee HL, Roellin A, Lim YW, Lim WY, et al. Quantifying the natural history of breast cancer. Br J Cancer. 2013;109(8):2035-43.
16. Jackson CH, Sharples LD, Thompson SG, Duffy SW, Couto E. Multistate Markov models for disease progression with classification error. Journal of the Royal Statistical Society: Series D (The Statistician). 2003;52(2):193-209.
17. Jackson C. Multi-State Models for Panel Data: The msm Package for R. 2011. 2011;38(8):28.
18. Aarts A, Duffy SW, Geurts S, Vulkan DP, Otten J, 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(3):147-53.
19. Chiu SY, Duffy S, Yen AM, Tabár L, Smith RA, Chen HH. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev. 2010;19(5):1219-28.
20. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2017. Cancer Res Treat. 2020;52(2):335-50.
21. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(4):268-78.
22. Bjurstam N, Björneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O, et al. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization. Cancer. 1997;80(11):2091-9.
23. Chen H, Duffy S, Tabar L, Day N. Markov chain models for progression of breast cancer. Part II: prediction of outcomes for different screening regimes. J Epidemiol Biostat. 1997;2(1):25-35.
24. Duffy SW, Chen HH, Tabar L, Fagerberg G, Paci E. Sojourn time, sensitivity and positive predictive value of mammography screening for breast cancer in women aged 40-49. Int J Epidemiol. 1996;25(6):1139-45.
25. Duffy SW, Day NE, Tabár L, Chen HH, Smith TC. Markov models of breast tumor progression: some age-specific results. J Natl Cancer Inst Monogr. 1997(22):93-7.
26. Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. Am J Epidemiol. 1983;118(6):865-86.

27. 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(1):167-72.
28. Jiang H, Walter SD, Brown PE, Chiarelli AM. Estimation of screening sensitivity and sojourn time from an organized screening program. Cancer Epidemiol. 2016;44:178-85.
29. Weedon-Fekjaer H, Vatten LJ, Aalen OO, Lindqvist B, Tretli S. Estimating mean sojourn time and screening test sensitivity in breast cancer mammography screening: new results. J Med Screen. 2005;12(4):172-8.
30. Wu JC, Hakama M, Anttila A, Yen AM, Malila N, Sarkeala T, et al. Estimation of natural history parameters of breast cancer based on non-randomized organized screening data: subsidiary analysis of effects of inter-screening interval, sensitivity, and attendance rate on reduction of advanced cancer. Breast Cancer Res Treat. 2010;122(2):553-66.
31. Lee SY, Jeong SH, Kim J, Jung SH, Song KB, Nam CM. Scheduling mammography screening for the early detection of breast cancer in Korean women. J Med Screen. 2007;14(4):205-9.
32. Lee EH, Kim KW, Kim YJ, Shin DR, Park YM, Lim HS, et al. Performance of Screening Mammography: A Report of the Alliance for Breast Cancer Screening in Korea. Korean J Radiol. 2016;17(4):489-96.

Tables

Table 1. Prevalence of dense breast tissue and the ratio of interval cancer to screen-detected cancer

Age groups	Total				% of density	Dense breast				Non-dense breast			
	No. screened	Interval cancer	Screen-detected cancer	I/S ratio*		No. screened	Interval cancer	Screen-detected cancer	I/S ratio*	No. screened	Interval cancer	Screen-detected cancer	I/S ratio*
Total	290 448	451	782	0.58	53.86	156 445	315	492	0.64	134 003	136	290	0.46
40-49	153 124	272	401	0.68	72.44	110 916	215	321	0.67	42 208	57	80	0.71
50-59	75 424	127	233	0.55	45.94	34 651	83	128	0.65	40 773	44	105	0.42
60-69	41 551	44	111	0.40	21.70	9 017	17	36	0.47	32 534	27	75	0.36
70+	20 349	8	37	0.22	9.15	1 861	0	7	0.00	18 488	8	30	0.27

*I/S ratio, Interval cancer ÷ Screen-detected cancer.

Table 2. Breast cancer cases from screen-detected cancer and interval cancer by screening rounds.

Screening rounds	Screen-detected		Interval cancer	
	Invasive	In situ	Invasive	In situ
Prevalence screen (2009)				
Total	337	71	219	26
40-49	150	44	125	13
50-59	109	23	67	8
60-69	55	1	22	5
70+	23	3	5	0
First incident screen (2011)				
Total	193	37	114	16
40-49	104	22	72	11
50-59	56	9	31	3
60-69	26	5	9	2
70+	7	1	2	0
Second incident screen (2013)				
Total	120	24	63	13
40-49	70	11	42	9
50-59	27	9	15	3
60-69	20	4	5	1
70+	3	0	1	0

Table 3. Parameters of the three-state Markov model for all breast cancers

Three-state Markov model for All breast cancers	Total	40-49	50-59	60-69
Preclinical incidence rate (λ_1)	0.0018 (0.0017-0.0019)	0.0019 (0.0017-0.0021)	0.0020 (0.0017-0.0022)	0.0014 (0.0012-0.0017)
Mean Sojourn Time ($1/\lambda_2$)	2.3940 (2.0918-2.7398)	1.9772 (1.6707-2.3399)	2.4936 (1.9252-3.2299)	3.0717 (2.1126-4.4662)
Sensitivity of test	0.67 (0.62-0.72)	0.61 (0.54-0.61)	0.65 (0.59-0.77)	0.70 (0.62-0.77)
Hazard ratio by BI-RADS levels* to transition rate				
Transition from healthy to preclinical (λ_1)				
Level 2 vs Level 1	1.9625 (1.5799-2.4370)	1.3655 (0.9185-2.0300)	1.9400 (1.3390-2.8110)	1.9601 (1.5891-2.4170)
Level 3 vs Level 1	2.3510 (1.9200-2.8780)	1.7721 (1.2311-2.5500)	2.6324 (1.8417-3.7620)	2.2083 (1.7236-2.8290)
Level 4 vs Level 1	2.3380 (1.8760-2.9140)	1.9122 (1.3223-2.7640)	2.3875 (1.5545-3.6650)	3.5950 (2.4920-5.1850)
Transition from preclinical to clinical (λ_2)				
Level 2 vs Level 1	1.5285 (0.9915-2.3550)	2.0632 (0.8106-5.2510)	1.3981 (0.5712-3.4220)	1.4073 (0.9266-2.1380)
Level 3 vs Level 1	2.0230 (1.3340-3.0680)	1.9771 (0.8162-4.7900)	1.9442 (0.8094-4.6690)	1.5950 (0.9891-2.5720)
Level 4 vs Level 1	1.9360 (1.2240-3.0630)	1.6214 (0.6538-4.0170)	2.2383 (0.8626-5.8080)	2.1330 (1.1020-4.1270)
Mean Sojourn Time by BI-RADS levels*				
Predominantly fatty	3.8923 (2.6077-5.8097)	3.5241 (1.5046-8.2538)	3.8394 (1.6505-8.9313)	4.2303 (2.3965-7.4623)
Scattered fibroglandular	2.5473 (2.0584-3.1524)	1.7082 (1.2330-2.3666)	2.7463 (1.9118-3.9451)	2.8843 (2.0214-4.1155)
Heterogeneously dense	1.9237 (1.6312-2.2686)	1.7823 (1.4272-2.2257)	1.9750 (1.4883-2.6208)	1.9665 (1.2572-3.0760)
Extremely dense	2.0100 (1.6187-2.4960)	2.1745 (1.6745-2.8239)	1.7153 (1.1002-2.6742)	1.3408 (0.6412-2.8038)

*BI-RADS density system: Level 1 (0-24%): predominantly fatty breasts; Level 2 (25-50%): scattered fibroglandular tissues; Level 3 (51-75%): heterogeneously dense; Level 4 (76-100%): extremely dense.

Figures

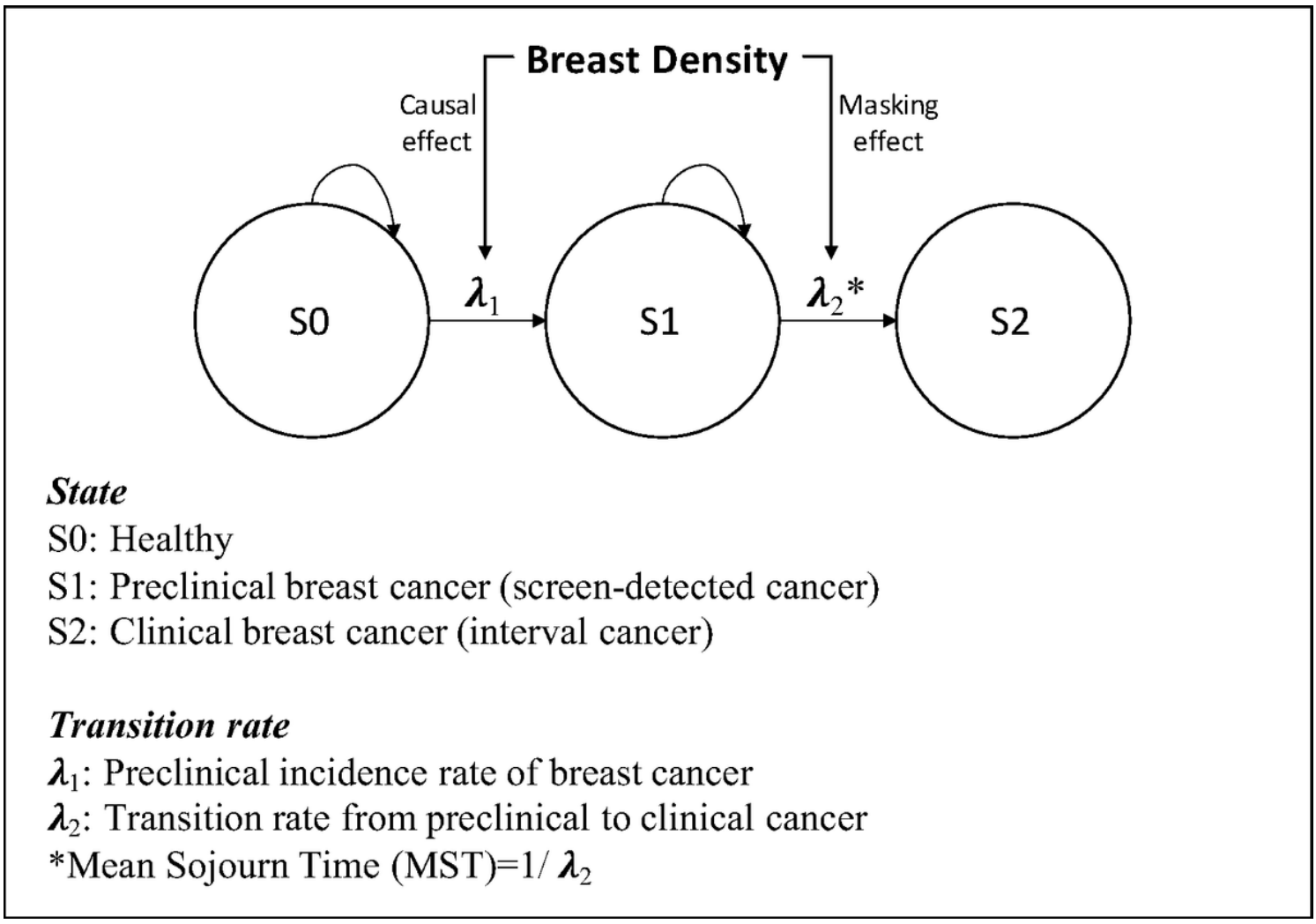

Figure 1

A three-state Markov model of natural history of breast cancer and effects of breast density.