RESEARCH ARTICLE

Development of a Sampling Strategy and Sample Size Calculation to Estimate the Distribution of Mammographic Breast Density in Korean Women

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Abstract

Mammographic breast density is a known risk factor for breast cancer. To conduct a survey to estimate the distribution of mammographic breast density in Korean women, appropriate sampling strategies for representative and efficient sampling design were evaluated through simulation. Using the target population from the National Cancer Screening Programme (NCSP) for breast cancer in 2009, we verified the distribution estimate by repeating the simulation 1,000 times using stratified random sampling to investigate the distribution of breast density of 1,340,362 women. According to the simulation results, using a sampling design stratifying the nation into three groups (metropolitan, urban, and rural), with a total sample size of 4,000, we estimated the distribution of breast density in Korean women at a level of 0.01% tolerance. Based on the results of our study, a nationwide survey for estimating the distribution of mammographic breast density among Korean women can be conducted efficiently.

Key words: Breast density - health survey - mammography - sample size

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Introduction

Human mammary gland tissue has 15–20 lobes, each with 20–40 lobules that form the anatomical and functional units of breast tissue. The lobules in turn, contain 10–100 acini, the secretory structures of the breast. The lobules are surrounded by stroma and fat, which varies in amount based on age and lactational status (Ghosh et al., 2010). The radiographic appearance of the breast on mammography varies among women, reflecting variations in breast tissue composition. Fat is radiologically lucent and appears dark on a mammogram, whereas fibroglandular tissue, stroma, and epithelium are radiologically dense and appear light. The proportion of the breast that comprises fibroglandular tissue, stroma, and epithelium is usually expressed as the mammographic breast density (Boyd et al., 2010).

To date, several methods have been used to assess mammographic density. These methods fall into two subtypes: qualitative and quantitative. The qualitative measures, such as the Wolfe, Tabár, and the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) classifications, take into account certain features that can be appreciated on a mammogram as well as the quantity of the breast density, whereas the quantitative measures consider only the quantity (Gram, 2005). The ACR BI-RADS classification has four categories of mammographic breast density: extremely fatty (<25% glandular), scattered density (25–50% glandular), heterogeneous density (51–75% glandular), and extremely dense (>75% glandular). Quantitative approaches have been used to measure the proportion of dense area in the breast including estimation by radiologists as well as planimetry and computer-assisted methods (Boyd et al., 2005).

Mammographic breast density is influenced by several risk factors for breast cancer, including age, body mass index (BMI), parity, and menstrual status (Boyd et al., 2006; Li et al., 2005; Martin and Boyd, 2008). The association of international and ethnic differences in mammographic breast density with breast cancer incidence rates has been studied (McCormack et al., 2008; Habel et al., 2007). It has been reported that the distribution of age-specific mammographic breast density among Korean women is different from that of Western women (Kim et al., 2000).

High mammographic breast density, measured qualitatively or quantitatively, has been recognised as a risk factor for breast cancer (McCormack and dos Santos Silva, 2006). It may also make breast cancer more difficult to detect by mammography and thus increase the risk of development of cancer between mammographic

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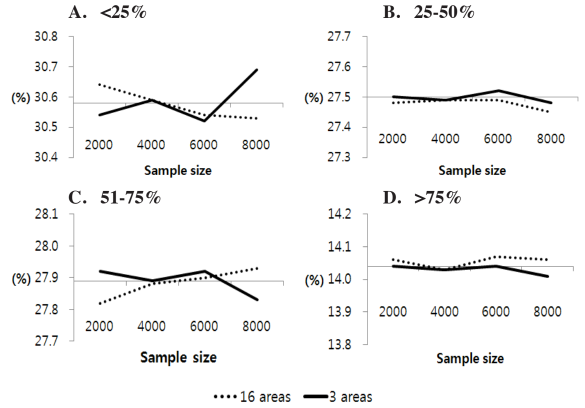

Figure 1. An Average of a 1,000 Simulation Estimates of the Distribution of Each Mammographic Density According to Stratification Types by Area for a Given Sample Size. The horizontal bar represents the value of each of the surrogate parameters by the classification of BI-RADS (30.6%, 27.5%, 27.9%, and 14.0%, respectively).

Table 1. Comparison of General Characteristics between Target Population and Study Population

	Target population (N = 3,568,941)		Participants (N = 1,422,941)	
	N	(%)	N	(%)
Age group, yrs				
40-49	1,270,138	(35.6)	476,433	(33.5)
50-59	1,021,769	(28.6)	473,121	(33.2)
60-69	597,215	(16.7)	295,815	(20.8)
70+	679,819	(19.0)	177,572	(12.5)
Resident area, size				
Metropolitan	1,561,512	(43.8)	609,388	(42.8)
Urban	1,524,803	(42.7)	606,585	(42.6)
Rural	482,626	(13.5)	206,968	(14.6)
Resident area, administrative district				
Seoul	642,196	(18.0)	242,624	(17.1)
Busan	287,907	(8.1)	122,205	(8.6)
Deagu	190,039	(5.3)	72,345	(5.1)
Deajeon	93,362	(2.6)	40,877	(2.9)
Incheon	194,110	(5.4)	69,324	(4.9)
Gwangju	94,061	(2.6)	39,369	(2.8)
Ulsan	59,837	(1.7)	22,644	(1.6)
Gyeonggi	711,841	(20.0)	273,859	(19.3)
Gangwon	128,777	(3.6)	54,969	(3.9)
Chungbuk	123,993	(3.5)	54,757	(3.9)
Chungnam	166,811	(4.7)	65,671	(4.6)
Jeonbuk	161,987	(4.5)	70,269	(4.9)
Jeonnam	185,141	(5.2)	82,370	(5.8)
Gyeongbuk	235,658	(6.6)	93,717	(6.6)
Gyeongnam	247,885	(7.0)	101,572	(7.1)
Jeju	45,336	(1.3)	16,369	(1.2)

screening tests, i.e. interval cancer (Boyd et al., 2007).

In fact, due to high mammographic breast density, recall rates of Korean women, especially premenopausal women, in the National Cancer Screening Programme (NCSP) are higher than those of postmenopausal women. Lower accuracy and higher recall rate of mammography is one source of low cost effectiveness of the NCSP for breast cancer screening (Oh et al., 2010).

To improve the cost effectiveness of breast cancer screening, it is important to investigate the current status of mammographic breast density among Korean women. In the future, we plan to conduct a survey to estimate the distribution of mammographic breast density in the target population of the NCSP for breast cancer. The purpose of the current study was to design the sampling strategy to ensure the Korean population is represented and to calculate the appropriate sample size required.

Materials and Methods

The purpose of this study was to develop the process to specify and sample the subjects who are representative of the population under study. Ultimately, the target population of a survey for estimating the distribution of the mammographic breast density among Korean women corresponds to that of the NCSP for breast cancer. However, as shown in Table 1, there were no differences in the general characteristics between the target population and the women screened in the NCSP for breast cancer. Thus, we used the examinees of NCSP for breast cancer as the target population of our study.

In 2009, the target population of the NCSP for breast cancer consisted of 3,568,941 women born before December 31, 1969. Among these, 1,422,941 were eliminated by removing 4,796 women who were listed multiple times and who underwent mammography from January 1, 2009 to December 31, 2009. A further 82,579 women were excluded due to lack of information on mammographic breast density.

To eliminate the need to re-read every mammogram entry in the NCSP, representative random sampling methods were used that stratified subjects according to residential area. Two regional stratification strategies, divided into 16 regions by administrative districts and into three regions by the size of residential area, i.e. 'metropolitan', 'urban', and 'rural', were used. Since 2009, in the NCSP, mammographic breast density has been reported according to the ACR BI-RADS classification, i.e. <25%, 25–50%, 51–75%, and >75%. On the assumption that the distribution of mammographic breast density reported as 30.58%, 27.50%, 27.89%, and 14.04%, respectively in the NCSP of 2009, is similar to that of Korean women, the reported values were used as surrogate parameters.

Following probability sampling strategies, the simulations were repeated 1,000 times using the study population. Estimated distributions of mammographic breast density were calculated by using the average of these 1,000 simulations. The range of simulations for the number of sampling subjects was set conservatively, and the precision analysis for the appropriate sample size was performed. If the data obtained were used in a simple probability sampling method, a sample size of between 2,000 and 9,500 would be required to estimate a parameter within ±1–2% at a 95% confidence level. In determining the appropriate sample size, it is also important to consider feasibility as well as statistical

Table 2. Simulation Results of Comparing Sampling Strategies for Estimating Distribution of Mammographic Density Using Stratified Random Sampling

Mammographic density (surrogate parameter, %)		Regional* strata	Sample size (N)	Mean (%)†	Simulation result (95% predicted interval)‡	(Trimmed interval)§	Diff.‖
<25%	(30.58)	16	2,000	30.64	(28.58-32.70)	(28.83-32.40)	0.06
			4,000	30.59	(29.18-32.00)	(29.40-31.76)	0.01
			6,000	30.54	(29.44-31.64)	(29.62-31.42)	-0.04
			8,000	30.53	(29.53-31.53)	(29.67-31.34)	-0.05
		3	2,000	30.54	(28.56-32.52)	(28.95-32.28)	-0.04
			4,000	30.59	(29.14-32.04)	(29.38-31.76)	0.01
			6,000	30.52	(29.36-31.68)	(29.55-31.48)	-0.06
			8,000	30.69	(29.73-31.65)	(29.89-31.51)	0.11
25-50%	(27.50)	16	2,000	27.48	(25.58-29.38)	(25.93-29.10)	-0.02
			4,000	27.49	(26.18-28.80)	(26.39-28.55)	-0.01
			6,000	27.49	(26.31-28.67)	(26.53-28.47)	-0.01
			8,000	27.45	(26.45-28.45)	(26.60-28.30)	-0.05
		3	2,000	27.50	(25.62-29.38)	(25.95-29.10)	0
			4,000	27.49	(26.14-28.84)	(26.41-28.58)	-0.01
			6,000	27.52	(26.36-28.68)	(26.54-28.44)	0.02
			8,000	27.48	(26.54-28.42)	(26.67-28.27)	-0.02
51-75%	(27.89)	16	2,000	27.82	(25.90-29.74)	(26.18-29.43)	-0.07
			4,000	27.88	(26.43-29.33)	(26.63-29.08)	-0.01
			6,000	27.90	(26.72-29.08)	(26.93-28.90)	0.01
			8,000	27.93	(26.95-28.91)	(27.07-28.75)	0.04
		3	2,000	27.92	(25.92-29.92)	(26.25-29.58)	0.03
			4,000	27.89	(26.56-29.22)	(26.76-29.02)	0
			6,000	27.92	(26.76-29.08)	(26.93-28.84)	0.03
			8,000	27.83	(26.81-28.85)	(27.01-28.70)	-0.06
>75%	(14.04)	16	2,000	14.06	(12.55-15.57)	(12.75-15.40)	0.02
			4,000	14.03	(12.97-15.09)	(13.13-15.03)	-0.01
			6,000	14.07	(13.15-14.99)	(13.27-14.86)	0.03
			8,000	14.06	(13.32-14.80)	(13.44-14.70)	0.02
		3	2,000	14.04	(12.57-15.51)	(12.85-15.30)	0
			4,000	14.03	(12.95-15.11)	(13.17-14.95)	-0.01
			6,000	14.04	(13.18-14.90)	(13.35-14.78)	0
			8,000	14.01	(13.27-14.74)	(13.41-14.63)	-0.03

*Study population was divided into 16 regions by administrative districts and three regions by the size of residential area; †An estimated proportion of women according to grades of mammographic breast density using the BI-RADS classification (calculated by an average of 1,000 simulated estimates); ‡95% predicted interval (mean±1.96 × standard deviation (SD) of 1,000 simulated estimates) for an estimated proportion; §Two-sided 5% trimmed range of an estimated proportion; ‖Difference between the average of 1,000 simulated estimates and the value of surrogate parameter. A negative value implies an underestimation of the parameter, and a positive value implies an overestimation.

considerations. Compared with a simple probability sampling method, the regional stratified sampling method lowers the size of samples; therefore, simulation numbers of 2,000, 4,000, 6,000, and 8,000 were evaluated.

We calculated a 95% predicted interval (PI) and two-sided 5% trimmed range for evaluating the reliability and stability of simulation results. The differences between the values of the estimated distributions and surrogated parameters were used to assess the degree of overestimation or underestimation. We used SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC).

Results

The simulations conducted through the sampling strategies estimated the distributions of the mammographic breast density in the range -0.07–0.11% of the surrogate parameters. As to regional stratification, estimates of the three-area method based on the size of the residential area were closer to the surrogate parameters than were those of the 16-area method based on administrative districts. The three-area method correctly estimated the surrogate parameters in all ACR BI-RADS categories except for the <25% category. According to the categories, different sample sizes were selected: 4,000 in categories <25% and 51–75% and 2,000 in categories 26–50% and >75%. The estimating errors in the 2,000 sample size were increased compared with those in the 4,000 sample size.

Based on the simulation results, the selected sampling strategy was 4,000 women randomly selected from three regional strata at a ratio of 43:43:14 divided by the size of residential area. As a result, values estimated according to ACR BI-RADS categories were 30.59% (95% PI 29.14–32.04), 27.49% (95% PI 26.14–28.84), 27.89% (95% PI 26.56–29.22), and 14.03% (95% PI 12.95–15.11), respectively. Therefore, our sampling strategy could estimate surrogate parameters, i.e. 30.58%, 27.50%, 27.89%, and 14.04%, within 0.01% of range of error.

Discussion

To conduct a survey to identify the distribution of mammographic breast density in Korean women, the sample of women needs to be large enough to control random error and representative enough to control systematic error. According to the results of our simulation, a strategy to select a sample of 4,000 women among three regional strata divided by the size of residential area is required.

Although data or information on the population of interest is known, the sampling survey may need to be conducted for various reasons. In this case, the simulations based on data of the target population might make it possible to calculate an appropriate sample size and to evaluate sampling strategies (Lee et al., 2009). The stratified random sampling method is one method of probability sampling. The gold standard for ensuring generalisability uses a random process to guarantee that each unit of the population has a specified chance of being included in the sample. The more homogenous the subjects in the strata are, the more precise the estimation using a smaller sample size becomes. In this study, sampling strategies stratified by region were evaluated for recruitment of subjects from a nationwide sample without over-representation of specific regions and ensuring the accessibility of mammograms.

Some limitations of this study should be considered. First, due to restricted data and information on the target population, only two regional stratification strategies were considered. Second, although it has been known that the prevalence of dense breast tissue among Korean women under 40 years is high (Kim et al., 2000), our study could not include these age groups. Despite these limitations, using a simulation based on the available data or information on the target population, our study suggested a representative sampling strategy that could make it possible to conduct a nationwide survey efficiently.

Although high mammographic density is known as a risk factor for breast cancer in Western women, there is little evidence of association between mammographic density and breast cancer in Asian women. Accordingly, the results of a nationwide survey for estimating the distribution of mammographic breast density among Korean women could be utilised as principal evidence for epidemiological studies and establishing breast cancer control strategies.

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References

Boyd NF, Rommens JM, Vogt K, et al (2005). Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol*, **6**, 798-808.

Boyd NF, Martin LJ, Sun L, et al (2006). Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, **15**, 2086-92.

Boyd NF, Guo H, Martin LJ, et al (2007). Mammographic density and the risk and detection of breast cancer. *N Engl J Med*, **356**, 227-36.

Boyd NF, Martin LJ, Bronskill M, et al (2010). Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst*, **102**, 1224-37.

Ghosh K, Vachon CM, Pankratz VS, et al (2010). Independent association of lobular involution and mammographic breast density with breast cancer risk. *J Natl Cancer Inst*, **102**, 1716-23.

Gram IT, Bremnes Y, Ursin G, et al (2005). Percentage density, Wolfe's and Tabár's mammographic patterns: agreement and association with risk factors for breast cancer. *Breast Cancer Res*, **7**, R854-61.

Habel LA, Capra AM, Oestreicher N, et al (2007). Mammographic density in a multiethnic cohort. *Menopause*, **14**, 891-9.

Kim SH, Kim MH, Oh KK (2000). Analysis and comparison of breast density according to age on mammogram between Korea and western women. *J Korean Radiol Soc*, **42**, 1009-1014.

Lee JS, Kim JY, Baik SH, et al (2009). An evaluation of sampling design for estimating an epidemiologic volume of diabetes and for assessing present status of its control in Korea. *J Prev Med Public Health*, **49**, 135-142.

Li T, Sun L, Miller N, et al (2005). The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. *Cancer Epidemiol Biomarkers Prev*, **14**, 343-9.

Martin LJ and Boyd NF (2008). Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. *Breast Cancer Res*, **10**, 201.

Maskarinec G, Pagano I, Lurie G, et al (2005). Mammographic density and breast cancer risk. *Am J Epidemiol*, **162**, 743-752.

McCormack VA, dos Santos Silva I (2006). Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **15**, 1159-69.

McCormack VA, Perry N, Vinnicombe SJ, et al(2008). Ethnic variations in mammographic density: a British multiethnic longitudinal study. *Am J Epidemiol*, **168**, 412-21.

Oh DK, Shim JI, Han MA, et al (2010). Breast cancer screening in Korean women: Report of the National Cancer Screening Program in 2008. *J Breast Cancer*, **13**, 299-304.

Oh D, Jung DW, Jun JK, et al (2011). On-schedule mammography rescreening in the National Cancer Screening Program for breast cancer in Korea. *Asian Pacific J Cancer Prev*, **12**, 2865-70.

Wolfe JN (1976). Breast patterns as an index of risk for developing breast cancer. *AJR Am J Roentgenol*, **126**, 1130-7.