History of Diabetes Mellitus and Risk of Breast Cancer in Asian Women: A Meta-Epidemiological Analysis of Population-Based Cohort Studies

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Objectives: Previous quantitative systematic reviews conducting subgroup analyses by race have reported that the association between diabetes and breast cancer in Asian women was inconclusive. The aim of this meta-epidemiological study (MES) was to evaluate this association from additional population-based cohort studies.

Methods: The potential subjects of this MES were six Asian cohort studies selected by previous systematic reviews. Additional reports were found from the selected articles using citation discovery tools. The study with the longest follow-up period was selected among prospective studies of the same cohorts. A summary relative risk (sRR) and its 95% confidence intervals (CI) were calculated using random effect models.

Results: Four cohort studies on Asian women were finally selected. The participants were from the women population of Korea, Japan, China, and Taiwan and included a total of 1,448,254 women. The sRR (95% CI) (I-squared value) was 1.20 (0.98–1.46) (63.1%).

Conclusions: This MES found that the history of diabetes mellitus was not associated with the risk of breast cancer in Asian women. As breast cancer in this population develops at a younger age, additional cohort studies are necessary to conduct a subgroup analysis by menopausal status at diagnosis of breast cancer in Asian women.

Key Words: Breast neoplasms, Cohort studies, Diabetes mellitus, Meta-analysis

INTRODUCTION

The incidence of breast cancer ranks second among all cancers and first among female cancer, with large differences in occurrence by country and race [1]. In addition to genetic factors, such as family history, non-genetic factors, such as menstruation status, fertility, and hormonal intake are known to increase breast cancer risk [2,3]. However, further studies on the recent rapid increase in the incidence of breast cancer in areas with previously low incidence, such as Asia are needed [4-7].

Meanwhile, the prevalence of diabetes is increasing worldwide, especially in Asia [8-10]. Therefore, there is a need to test hypotheses such as the relationship between diabetes and the risk of breast cancer. Table 1 summarizes the results of the seven systematic reviews (SR) conducted to analyze this hypothesis [11-17]. In all SR except Anothaisintawee et al. [16], a history of diabetes mellitus increased the risk of breast cancer. However, the results of subgroup analyses according to menopausal history in four SR [12-15] showed that the statistical significance of the risk was maintained in post-menopausal women, while the risk level and statistical significance lowered in pre-menopausal women.

The risk for Asian women were inconsistent in the results of two SR with ethnic subgroup analysis [13,14]. This needed to be re-analyzed by study design because

Table 1. Summary of subgroup analyses in previous systematic reviews

Study (year) [reference number]	Search to	Variable	Selected articles	Summary RR	95% CI
Wolf (2005) [11]	Jun. 2004	Cohort	6	1.25	1.19–1.31
Xue (2007) [12]	Dec. 2006	Cohort	11	1.16	1.12–1.20
		Pre-menopause	3	0.92	0.78–1.10
		Post-menopause	6	1.19	1.15–1.22
Larsson (2007) [13]	Feb. 2007	Cohort	15	1.20	1.12–1.28
		Pre-menopause	3	0.91	0.62–1.34
		Post-menopause	8	1.16	1.08–1.23
		America	9	1.12	1.06–1.18
		Europe	7	1.19	1.08–1.31
		Asia	4	1.45	1.07–1.97
Liao (2011) [14]	Mar. 2010	Cohort	7	1.22	1.10–1.34
		Pre-menopause	3	1.15	0.91–1.64
		Post-menopause	5	1.25	1.20–1.30
		America	6	1.16	1.12–1.20
		Europe	3	1.88	1.56–2.25
		Asia	3	1.01	0.84–1.21
Boyle (2012) [15]	Oct. 2011	Cohort	22	1.23	1.12–1.35
		Pre-menopause	5	0.86	0.66–1.12
		Post-menopause	10	1.15	1.07–1.24
Anothaisintawee (2013) [16]	Jan. 2011	Cohort	9	0.97	0.80–1.17
Bernard (2016) [17]	2015	Cohort	8	1.32	1.06–1.65

RR: relative risk, CI: confidence interval.

the result was a combination of prospective cohort studies and case-control studies. In addition, the literature search period was March 2010 in Liao et al. [14] so it is necessary to further select and re-analyze the results of cohort studies on East Asian women published since then. Thus, the author performed a meta-epidemiological study (MES) to investigate the association between diabetes and risk of breast cancer in East Asian women [18,19].

MATERIALS AND METHODS

The subjects of this MES are the articles selected from previous SRs evaluating the same hypothesis [18]. Seven SR presented in Table 1 selected six Asian women's cohort papers [20-25]. As the latest publication year of these was 2014, it was necessary to include additional papers up until the time of writing, September 18, 2019 [25]. A list of articles citing seven SRs in Table 1 and six Asian cohort papers selected by them was constructed

using the 'cited by' option suggested by PubMed [26]. In the papers listed, the papers for inclusion in this MES were selected according to the following criteria: (1) The study participants were healthy women of East Asian descent; (2) the study was conducted by a prospective cohort design; (3) the results showed the effect size for risk of breast cancer according to diabetes mellitus status.

In the studies with same cohort participants, the paper having with the longest follow-up period was selected as representative of the cohort. The effect size of the selected papers was estimated from the adjusted relative risk (RR) and 95% confidence intervals (CI). Then, logarithm RR (logRR) and standard error of logRR of each paper was calculated.

The level of heterogeneity was evaluated with the I-squared value (%) and summary RR (sRR) and 95% CI were estimated by applying the random effect model if over 50% of I-squared value [27]. Egger's test was conducted for publication bias [28] and statistical signifi-

cance level was set at 0.05.

RESULTS

There was a total of 734 articles cited as of September 18, 2019 by the citation discovery tools (CDT) [26]. Four new cohort studies could be added after applying the selection criteria [29-32]. Two articles among the six cohort studies selected in 7 SRs of Table 1 were deleted because Goodman et al. [20] used a cohort of atomic bomb survivors and Bi et al. [25] reported results as a prevalence ratio.

Thus, critical appraisals for extracting information were performed on a total of eight articles from the four cohorts selected by the previous SRs and the four cohorts added by the CDT [21-24,29-32]. The distribution of nationality was 3 from Japan [22,23,31], 3 from Taiwan [24,29,30], 1 from Korea and 1 from China.

Sasazuki et al. [31] conducted a pooled analysis from 8 major cohorts in Japan so that two cohorts in Japan [22,23] were excluded for meta-analysis. All three Taiwan cohort studies conducted from National Health Insurance Databases, therefore Lee et al. [29] with the longest follow-up period was selected among them. Thus, four cohort studies [21,29,31,32] were finally selected as the prospective cohort studies that reported the risk of breast cancer with diabetes in East Asian women. The total number of participants was 1,448,254, and only Pan et al. [32] included the results adjusted for menopausal history (Table 2).

The studies in Korea and China among 4 cohorts showed a statistically significant result [21,32]. However, the meta-analysis applying the random effect model showed no statistical significance (sRR = 1.20, 95% CI = 0.98–1.46, I-squared = 63.1%) (Fig. 1). The P value of Egger's test was 0.50.

Table 2. Four selected cohort studies in Asian women

Characteristic	Study (year) [reference number]			
	Jee (2005) [21]	Lee (2012) [29]	Sasazuki (2013) [31]	Pan (2018) [32]
Nation	Korea	Taiwan	Japan	China
Source of cohorts	KCPS	NHI	8 cohorts	CKBS
Participants (women)	468,615	497,037	182,542	300,060
Age of entry (y)	49.6 (mean)	<30 (mode)	40 (minimum)	51.5 (mean)
Follow-up periods (year)	1993–2002	1998–2009	1984–2009	2009–2013
HR (95% CI)	1.51 (1.26–1.80)	1.01 (0.74–1.37)	0.98 (0.69–1.38)	1.21 (1.01–1.47)
Adjusted variables	Age, age squared, amount of smoking, alcohol use	Age, history of hypertension, dyslipidemia, gout	Age, area, history of cerebrovascular disease, coronary heart disease, cigarette smoking, alcohol consumption, body mass index, physical exercise, green leafy vegetables, coffee intake	Age, study area, education, parental history of cancer, body mass index, cigarette smoking, alcohol drinking, physical activity, menopausal status

KCPS: Korean Cancer Prevention Study, NHI: National Health Insurance, CKBS: China Kadoorie Biobank Study, HR: hazard ratio, CI: confidence interval.
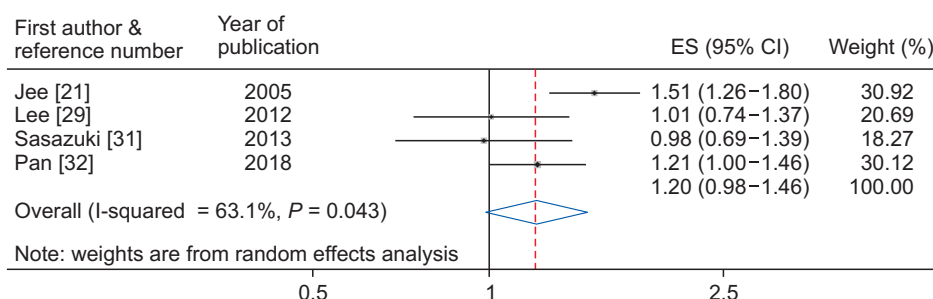

First author & reference number	Year of publication		ES (95% CI)	Weight (%)
Jee [21]	2005		1.51 (1.26−1.80)	30.92
Lee [29]	2012		1.01 (0.74−1.37)	20.69
Sasazuki [31]	2013		0.98 (0.69−1.39)	18.27
Pan [32]	2018		1.21 (1.00−1.46)	30.12
			1.20 (0.98−1.46)	100.00
Overall (I-squared = 63.1%, P = 0.043)				
Note: weights are from random effects analysis				

Fig. 1. Forest plot for estimating the summary effect size (ES). CI: confidence interval.

DISCUSSION

To summarize, there is no association between diabetes and risk of breast cancer in East Asian women. However, it could not be concluded that this was caused by racial difference between Westerners and Asians. The reasons were as follows: first, results of Pan et al. [32] showed the risk of breast cancer with diabetes in post-menopausal women (RR = 1.26, 95% CI = 1.02–1.56), but there was no statistical significance in pre-menopausal women (RR = 1.05, 95% CI = 0.65–1.69); secondly, it should be considered that the age of onset of breast cancer in East Asian women including Korean is younger than for Western women [4]. In other words, the main reason for a lack of statistically significant association between diabetes and breast cancer risk in East Asian women compared to Western women was the fact that breast cancer patients in East Asians had relatively younger age and therefore studies on this population included more pre-menopausal breast cancer patients.

Wolf et al. [11] pointed out that a detection bias could be introduced because diabetic patients could have higher possibility of screening for breast cancer. However, subsequent studies have reported similar or fewer breast cancer screenings to those with diabetes than those without diabetes [33]. Additionally, Bowker et al. [34] argued a possibility of detection bias because post-menopausal women were at increased risk of breast cancer within the first three months of diagnosing diabetes (RR = 1.31, 95% CI = 0.92–1.86). However, there is insufficient evidence to interpret the difference in risk according to menopause as a detection error since there is no statistical significance.

For the different effects on menopause status on the relationship between diabetes and the risk of breast cancer, it was thought to be due to anatomical differences in breast cancer before and after menopause [35] or an estrogen effect [36]. Although it is still controversial [37], it is possible that obesity may increase the risk of breast cancer in post-menopausal women but not in pre-menopausal women [38,39], as diabetes and breast cancer both have obesity as a common risk factor [11,40]. However, Pan et al. [32] suggested that diabetes increased the risk of breast cancer even when the menopause and obesity levels were adjusted for (RR = 1.21, 95% CI = 1.01–1.47).

Therefore, research from various perspectives is needed to provide a clearer interpretation. In particular, for a more valid interpretation of the risk of breast cancer with diabetes according to menopausal status, it is necessary to consider menopausal status and hormone intakes to alleviate menopausal symptoms, as well as the blood sugar level at the time of first diagnosis, the duration of diabetes after the first diagnosis, the history of diabetes control, and the complications of diabetes [40]. In addition, in view of the relatively young age of breast cancer in Asian women, it is necessary to conduct a nested case-control study to investigate the risk of breast cancer in diabetic disease according to the menopause history at the time of breast cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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