

Two hypotheses of dense breasts and viral infection for explaining incidence of breast cancer by age group in Korean women

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Breast cancer, the second leading type of cancer in Korean women, has shown increasing incidence over the past 10 years. However, the curves of incidence by age group cast doubt on the birth cohort effect hypothesis. To explain the curves, here I suggest two alternative hypotheses of breast density and viral infection based on pre-existing evidences. Evaluating these hypotheses would require important clues to find unknown risk factors of breast cancer and to plan more effective strategies for breast cancer control in Korean women.

KEY WORDS: Breast neoplasm, Risk factors, Cancer screening, Mammography, Papillomaviridae

INTRODUCTION

Breast cancer ranks first in incidence and mortality rates for women throughout the world [1]. The number of patients with breast cancer in developing countries has recently become comparable to that of women in developed countries [2]; in Asia in particular, the incidence is increasing in younger age groups [3,4]. Similarly, the incidence of breast cancer in South Korea has been increasing over the last 10 years [5], which is being interpreted as a birth cohort effect [3,6] from a westernized lifestyle [7-9] or the effects of early screening program for breast cancer [5].

However, when incidences are examined by age group, an unusual phenomenon occurs since, as seen in Figure 2 of Bae [10], the peak appears in the age range of 45-49 years and declines thereafter. Moreover, Figure 1(b) of Lee et al. [11] shows that the incidence curves for the years 1993-2002 appear the same. Figure 1 in this paper shows that the incidence curves by age group were redrawn for different years. This appearance of

peaking at 45-49 years, declining thereafter, and showing no changes for the past 20 years can be interpreted as no or little cohort effect in the three observation axes in the age-period-cohort analysis [12].

As such, it can be suspected that the characteristics of breast cancer incidence in Korean women could involve reasons other than a birth cohort effect from lifestyle westernization. In an effort to explain these reasons, an opportunity to identify the causal factors specific for Korean women is created and effective preventative measures can be established. Therefore, here I present two hypotheses based on literature reviews on breast cancer.

THE FIRST HYPOTHESIS: CHANGES IN DENSE BREAST DISTRIBUTION BY AGE GROUP

The evidence for this hypothesis is described in detail in the forthcoming published report by Kim & Bae [13]. Summary and supplementary explanations are given here.

The identification of dense breasts on mammography increases the breast cancer occurrence rate by 4-6 times in Western Caucasian women; as such, it has become the strongest known risk factor to date [14-17]. In particular, in terms of the risk associated with dense breasts, it is reportedly increasing the incidence of breast cancer diagnoses in young women <50 years of age [18]. However, only a few studies have closely examined the hypothesis that dense breasts represent a risk factor for breast cancer in Korean women, and its effect is not yet known [19-

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Received: Aug 8, 2014, Accepted: Sep 26, 2014, Published: Sep 26, 2014

This article is available from: <http://e-epih.org/>

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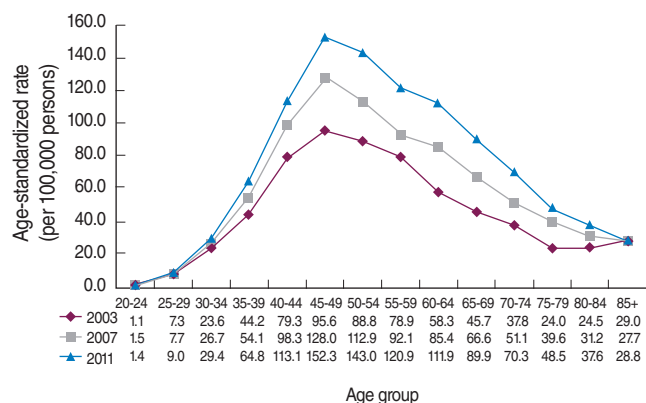


Figure 1. Curves of breast cancer incidence in Korean women by age group and in 4-year intervals.

21]. The reasons for these are twofold: first, Asian women, including Korean women, have more dense breasts than Caucasian women [22,23]; and second, although breast density decreases rapidly after the 30s due to pregnancy, childbirth, and lactation, most studies did not reflect changing trends by age group since only mammographic density immediately preceding breast cancer diagnosis was examined.

On the other hand, according to a report that risk of dense breasts is maintained even after 10 years [24], examining the previous mammographic density from 10 years prior to a cancer diagnosis is also necessary. The fact that the 35-39-year age group, which is 10 years younger than the 45-49-year age group and shows the peak in incidence, had the highest rate of dense breasts [22] leads to a stronger implication of the association [13]. In addition, over the past 10 years, the proportion of dense mammography in screening is increasing in every age group in [25]. In these respects, useful evidences can be obtained from cohort studies that track cancer incidences using multiple test results of women who have repeatedly undergone breast cancer screenings [13].

THE SECOND HYPOTHESIS: CHANGES IN INFECTION RATES OF CANCER-INDUCING VIRUSES

As breast cancer in developing countries is becoming more common in relatively younger age groups, the possibility of infection is being actively suggested, leading to the emergence of the concept of breast cancer being an infectious disease [26,27]. With Korean women also showing the highest incidence at ages 45-49 years [5,10], we must consider the possible association with infection. To date, three types of viruses, mouse mammary tumor virus (MMTV), Epstein-Barr virus (EBV), and human papillomavirus (HPV), have been reported to increase the risk

Table 1. Studies on Asians that evaluated the association between human papillomavirus infection and female breast cancer risk

Design	Likely	Unlikely
Cancer tissues only	[51] (Japan & China)	[53] (Japan) [54] (India)
Case-control comparison	[50] (Iran)	[52] (Taiwan)

Values are presented as [reference number] (nation of subjects).

of breast cancer occurrence [28].

Mouse mammary tumor virus

MMTV was isolated from mice with breast cancer that were raised in the same cage, so it is natural to suspect that MMTV can also cause breast cancer in humans [29]. The work by Labat [30] details the laboratory experiment results on the association between MMTV and breast cancer. In 2012, Glenn et al. [31] claimed that co-infections with the following two viruses increased the risk of breast cancer compared to that of MMTV alone.

Epstein-Barr virus

EBV, widely known to cause Burkitt’s lymphoma [32], received much attention after Labrecque et al. [33] reported that EBV-related DNA were found in the tissues and blood of patients with breast cancer. However, other research papers have reported no association [34-36], causing much confusion. Glaser et al. [37] and Lawson et al. [38] concluded that additional studies are needed through their review of articles on related studies.

Human papillomavirus

HPV, known as a virulence factor for uterine cervical cancer [39], reportedly has a relationship with breast cancer [40-42], and the systematic reviews revealed an association [43,44]. Li et al. [44] reported that 24.49% of breast cancer cases were related to HPV; geographically, this finding was more common in Asians (32.42%) than in Europeans (12.91%). However, a search for studies on Korean women returned only one report indicating that HPV DNA was detected in breast cancer tissue by a DNA chip [45].

The mechanism by which HPV infection causes breast cancer is explained by HPV infiltration through the mammalian duct from the genital to oral route of the sex partner or propagation through the blood [27,46]. Moreover, HPV-related breast cancer is known to occur in younger age groups [31,47], with higher malignancy [48,49]. Furthermore, while studies from Europe and Iran have reported an association between HPV types 16 and 18 and breast cancer [41,50], another study reported that HPV type 33 was related to breast cancer in Japanese and Chinese women [51]. However, as shown in Table 1, most reports on breast cancer tissues in Asians have shown negative results

[52-54]. As some studies claim that the reason why existing studies failed to identify the relationship with HPV was due to the examined breast cancer tissues being treated with paraffin [55] or limitations of the experimental techniques [42].

CONCLUSIONS AND RECOMMENDATIONS

In this paper, two hypotheses that were proposed to explain the trends in increasing incidence of breast cancer in Korean women for the last 20 years were investigated. To obtain evidence that support the first hypothesis that dense breasts are related to breast cancer occurrence, the direction of future studies should be to: (1) verify whether the distribution of dense breasts by age correlates with the annual incidence of breast cancer; (2) use a case-control study method to identify the association between dense breasts and well-known breast cancer risk or protective factors; and (3) conduct a cohort study to verify the relative risk for the onset of breast cancer based on patterns of change in breast density in subsequent screening mammography. If these studies can prove the hypotheses, it would be necessary to establish a new screening strategy, in which patients with dense breasts are selected as a risk group; breast ultrasonography, in addition to mammography, is performed regularly; and the interval of follow-ups is better coordinated [56]. To obtain evidences for the second hypothesis that HPV is related to breast cancer in Korean women, the direction of future studies should be to (1) obtain fresh breast cancer tissues, if possible, to determine the degree of association of HPV DNA to breast cancer using a case-control study, and (2) if relevance is found, identify what subtype is responsible. Moreover, the proposed epidemiological study directions are to: (3) investigate whether patients with HPV infection detected by a Pap smear have higher future risks of breast cancer, and (4) identify any difference in breast cancer occurrence based on HPV vaccination. If a relationship between HPV and breast cancer risk can be established through these studies, HPV vaccinations for the prevention of cervical cancer can also lead to the prevention of breast cancer [40,57-59]. Under the current circumstances in South Korea, co-inoculation of HPV vaccine during the time of rubella vaccination for reproductive-age women should be considered. In conclusion, it is hoped that this paper will stimulate active epidemiological and experimental studies in Korean women.

ACKNOWLEDGEMENTS

This study was supported by funding from the Korean Foundation for Cancer Research in 2013 (no. 2013-2).

CONFLICT OF INTEREST

The author has no conflicts of interest to declare for this study.

SUPPLEMENTARY MATERIAL

Supplementary material is available at <http://www.e-epih.org/>.

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