COMMENTARY

Lifestyle, Genetic Susceptibility and Future Trends of Breast Cancer in Korea

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Abstract

Not only the incidence but the mortality of breast cancer has been steadily increasing in Korea over the last twenty years, and it became the most common female neoplasm in 2002. In fact, the increase in the rate of breast cancer mortality in Korea over the past 10 years has been higher than anywhere else in the world, and it is particularly noteworthy that more than half of the incident cases occur among those younger than 50 years of age. The rapid westernization of dietary habits and changes in reproductive behavior of Korean women presumably played a central role in this extraordinary increase in breast cancer occurrence. A large-scale multi-center case-control analysis showed that an older age, a family history of breast cancer, early menarche, late menopause, late full-term pregnancy, never-having had a breast-fed child, and postmenopausal obesity are breast cancer risk factors in Korea. Environmental and genetic factors are known to play interactive roles in human carcinogenesis and recent studies have shown that genetic polymorphisms may predispose individuals to breast cancer via gene-to-environment or gene-to-gene interactions. Thus research into genetic variation in xenobiotic metabolism, estrogen metabolism, DNA repair, cytokine metabolism, or cell cycle control may give insights into both the etiology and prevention of breast cancer. Epidemiologic evidence obtained from migrant and lifestyle change studies and investigations of main risk factors strongly suggests that breast cancer will further increase in Korea. Future predictions point to a 2- to 3-fold increase in incidence by 2020. Here, we briefly introduce health education programs and breast cancer campaigns, in the broad context of the Korean National Cancer Control Program.

Key Words: Breast cancer - Korea - environmental factors - genetic polymorphisms - intervention strategies

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Introduction

One of the most dramatic features of breast cancer epidemiology is the wide variation in incidence across the world; apparently highest in North America, Western Europe and Australia, while the incidence is relatively low in Japan and Korea (Parkin et al., 1997). However, data from the Korean Central Cancer Registry show the incidence of breast cancer to have risen 1.7-fold over the last 5 years, while colorectal cancer increased 1.5-fold in females (Figure 1) (Ministry of Health and Welfare, 2002). Moreover, a striking fact is that Korea is becoming a country where the associated mortality rate is rapidly changing more than in any other countries in the world. Thus reported changes in breast cancer mortality among middle aged-women during the 1985s to 1995s were the highest in Korea, followed by China and Japan (Bray et al., 2004). It is evident that the magnitude of the difference between the Far East and the West is markedly decreasing, apparently due to rapid changes in the life style of Korean women.

Korean Data

The recent increase in breast cancer mortality in Korea is apparently due to a birth cohort effect, showing almost 1- to 2-fold increase between the 1930s and 1950s birth cohorts as assessed using the Age-Cohort effect model (Choi et al., 2005). There abundant epidemiological evidence of further increase of breast cancer in the future in Korea (Yoo et al., 2002). The finding that Korean migrants living in the United States have substantially higher incidence levels of breast cancer than women in their mother country, suggests the breast cancer might further increase according to the changes in environmental habits, including diet, at present and in the future. Based on the trend in mortality during the last 20 years, the rate is projected to increase almost 3.8-fold by the year 2020, which will surely be a great burden on women's lives, with associated massive costs to society (Figure 2) (Choi et al., 2005). The age-specific incidence rate is presently bimodal; the peak age group is around late 40s, not the 50s to 60s. Distinctively, recent statistics show

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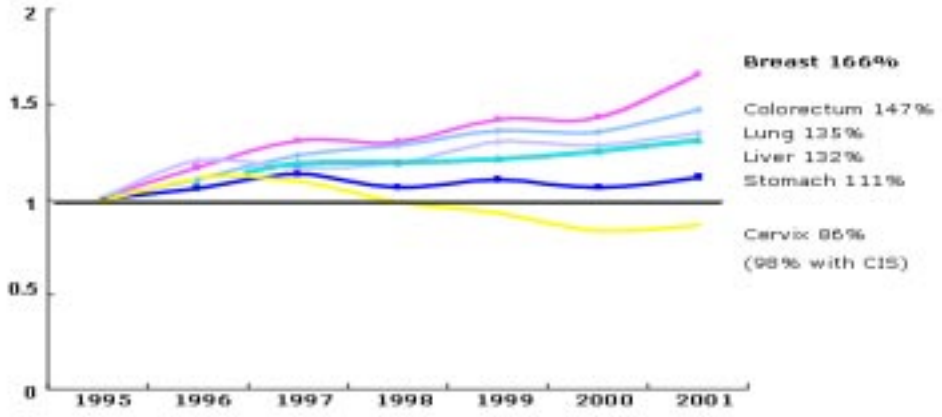

Figure 1. Standardized Cancer Incidence Rates for Females in Korea

that breast cancer patients under age 50 now account for more than half of the patients diagnosed in Korea (Figure 3). This curve must have been influenced by the birth cohort effect, in part, and probably also could reflect selective participation of women of this age in cancer screening (Yoo et al., 2002). It has been suggested that the age incidence curve may be affected by the estrogen receptor (ER) and progesterone receptor (PR) status. Korean data show that the ER+ rates was 59.6% and the PR+ rate 52.9%, with no major variation with the menopausal status (Korean Breast Cancer Society, 2004).

Risk Factors

In order to ascertain the background of the recent increase in breast cancer in Korea, we have been conducted a large-scale multi-center case-control study since 1993. We have now collected information on life style through interviewer-administered questionnaire, together with blood samples, from over a thousand study subjects. This is the largest case-control study in Korea, covering almost 30% of total breast cancer cases. Table 1 shows a summary of risk factors identified through epidemiologic studies in our laboratory.

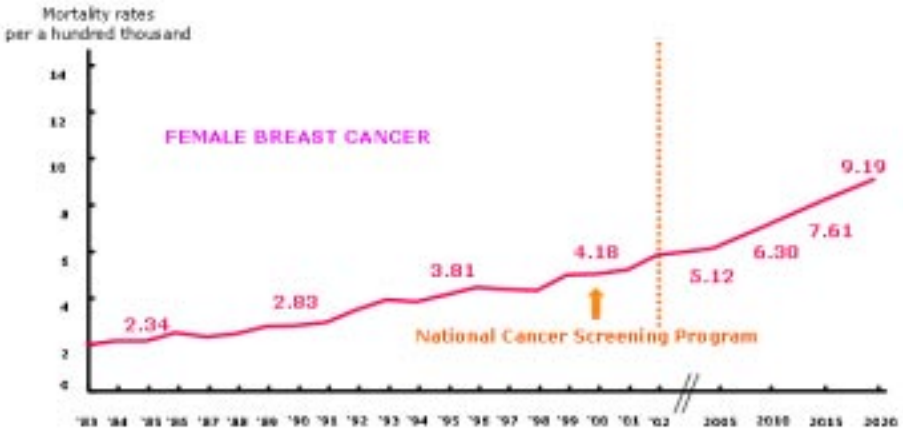

Figure 2. Projection of Breast Cancer Mortality (Korea, all ages, 2005-2020)

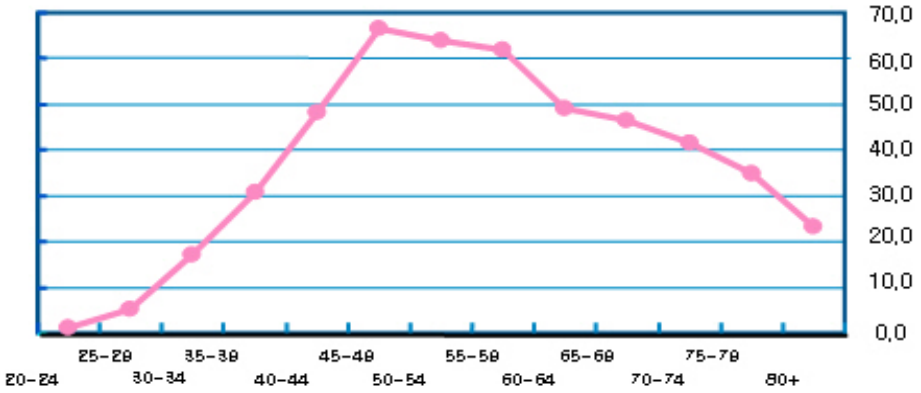

Figure 3. Age-specific Incidence Rates of Breast Cancer (1993-1997, Seoul Cancer Registry)

Table 1. Risk and Protective Factors Related to Breast Cancer in Korea

Established	Probable
- early menarche	- smoking
- late menopause	- physical activity
- nulliparity	- NSAID use
- later FFTP	- oral contraceptives
- family history	- ionizing radiation
- obesity (postmenopausal)	
- alcohol drinking	
- breast feeding	
- HRT	

Early age at menarche and late age at menopause act as breast cancer risk factors in Korean women. Late age at first full-term pregnancy and smaller number of full-term pregnancy clearly confer an increased risk, probably due to changes in breast tissue susceptibility or to the hormonal milieu. Breast feeding has been one point of controversy. As has been observed in other Asian countries, we found longer duration of breast feeding per child to have a protective effect against breast cancer, independent of parity. Particularly this was also evident when the analysis was restricted to the first child (Kim et al., 2006). Height itself was independently confirmed as a breast cancer risk factor, significant only for the postmenopausal women. Similarly, body mass index solely increased the risk of breast cancer in postmenopausal women. Particularly, body weight at late teens shows a statistical significant association with risk of breast cancer only in postmenopausal women. There have been dramatic changes in life style related with breast cancer occurrence in Korean women (Table 2). Age at menarche has rapidly decreased from 15 years in the 1960s to 12.7 years in 1998, while the age at first marriage has changed from 21 years-old in the 1960s to over 27 years in 2002. Consequently, the total fertility rate was reduced to 1.19 in 2003, which is one of the most serious health and social problems in Korea. Breast feeding practice of mothers who have infants is continuously decreasing, probably due to rapid changes in social norm and the role of women in the modern society of Korea, which needs special attention through public campaigns. As a consequence of the marked improvement in nutritional status due to rapid growth in theNational economy, the mean height of 12-year-old Korean girls has markedly increased, and the mean body weight is showing the same trend. Dietary fat once had been hypothesized to be the key factor underluing international differences. The National Health & Nutrition Survey showed the intake of grain and plant foods to be substantially decreasing, while an increasing tendency for animal food intake has been apparent during the past 30 years in Korea. An ecologic correlation study showed the age-adjusted mortality rates for breast cancer to be positively correlated with protein from animal source and total lipid, and inversely correlated with total carbohydrate intake and energy from cereals, suggesting that the increase in breast cancer mortality might be related with increase in fat intake in Korea (Table 3). However, we were not able to demonstrate consistent results on dietary factors related to the breast cancer risk through our conventional case-control studies. We need further studies with more sensitive evaluation of dietary habits, or other approaches, i.e., with a prospective cohort design and incorporating biomarkers.

Table 2. Changes of Lifestyle in Korea

Mean age at first marriage	24.9 (1990)	27.3 (2003)
Total fertility rate	2.0 (1980)	1.19 (2003)
Age at menarche	13.5 (1998)	12.7 (1998)
Total calorie supply (Kcal per capita per day)		
	2.531 (1981)	2.984 (2003)

Table 3. Ecologic Correlation Study of Associations between Nutrient Intake with Different Lag Periods (yrs) and Breast Cancer Mortality in Korea

Nutrients/capita/day	lag	r	lag	r	lag	r
Protein.animal source (%)	12	0.83	11	0.74	10	0.77
Total lipid (g)	12	0.58	11	0.63	10	0.64
Total carbohydrate (g)	12	-0.70	11	-0.63	10	-0.37
Energy from cereals (%)	12	-0.77	11	-0.53	10	-0.74

A recent publication on parental age and breast cancer risk from our laboratory tells an interesting story, i.e., older paternal age increases the risk of breast cancer in female offspring, suggesting the possibility of germ cell mutation (Choi et al., 2005). Indeed, understanding the causes of human cancer is never simple since carcinogenesis is a multi-factorial and multi-stage process. In order to get new insight into the etiology and the preventive strategy as well as the nature of the future trend of breast cancer, the potential roles of inherited genetic component to the burden of disease should be considered. Human genome epidemiology involves the epidemiological application of genome technology to assess the impact of genetic variations on health and disease. Recent developments in molecular biology allow us to use biomarkers to determine an individual's predisposition and to detect disease at an early stage. Moreover, advances in genomics and proteomics could play a central role in research into disease prediction and prevention.

Recent data show polymorphisms of some selected genes to differ in frequency between Caucasians and Koreans. Among the enzymes involved in catechol metabolism of estrogens, the CYP1B1 variant allele of codon 432 polymorphism has about 21% penetration in Koreans, but over 70% in Caucasians. Likewise, findings for the XRCC1 enzyme (base excision repair) and CYP 17 (steroid metabolism) polymorphisms point to the value of ethno-epidemiology through international genomic research. Areas that have been investigated in our laboratory can be summarized as follows (see Table 4); xenobiotic metabolism, estrogen metabolism, DNA repair, cytokines, and cell cycle control (Yoo and Kang, 2003). Hospital based case-control studies also gave us important results with regard to risk factors, genetic determinants and also survivorship of breast cancer.

Table 4. Genome Epidemiologic Studies on Breast Cancer at Seoul National University

Genetic Polymorphism Studies (from 2000): 35 papers, SCI only	
GST M1 T1 alcohol	Pharmacogenetics (2000)
COMT	Pharmacogenetics (2001)
XRCC1	Pharmacogenetics (2002)
GST reproductive factors	Breast Cancer Res Treat (2002)
CYP2E1 ALDH2	Pharmacogenetics (2003)
hOGG1	Breast Cancer Res Treat (2003)
Cytochrome P450-19/1B1	Br J Cancer (2003)
ER-alpha	Breast Cancer Res Treat (2003)
TGF-•,1 & TNF-•,	Breast Cancer Res Treat (2005)
ATM	CEBP (2005)
SULT1A1 SULT1E1	CEBP (2005)
Groups of Genes	
Xenobiotic metabolism	
CYP1A1/2E1, GSTM1/T1/P1, NAT1/2, ALDH2, EPHX, NQO1	
Estrogen synthesis and metabolism	
CYP17/19/1B1, COMT, ER-a, SULT1E1	
DNA repair	
XRCC1-6, ERCC2/4, ATM, AGT, LIG4, RAD51/52, hOGG1	
Cytokine and growth factors	
HER2, TGF-b1, TNF-b, IGF-1, IL-1b, IL-RN	
Cell cycle control	
CCND1, CDK7,BCL6, MTHFR	

Cohort-based Approaches

Our large-scale multi-center hospital-based case-control study on breast cancer is now being expanded into a population-based case-control design in Korea. However, prospective cohort studies provide the most convincing evidence on cancer etiology, and are the ultimate application of human genome epidemiology. The Korean Multi-Center Cancer Cohort (KMCC) is the oldest genomic cohort established for this purpose in 1993 in Korea (Yoo et al., 2002). This is a community-based, cancer-free cohort with an interviewer-administered questionnaire and a complete biospecimen bank in Korea. It his producing many valuable study results on cancer etiology but the major limitation of the cohort is that the size is not sufficient to deal with the diversity of genomic components; the number of biobank specimens is 20,000 with 12 year follow-up. Fortunately, a new Korean Genome Epidemiologic Study, KoGES, begun in November of 2004, is targeting recruitment of 250,000 individuals: 90,000 from the community-based model and 160,000 from the health examinee model (Yoo et al., 2005). This big project is funded by the Health Promotion Fund mainly from the tobacco sales tax.

The site map of the new Genome Cohort covers 12 community-based cohort sites and 12 medical institutes for the health-examinee cohort. Information on life style is obtained by interviewer-administered questionnaire, and blood and urine sampling is performed for all the participants under informed consent. The participants in the community model will be re-examined every 5 years, while participants in the health examinee model will be re-examined every 2 years. The actual number of current participants enrolled is 35,000 as of last August. This cohort, along with other existing cohorts, like the Korean National Cancer Center cohort, will be core members of the Asia Cohort Consortium, which is now developing a common protocol of questions that must be included at the time of enrolment. Ultimately, a large genomic cohort is a critical issue in the long journey to breast cancer prevention and health promotion.

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