Cancer of the breast is a common malignant female cancer in Korea\(^1\). Its incidence is ranked second to stomach cancer in both Seoul (1994-1998) and Busan (1998-1999) in Korea. However, the age-adjusted mortality rate of female breast cancer in Korea has steadily increased from 2.2 per 100,000 in 1983 to 4.8 per 100,000 in 2003 (Fig 1). A recent analysis reported that changes in breast cancer mortality between 1985-87 and 1995-97 in women aged 50-74 and 25-49 years was higher in Korea than in the rest of the world\(^2\). This increasing trend might be attributed to rapid changes in dietary habits, nutritional status, and reproductive behaviors, which have all been identified as risk factors for breast cancer in Korean women\(^3\). Moreover, as these changes in lifestyle are likely to continue in parallel with economic growth, further increases in breast cancer incidence seem inevitable\(^4,5\).

Investigations on breast cancer incidence and mortality rates provide clues about etiology. Many studies have been performed to determine how the birth cohort contributes to trends in breast cancer incidence\(^6,7\). Moreover, breast cancer mortality in Korea is predicted to further increase\(^8\). In the present study, age-period-cohort analysis was performed using female breast cancer mortality data to determine the potential role of the birth cohort effect on the recent increase in breast cancer in Korea.

**Materials and Methods**

Data on the annual number of deaths due to female breast cancer and female population statistics from 1984 to 2003 were obtained from the...
Korean National Statistical Office\textsuperscript{11}. Using original data, we calculated age-specific breast cancer mortality rates for ten 5-year age groups (i.e., 30-34, 35-39, 40-44, ..., 70-74 and 75-79-year-olds) for four 5-year calendar periods (1984-1988, 1989-1993, 1994-1998 and 1999-2003) (Table 1). Since breast cancer deaths below 30 years old are rare, and the life expectancy of Korean women is around 80 years, the analysis was restricted to those aged between 30 and 79 years. Using age and calendar period classifications, 12 overlapping 10-year birth cohorts were identified and defined from 1909-19 to 1959-1969.

Age-adjusted mortality rates were calculated using the 1992 female population as a standard. Breast cancer cases were defined as code C50 (malignant neoplasm of breast) in accord with the International Classification of Diseases 10th Revision (ICD-10).

To evaluate the effects of age, period, and birth cohort on female breast cancer mortality, log-linear models with Poisson random variates were employed. In these models, it was assumed that each factor has an additive effect on the log rate ($\lambda_{iab}$),

$$\log \lambda_{iab} = \mu + \alpha_i + \pi_j + \gamma_k + \varepsilon_{iab}$$

Where, the age effect is represented by $\alpha_i$, the period effect by $\pi_j$, and the cohort effect by $\gamma_k$. The term $\varepsilon_{iab}$ represents random error. The models were fitted using the maximum likelihood method under the constraints $\sum_i \alpha_i = \sum_j \pi_j = \sum_k \gamma_k = 0$. Based on this general form, we established 5 models in sequence: a one-factor age model first, then two-factor age-drift model, age-period model, age-cohort model, and finally the age-period-cohort model. The drift term in the age-drift model represents a temporal change in mortality rates not identifiable as a period or cohort effect. Goodness of fit was tested and not rejected in all of the models with more than two factors. Hence, it was unnecessary to assume over-dispersed Poisson random variates in our analysis.

By comparing scaled deviances from the models, the statistical significance of each factor was tested after adjusting for the others. Since age is a significant predictor of cancer mortality, a goodness of fit considering age would be valuable. Therefore, age-adjusted $R^2$ was used to evaluate goodness of fit\textsuperscript{12}, as it measures how much variability is explained by factors other than age\textsuperscript{7}. For example, the variability contribution by period is given by:

$$adj - R^2 = 1 - \frac{D_d df_{a-p}}{D_{a} df_{a}}$$

where $D$ and $df$ are the model deviance and degree of freedom, respectively.

Even in an age-period-cohort models, if there is a fundamental problem called non-identifiability, the deviance is constant regardless of a constraint used for the model. In this study, an arbitrary constraint was used to obtain only the deviance for the age-period-cohort model. All analyses were performed using SAS 8.0\textsuperscript{13}.

### Results

**Graphical Presentation**

Age-specific mortality rates for different time periods are depicted in Fig 2. Age-specific breast
cancer mortality rates are higher in the later periods. Within each period, mortality rates increase and then decrease with age, but the patterns differ. The age group which shows the highest mortality rate shifts to the older group, and, at the same time, the mortality in the over 70 decreased in 1984-1988, but increased in recent years. Such different patterns in cross-sectional age curves by time period may imply a birth cohort effect. 

Fig 3 depicts the age-specific mortality trends for female breast cancer by year of birth, 1909-1969, Korea.

**Age-Period-Cohort Models**

Table 2 shows the goodness of fit (scaled deviance) for the age-period-cohort models. First, we considered the model with a drift term. However, the model gave a lower value for $adj - R^2$ than that for age-cohort or age-period-cohort model, and thus we excluded it from the possible models of mortality in breast cancer. The period effect was significant ($p < 0.01$) in the age-period model after adjusting for age, while the cohort effect was marginally significant in the age-cohort model ($p = 0.08$). The period effect after adjusting age and birth cohort and the cohort effect after adjusting age and period were not statistically significant ($p > 0.05$). The value of $adj - R^2$ for the age-cohort model (0.97) was higher than that of the age-period model (0.87) and the same as that of the full model (0.97). Note that a strong and highly significant covariate, such as a period effect in...
this study, may not automatically translate into sufficiently accurate prediction\(^{10}\). Therefore, we concluded that the age-cohort model represented breast cancer mortality more precisely than the age-period model based on the values of \(\text{adj-}R^2\).

**Discussion**

Age-period-cohort model analysis revealed that increasing breast cancer mortality in Korea is explained by a cohort effect, although this was only marginally significant. The risk of breast cancer death has steadily increased in recent birth cohorts. Data directly showing the long-term trend of breast cancer incidence rate is not available in Korea yet, and mortality data appears to be the only index of breast cancer incidence. The analysis of trends of the age-adjusted mortality rate of breast cancer reveals that breast cancer is increasing in Korea even after adjustment for the age structure of the population\(^{10}\). In fact, the incidence of female breast cancer has been increasing since 1996\(^{15}\), and the incidence rate has 20.4 per 100,000 in 1999-2001\(^{16}\). The most notable weak point of mortality data analysis for breast cancer concerns the reduction in case-fatalities by year due to technologic improvements, thus the simple use of mortality data may underestimate true increases\(^{17}\).

The breast cancer mortality rate by age shows a peak at age group 55-59 (Table 1). This peak occurs almost ten years later than that of the age-specific incidence rate, which is 45-49 year old\(^{15}\). This is possibly because, on average, breast cancer death occurs between five and ten years after diagnosis. However, when we observed the mortality rate adjusted by birth cohort effect (Fig 4a), the longitudinal age curve showed that the risk of female breast cancer increases with age. Therefore, the cross-sectional age curve in Fig 2 may be explained by the cohort effect on breast cancer in Korea.

In our analysis, drift term or period effects were found to be significant (\(p < 0.05\)) after adjusting for age, whereas the cohort effect was not. If it is true that the period effect was an important predictor of breast cancer mortality, the age-cohort model without the period effect, should give a statistically significant result for goodness of fit. However, the goodness of fit for age-period and age-drift models, using scaled deviance, were not statistically significant (\(p > 0.05\)). This may imply that the period and cohort effects in our data entangle to some degree\(^{18}\). In other words, there exists a statistically significant temporal trend in breast cancer death, but it is difficult to clarify whether this is due to a period or a birth cohort effect. Hence, the final model selection was made considering \(\text{adj-}R^2\), and it measures how much variability is explained by factors other than age. Even though, statistically, the cohort effect was marginally significant, the age-cohort model describes breast cancer death as well as the full model (\(\text{adj-}R^2 = 0.97\)), whereas the age-period and age-drift models did not (\(\text{adj-}R^2 = 0.87\) and 0.86, respectively). Therefore, we believe that it is more valid to explain female breast cancer death based on the age-cohort model than on the age-period model. On the other hand, merely 20-year follow-up and categorizing the variables for age and calendar year may decrease the statistical power to detect the significance of the cohort effect. In fact, the computed statistical power was 0.35 under the 5% type I error and 19.0 for the real difference of the deviances between the age and age-cohort model.

Even though the trend of breast cancer mortality was mainly explained by a birth cohort effect, there was also a minor but definite period effect. According to Fig 2, breast cancer mortality is increasing throughout the periods. This might be

<table>
<thead>
<tr>
<th>Terms in model</th>
<th>Summary Statistics</th>
<th>(\text{DEVIANCE (df)})</th>
<th>(\Delta D (\Delta df))</th>
<th>(p)-value</th>
<th>Effect</th>
<th>(\text{adj-}R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>19.7902 (30)</td>
<td>17.1161 (1)</td>
<td>0.00004</td>
<td>(\delta</td>
<td>A)</td>
</tr>
<tr>
<td>Age + drift</td>
<td></td>
<td>2.6741 (29)</td>
<td>17.4145 (3)</td>
<td>0.0006</td>
<td>(P</td>
<td>A)</td>
</tr>
<tr>
<td>Age + Period</td>
<td></td>
<td>2.3757 (27)</td>
<td>19.4303 (12)</td>
<td>0.08</td>
<td>(C</td>
<td>A)</td>
</tr>
<tr>
<td>Age + Cohort</td>
<td></td>
<td>0.3599 (18)</td>
<td>0.0865 (2)</td>
<td>0.96</td>
<td>(P</td>
<td>A, C)</td>
</tr>
<tr>
<td>Age + Period + Cohort</td>
<td></td>
<td>0.2734 (16)</td>
<td>2.1023 (11)</td>
<td>0.998</td>
<td>(C</td>
<td>A, P)</td>
</tr>
</tbody>
</table>
mainly due to the rapid increase of breast cancer incidence. It may represent a rapid increase in environmental risk factors, which act as promoters, especially changes in diet. The proportion of calories from animal foods increased two times from 1965 to 1995, on the other hand, while the proportion of calories from plant foods decreased from 97% in 1965, to 79% in 1995. A Western diet favours earlier onset of menarche and also earlier manifestation of hyperinsulinenic insulin resistance. Postmenopausal obesity is suggested to be a risk factor for breast cancer in Korea, and the proportion of postmenopausal obese women has increased recently. Adipose tissue in postmenopausal women converts androgens to estrogen then increases circulating estradiol and reduces levels of sex-hormone binding globulin.

Epidemiologic studies in Korea have identified that reproductive factors are associated with breast cancer risk. Especially, early menarche, late menopause, a late full-term delivery, and never breast feeding are related to the cohort effect of breast cancer mortality. Unfortunately, there are no data directly concerning the change of those factors over such a long period, but recent data are available. The total fertility rate (TFR) fell from 4.53 children per fertile Korean woman in 1970 to 1.19 in 2003. In addition, age at first marriage increased from 21.6 years in 1960 to 27.3 in 2003, and the age at first full-term delivery has increased. The proportion of women breast feeding their last child decreased from 19.2% in 1995 to 7.4% in 2002. The above observed changes can be attributed to economic advances, and they act to increase breast cancer incidence in modern Korean society, thus supporting the cohort effect on breast cancer. It should be noted that our data concerns women born before 1969, and that economic growth has gradually increased in Korea since then. Hence, the cohort effect on breast cancer mortality is expected to be more significant in the future, and breast cancer is similarly expected to become more prevalent.

The interpretation of breast cancer mortality trends is difficult because of the combined effects of trends in breast cancer risk, screening and better survival due to surgical, radiological and adjuvant systemic therapy. In Korea, the National Cancer Screening Project recommended since 1999 that women older than 40 years undergo a mammographic examination biennially. The breast cancer screening rates for the two year period 2000-2001 was 28% for those in their 40's, 27.2% for those in their 50's, 16.9% for those in their 60's and 5.9% for those in their 70's nationwide. Although awareness of breast cancer has increased, the screening rate still remains lower than the US. The percent of all American women over 40 who have had a mammogram within the past 2 years is 67.9%. Low coverage rates and a short history of breast cancer screening make it impossible to observe the impact of screening methods on mortality data. Early detection and diagnosis during the preclinical phase in the absence of symptoms or a palpable mass is crucial for achieving a low mortality rate of breast cancer.

Japan and Taiwan, two low-incidence rate countries, reported a sharp linear increase of the cohort effect. However, in the countries of northern Europe and America, there has been a continuous increase in invasive breast cancer incidence, and declining or stable mortality. This may be attributed to the impact of treatment and cohort effects of risk factors, especially those related to hormones. Both the individual risk factors and long-term medical and social factors contribute to the period effects and cohort effects, such that we would not expect the mortality rate to decrease in the near future, even though there is now little discrepancy in treatment methods between Korea, Japan and Western countries.

In summary, the mortality pattern of breast cancer in Korea is explained by a birth cohort effect in this study. Hence, it is expected that not only the mortality but also the incidence of breast cancer will further increase in Korea because the cohort effect is mediated by environmental factors. Among the various risk factors for breast cancer, reproductive and dietary factors have been accepted as the most important contributing factors. Although the cohort effect on breast cancer mortality was found to be marginally significant, we believe that it will become more significant in the near future due to the comparatively recent changes in diet and reproductive behavior in the Korean population. Furthermore, given that Japan revealed a significant cohort effect in the breast cancer mortality from 1959-1997, but unclear cohort effects from 1959-1987, further analysis with data covering a longer period would be valuable.
References


