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
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-

| 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 |
|                                 |           |          |                  | 0.92       | 0.78–1.10 |
| Larsson (2007) [13]            | Feb. 2007 | Cohort   | 15               | 1.20       | 1.12–1.28 |
|                                 |           |          |                  | 0.91       | 0.62–1.34 |
|                                 |           |          |                  | 1.16       | 1.08–1.23 |
|                                 |           |          |                  | 1.12       | 1.06–1.18 |
|                                 |           |          |                  | 1.19       | 1.08–1.31 |
|                                 |           |          |                  | 1.45       | 1.07–1.97 |
| Liao (2011) [14]               | Mar. 2010 | Cohort   | 7                | 1.22       | 1.10–1.34 |
|                                 |           |          |                  | 1.15       | 0.91–1.64 |
|                                 |           |          |                  | 1.25       | 1.20–1.30 |
|                                 |           |          |                  | 1.16       | 1.12–1.20 |
|                                 |           |          |                  | 1.88       | 1.56–2.25 |
|                                 |           |          |                  | 1.01       | 0.84–1.21 |
| Boyle (2012) [15]              | Oct. 2011 | Cohort   | 22               | 1.23       | 1.12–1.35 |
|                                 |           |          |                  | 0.86       | 0.66–1.12 |
|                                 |           |          |                  | 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.
DM and Breast Cancer in Asian Women

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] | Year of publication | ES (95% CI)       | Weight (%) |
|------------------------------------|---------------------------------|---------------------|-------------------|------------|
| Jee (2005) [21]                    | 2005                            |                     | 1.51 (1.26–1.80)  | 30.92      |
| Lee (2012) [29]                    | 2012                            |                     | 1.01 (0.74–1.37)  | 20.69      |
| Sasazuki (2013) [31]               | 2013                            |                     | 0.98 (0.69–1.39)  | 18.27      |
| Pan (2018) [32]                    | 2018                            |                     | 1.21 (1.00–1.46)  | 30.12      |
| Overall (I-squared = 63.1%, P = 0.043) |                   |                     | 1.20 (0.98–1.46)  | 100.00     |

Note: weights are from random effects analysis.

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

First author & reference number Year of publication | ES (95% CI)       | Weight (%) |
---|-------------------|-------------------|------------|
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Note: weights are from random effects analysis.
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.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
2. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001; 2: 133–40.
3. Gray JM, Rasanayagam S, Engel C, Rizzo J. State of the evidence 2017: an update on the connection between breast cancer and the environment. Environ Health 2017; 16: 94.
4. Shin HR, Joubert C, Boniol M, Hery C, Ahn SH, Won YJ, et al. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. Cancer Causes Control 2010; 21: 1777-85.
5. Bae JM. Two hypotheses of dense breasts and viral infection for explaining incidence of breast cancer by age group in Korean women. Epidemiol Health 2014; 36: e2014020.
6. Ahn SH, Yoo KY; Korean Breast Cancer Society. Chronological changes of clinical characteristics in 31,115 new breast cancer patients among Koreans during 1996–2004. Breast Cancer Res Treat 2006; 99: 209-14.
7. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004; 6: 229-39.
8. Kim SH, Lee ES, Yoo J, Kim Y. Predicting risk of type 2 diabetes mellitus in Korean adults aged 40-69 by integrating clinical and genetic factors. Prim Care Diabetes 2019; 13: 3-10.
9. Rhee EJ. Diabetes in Asians. Endocrinol Metab (Seoul) 2015; 30: 263-9.
10. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and
11. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. Lancet Oncol 2005; 6: 103-11.
12. Xie F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr 2007; 86: s823-35.
13. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007; 121: 856-62.
14. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev 2011; 12: 1061-5.
15. Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, et al. Diabetes and breast cancer risk: a meta-analysis. Br J Cancer 2012; 107: 1608-17.
16. Anothaisintawee T, Wiratkapun C, Lerdsitthichai P, Kasamesup V, Wongwaisayawan S, Srinakarin J, et al. Risk factors of breast cancer: a systematic review and meta-analysis. Asia Pac J Public Health 2013; 25: 368-87.
17. Bernard L, Reix N, Benabu JC, Gabriele V, Mathelin C. Breast cancer and diabetes mellitus: Complex interactions. Gynecol Obstet Fertil 2016; 44: 701-11. French.
18. Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. Evid Based Med 2017; 22: 139-42.
19. Bae JM. Body mass index and risk of gastric cancer in Asian adults: a meta-epidemiological meta-analysis of population-based cohort studies. Cancer Res Treat 2019. doi: 10.4143/ctr.2019.241.
20. Goodman MT, Cologne JB, Moriwaki H, Vaeth M, Mabuchi K. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. Prev Med Med 1997; 26: 144-53.
21. Lee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293: 194-202.
22. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006; 166: 1871-7.
23. Khan M, Mori M, Fujino Y, Shibata A, Sakauchi F, Washio M, et al. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 2006; 7: 253-9.
24. Lin CC, Chiang JH, Li CI, Liu CS, Lin WY, Hsieh TF, et al. Cancer risks among patients with type 2 diabetes: a 10-year follow-up study of a nationwide population-based cohort in Taiwan. BMC Cancer 2014; 14: 381.
25. Bi Y, Lu J, Wang W, Mu Y, Zhao J, Liu C, et al. Cohort profile: risk evaluation of cancers in Chinese diabetic individuals: a longitudinal (REACTION) study. J Diabetes 2014; 6: 147-57.
26. Bae JM, Kim EH. Citation discovery tools for conducting adaptive meta-analyses to update systematic reviews. J Prev Med Public Health 2016; 49: 129-33.
27. Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. meta: fixed- and random-effects meta-analysis. Stata J 2008; 8: 3-28.
28. Sedgwick P. Meta-analysis: testing for reporting bias. BMJ 2015; 350: g7857.
29. Lee MY, Lin KD, Hsiao PJ, Shin SJ. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism 2012; 61: 242-9.
30. Chen HF, Liu MD, Chen P, Chen LH, Chang YH, Wen PC, et al. Risks of breast and endometrial cancer in women with diabetes: a population-based cohort study. PLoS One 2013; 8: e67420.
31. Sasazuki S, Charvat H, Hara A, Wakai K, Nagata C, Nakamura K, et al. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. Cancer Sci 2013; 104: 1499-507.
32. Pan XF, He M, Yu C, Lv J, Guo Y, Bian Z, et al. Type 2 diabetes and risk of incident cancer in China: a prospective study among 0.5 million Chinese adults. Am J Epidemiol 2018; 187: 1380-91.
33. Calip GS, Yu O, Boudreau DM, Shao H, Oratz R, Richardson SB, et al. Diabetes and differences in detection of incident invasive breast cancer. Cancer Causes Control 2019; 30: 435-41.
34. Bowker SL, Richardson K, Marra CA, Johnson JA. Risk of breast cancer after onset of type 2 diabetes: evidence of detection bias in postmenopausal women. Diabetes Care 2011; 34: 2542-4.
35. Rose DP, Vona-Davis L. Interaction between menopausal status and obesity in affecting breast cancer risk. Maturitas 2010; 66: 33-8.
36. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer 2005; 12: 1071-82.
37. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci 2013; 104: 9-14.
38. La Vecchia C, Giordano SH, Hортобágyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. Oncologist 2011; 16: 726-9.
39. Andò S, Gelsomino L, Panza S, Giordano C, Bonofiglio D, Barone I, et al. Obesity, leptin and breast cancer: epidemiological evidence and proposed mechanisms. Cancers (Basel) 2019; 11: E62.
40. Habib SL, Rojna M. Diabetes and risk of cancer. ISRN Oncol 2013; 2013: 583786.