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Review

The Relation of Type 2 Diabetes and Breast Cancer Incidence in Asian, Hispanic and African American Populations—A Review

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Key Messages

- Meta-analyses in primarily Caucasian populations suggest that women with type 2 diabetes experience an approximately 20% elevated breast cancer risk.
- Studies in Asian women indicate a higher breast cancer risk associated with type 2 diabetes but lack of adjustment for important confounders is a concern.
- No significant associations between type 2 diabetes and breast cancer risk have been reported in African American and Hispanic women so far.

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ABSTRACT

In addition to rising type 2 diabetes and breast cancer incidence rates worldwide, diabetes may also increase breast cancer risk, and the association may vary by ethnicity. This review summarizes published data evaluating the association between diabetes and breast cancer in women of Asian, Hispanic and African American ancestry while considering a measure of obesity, body mass index (BMI). Published reports were identified through a search of PubMed and previous publications. Of 15 age-adjusted studies, 11 reported on Asian women from various countries, 3 on Hispanics and 1 on African Americans. The studies of Asian women described significant associations in 8 reports, with risk estimates of 1.5 to 8.4, but 3 were case-control studies and 6 did not adjust for BMI. The 3 case-control studies of Hispanic people included BMI, but only 1 detected a weak association between diabetes and breast cancer risk and was limited to postmenopausal women. The only study of African American women was a prospective cohort, and it showed no significant association between diabetes and breast cancer. In contrast to a 10% to 20% higher risk for breast cancer associated with diabetes reported for Caucasian women, there is little evidence for an association in Hispanics and African Americans. Although several studies of Asian women included in our review reported a higher risk for breast cancer with diabetes, methodologic shortcomings, such as lack of adjustment for obesity, use of a general population as controls, case-control design and small sample sizes, raise questions about the validity of the findings.

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R É S U M É

Les taux d'incidence du diabète de type 2 (DT2) et du cancer du sein sont en hausse dans le monde entier. En outre, le DT2 peut augmenter le risque de cancer du sein, et l'association peut varier selon l'origine ethnique. Cet article de synthèse résume les données publiées permettant d'évaluer l'association entre le DT2 et le cancer du sein chez les femmes d'ascendance asiatique, hispanique ou afro-américaine. Il aborde parallèlement une mesure de l'obésité, l'indice de masse corporelle (IMC). Une recherche sur le site PubMed et dans les publications antérieures a permis de recenser les comptes rendus publiés. Sur

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15 études au cours desquelles des corrections ont été effectuées en fonction de l'âge des sujets, 11 ont été menées chez des femmes asiatiques issues de différents pays, 3 chez des femmes hispaniques et 1 chez des femmes afro-américaines. Huit comptes rendus d'études menées chez des femmes asiatiques font état d'associations significatives et d'un risque estimatif allant de 1,5 à 8,4; toutefois, trois études étaient de type cas-témoins et six ne comportaient aucune correction en fonction de l'IMC. Les trois études cas-témoins menées chez des femmes hispaniques tenaient compte de l'IMC, mais une seule a permis de déceler une faible association entre le DT2 et le risque de cancer du sein se limitant aux femmes en postménopause. La seule étude menée chez des femmes afro-américaines portait sur une cohorte suivie prospectivement et n'a révélé aucune association significative entre le DT2 et le cancer du sein. Alors que le risque de cancer du sein associé au DT2 est de 10 à 20 % plus élevé chez les femmes blanches, peu de signes d'une association ont été notés chez les femmes hispaniques et afro-américaines. Bien que plusieurs des études menées chez des femmes asiatiques incluses dans notre article de synthèse aient fait ressortir un risque plus élevé de cancer du sein associé au DT2, les lacunes méthodologiques telles que l'absence de correction en fonction de l'obésité, l'utilisation de la population générale en guise de témoin, le plan d'étude cas-témoins et la petite taille des échantillons soulèvent des questions sur la validité des conclusions qui en ont été tirées.

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Introduction

The rising burden of type 2 diabetes affects populations around the world, but the prevalence of diabetes is 2 to 3 times higher in many non-Caucasian groups than in Caucasian groups (1–3). Breast cancer is the most common cancer among women worldwide (4). However, the incidence rates vary widely across populations, with the highest rates occurring in North America, Australia and Europe and the lowest rates occurring in large parts of Africa and Asia. Although the incidence rates have been stable in North America (5), rates in developing countries continue to rise (4). The prevalence of obesity is increasing at a rapid rate in all parts of the world (6,7) and constitutes the major modifiable risk factor for diabetes (8). At the same time, excess body weight is considered of the most important risk factors for postmenopausal breast cancer, along with levels of physical activity, hormone treatments and alcohol intake (9–12). For diabetes (3,13,14) and breast cancer (15,16), obesity appears to predict a higher risk for Asian women than for Caucasian women.

Considerable evidence suggests an association between diabetes and a higher breast cancer risk independent of obesity, but this question has been investigated primarily in Caucasian populations, as summarized in several meta-analyses (17–19). Two meta-analyses reported a nearly 20% higher risk for breast cancer in women with diabetes (17,19), while a larger review of 40 studies found a relative risk (RR) of 1.16 (95% CI 1.08 to 1.24) for body mass index (BMI)-adjusted studies as compared to 1.33 (95% CI 1.18 to 1.51) in studies that did not include BMI as a confounder (18). Studies reporting on the association between diabetes and breast cancer risk in differing geographic locations are contradictory. Whereas in 1 meta-analysis, diabetes was associated with similar risk for breast cancer in women with diabetes from Asia (RR 1.45; 95% CI, 1.07 to 1.97) compared with reports from North America (RR 1.12; 95% CI 1.06 to 1.18) and Europe (RR 1.19; 95% CI 1.08 to 1.31) (17), a more recent meta-analysis (19) showed a stronger association between diabetes and breast cancer in studies from Europe (RR 1.88; 95% CI 1.56 to 2.25) as compared to Asia (RR 1.01; 95% CI 0.84 to 1.21). As for biologic mechanisms, it has been hypothesized that ethnic differences in visceral fat and adipokines (20,21) or the adverse metabolic consequences of obesity on glucose control and chronic inflammation (22) may modify the relationship between diabetes and breast cancer risk. The goal of the current study was to explore how the association between diabetes and breast cancer risk differs among populations of Asian, Hispanic and African American ancestry.

Methods

We reviewed observational studies that examined the association between diabetes and breast cancer incidence by ethnicity. A summary

of previous results in Caucasian populations was obtained from 3 meta-analyses (17–19). The publications for the current review were limited to English-language studies that were designed as case-control or cohort studies and provided risk estimates for the incidence of breast cancer in women with diabetes. The majority of reports were identified through a search in PubMed using the terms *breast, cancer, diabetes* and *risk* plus *Hispanic or Japan or Thailand or Latino or Black or African American or Asian or Chinese or Japanese or Indian or Filipino*. In addition, we examined the bibliographies in publications that included cancer sites other than breast (23–26). We summarized the results for women with Asian, Hispanic and African American ancestry separately and listed covariates that were included in each study. We were presented the risk estimates as forest plots taking into consideration adjustment of the statistical results for BMI. Depending on the study design, the risk estimates were presented as odds ratio (OR), hazard ratio (HR), relative risk (RR), incidence rate ratio (IRR), standardized incidence ratio (SIR) or mortality rate ratio (MRR).

Results

Of the total 170 publications identified (Figure 1), 166 articles were discovered in PubMed and 4 in published reports (23–26). After screening the abstracts of all records, we excluded 140 papers that were not relevant to our research question. Of the 30 publications examined as full articles, 15 reports (Table 1) were found to refer to epidemiologic investigations that examined the association between diabetes and breast cancer incidence or of breast cancer mortality as a surrogate of incidence (27).

Among the 11 investigations in differing Asian populations, 3 in Hispanics, and 1 in African American women (Table 1), we included 9 cohort and 6 case-control studies; 3 of the Asian cohorts used the general population as controls to estimate the relative risk for breast cancer. For the other 6 cohort studies, women without breast cancer served as comparison, while in the 6 case-control studies, controls were identified from population-based sources (3) or clinical settings (3). All risk estimates were adjusted for age, but 6 of the studies of Asians were not able to adjust the models for BMI. The inclusion of other potential confounding variables also varied across reports (Table 1). The number of breast cancer cases ranged from 36 to 1380, while the cohort sizes varied from 4155 women with diabetes (28) to more than 400,000 Korean health-plan members (23). All studies except 1 of Hispanic women (29), which also included non-Hispanic whites, were conducted uniquely within a single ethnic group.

Asians

Of the 11 reports concerning women of Asian ancestry (Figure 2), all but 3 investigations reported on East Asians; 4 were conducted

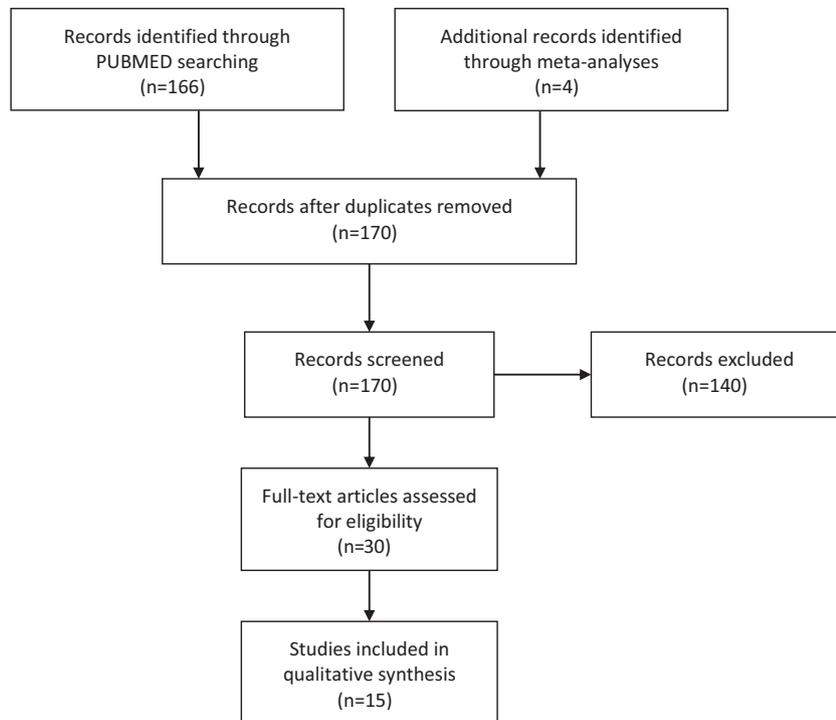


Figure 1. Flow diagram of study selection for systematic review.

in Japan (24–26,30), 2 in China (28,31) and 1 each in Korea (23), Taiwan (27), Thailand (32), Pakistan (33) and Asian Americans (women of Chinese, Japanese or Filipino ancestry) in California (34). All but 1 study reported breast cancer incidence, 1 had only breast cancer mortality as the outcome (27) and 1 showed risk estimates for incidence and mortality (23). Significant associations ranging between risk estimates of 1.5 and 8.4 were reported in 8 studies, but 6 of the studies were not adjusted for BMI (23,27,28,30–32). When looking at studies that adjusted for BMI, diabetes was a significant predictor of breast cancer in a case-control study of Asian Americans (34) and in Pakistan (33), with respective estimates of 1.66 (95% CI 1.12 to 2.45) and 2.96 (95% CI 1.30 to 6.30) but not in other studies of Asians (24–26). A large study of 182,542 Japanese women and 1380 breast cancer cases from 6 Japanese cohorts (26) reported a risk estimate of 0.98 (95% CI 0.69 to 1.38) for breast cancer associated with diabetes, though it reported a higher risk for all cancers in women with diabetes (HR 1.19; 95% CI 1.12 to 1.25).

Of the 2 cohorts that investigated breast cancer mortality as a surrogate for incidence, 1 examined deaths due to breast cancer in a large cohort of Korean insurance company members (23), whereas the other followed 131,573 women with diabetes aged 25 years of age or older from a national cohort in Taiwan, determined mortality from the National Register of Deaths and calculated MRR in comparison to the general population (27). Breast cancer-specific mortality was significantly elevated for women with diabetes in both reports, but the models were not adjusted for BMI and risk factors other than age.

With the important role of menopausal status in breast cancer etiology (35), results for pre- and postmenopausal women are of interest, but only 2 studies of Asian populations provided these estimates. Among Asian Americans (34), diabetes was associated with a statistically significant higher risk for breast cancer in postmenopausal women (OR 1.74; 95% CI 1.11 to 2.74) but not in premenopausal women (OR 1.55; 95% CI 0.64 to 3.73). In contrast, a Taiwanese study reported higher breast cancer mortality in women with

diabetes aged 25 to 54 years (OR 3.00; 95% CI 2.18 to 4.12) but not in older women (27).

Hispanics

We identified 3 studies of Hispanic populations. All were case-control studies (29,36,37) and were adjusted for age and BMI. A study from Uruguay reported a higher risk for breast cancer among women with diabetes, but the elevated risk was limited to postmenopausal women (OR 1.90; 95% CI 1.04 to 3.52). On the other hand, the 2 studies of Hispanic populations from the United States reported null findings (Table 1). A population-based study in the southwestern United States (29) reported no significant association between history of diabetes and premenopausal (OR 0.89; 95% CI 0.64 to 1.26) or postmenopausal breast cancer (OR 0.96; 95% CI 0.78 to 1.19) among Hispanic women. Interestingly, 1 study found that Hispanic women with diabetes who exercised had a significantly reduced risk for breast cancer (OR 0.41; 95% CI 0.21 to 0.83) than those who did not exercise (OR 0.96; 95% CI 0.63 to 1.48); both groups were compared to women who had no history of diabetes and did not engage in physical activity (36).

African Americans

We identified a large prospective study of African American women, the Black Women's Health study (38). The cohort consisted of nearly 50,000 participants and included 1900 women with diabetes. During more than 10 years of follow up, 1228 breast cancer cases were diagnosed; age and BMI were included as covariates. This study did not find an association between diabetes and breast cancer (IRR 0.61; 95% CI 0.23 to 1.65). It is interesting that neither obesity (IRR 1.05; 95% CI 0.85 to 1.29) nor a combination of 3 or more cardiometabolic factors was associated with breast cancer risk (IRR 1.04; 95% CI 0.86 to 1.25) in this analysis.

Table 1
Ethnic-specific studies reporting on the relationship between type 2 diabetes and breast cancer

Ethnicity	Author (year) (location)	Number of participants	Study design	Outcome	Risk estimate (95% CI)	Adjustment		
						Age	BMI	Other*
Asian	Goodman (1997) (Japan) (30)	22,200 women 161 cases	Cohort	Incidence	RR 2.06 (1.27 to 3.34)	Yes	No	D, O
	Jee (2005) (Korea) (23)	468,615 women Number of cases: NA	Cohort	Incidence Breast cancer mortality	HR 1.51 (1.26 to 1.80) HR 2.23 (1.49 to 3.33)	Yes	No	L
	Khan (2006) (Japan) (24)	33,503 women 120 cases	Cohort	Incidence	IRR 1.27 (0.51 to 3.14)	Yes	Yes	L
	Inoue (2006) (Japan) (25)	51,223 women 451 cases	Cohort	Incidence	HR 0.93 (0.44 to 1.98)	Yes	Yes	L, M
	Wu (2007) (US, Asian Americans) (34)	1248 cases 1148 controls	Case control	Incidence	OR 1.66 (1.12 to 2.45)	Yes	Yes	D, L, R
	Tseng (2009) (Taiwan) (27)	131,573 women 482 cases (population as control)	Cohort	Breast cancer mortality (MRR)	25 to 54 yrs: 3.00 (2.18 to 4.12) 55 to 64 yrs: 1.27 (0.95–1.70) 65 to 74 yrs: 1.68 (1.26–2.23) 75+yrs: 2.12 (1.40 to 3.22)	Yes	No	None
	Jordan (2009) (Thailand) (32)	43 cases 860 controls	Case control	Incidence	OR 8.40 (1.70 to 41.00)	Yes	No	D, R
	Zhang (2012) (China) (28)	4155 women with diabetes 36 cases (population as control)	Cohort	Incidence	SIR 2.21 (1.49 to 2.93)	Yes	No	None
	Sasazuki (2013) (Japan) (26)	182,542 women 1380 cases	6 Cohorts	Incidence	HR 0.98 (0.69 to 1.38)	Yes	Yes	D, L, N, R
	Xu (2015) (China) (31)	20,213 women with diabetes 132 cases (population as control)	Retrospective cohort	Incidence	SIR 1.66 (1.38–1.95)	Yes	No	None
Hispanic	Tabassum (2015) (Pakistan) (33)	200 cases 200 controls	Case control	Incidence	OR 2.96 (1.30 to 6.30)	Yes	Yes	L, R
	Rollison (2008) (US) (29)	798 cases 924 controls	Case control	Incidence	OR 0.98 (0.81 to 1.18)	Yes	Yes	D, L, R
	Sanderson (2010) (US) (36)	190 cases 979 controls	Case control	Incidence	All: OR 1.02 (0.71 to 1.48) No PA*: 0.96 (0.63 to 1.48) PA: OR 0.41 (0.21 to 0.83)	Yes	Yes	D, L, R
	Ronco (2012) (Uruguay) (37)	367 cases 545 controls	Case control	Incidence	OR 1.64 (1.00–2.69) Pre OR 1.19 (0.50 to 2.89) Post OR 1.90 (1.04 to 3.52)	Yes	Yes	D, R
African American	Bosco (2012) (US) (38)	49,172 women 1228 cases	Cohort	Incidence	IRR 0.61 (0.23 to 1.65)	Yes	Yes	D, L

D, demographics; HR, hazard ratio; IRR, incidence rate ratio; L, lifestyle; M, medical history; MRR, mortality rate ratio; OR, odds ratio; O, other.

* PA, physical activity; R, reproductive; RR, relative risk; SIR, standardized incidence ratio.

Discussion

In contrast to the findings from 3 large meta-analyses suggesting a 20% higher breast cancer risk for women with diabetes (17–19), this review of 15 studies among non-Caucasian groups detected little evidence for a higher risk of breast cancer with diabetes among Asian, Hispanic and African American women (Figure 2). Although 8 studies in Asian women reported statistically significant relative risk estimates, some of the higher risk estimates may have been affected by the lack of control for BMI and other covariates. Only 2 case-control studies included BMI in their models (33,34), and the largest investigation based on prospective cohorts detected no significant association (26). The small samples sizes and the low power are probably responsible for the inconclusive results. Based on this review, it remains unclear whether the magnitude of this association differs by ethnic background.

Possible mechanisms of diabetes' influence on breast cancer risk in differing ethnic groups include differences in visceral fat and adipokines that have been hypothesized to act as effect modifiers in obesity-related disease (20,21,39,40). Differences in adverse metabolic consequences of obesity on glucose control and chronic inflammation may be responsible for effects on diabetes risk (3,13,14) and breast cancer incidence (15,16) in Asian women compared to Caucasian women. Alternatively, the level of glucose control may moderate the risk factor for breast cancer more than a diagnosis of diabetes per se (41). In 1 of the studies of Hispanic women, women

with untreated diabetes had the highest risk for breast cancer (29). Thus, if treatment of diabetes may lead to better glucose control in some populations than in others, the associated breast cancer risk might vary accordingly. Because the controversial questions of diabetes medications and the possible protective effect of metformin, as well as the adverse influence of certain insulin preparations, on breast cancer risk were not addressed in these studies among non-Caucasian women (42,43), it is difficult to assess the influence of treatment and glucose control across populations. Just as obesity constitutes a risk factor primarily for hormone receptor-positive and not triple-negative breast cancer (44), diabetes may increase the risk factor for some molecular breast cancer subtypes and not others and, thereby, contribute to the unique racial/ethnic-specific incidence of breast cancer subtypes (45).

The possibility of a shared genetic component was examined in a recent analysis of diabetes risk variants and breast cancer risk by the Breast Cancer Association Consortium. The findings suggest that the associations previously observed for diabetes and breast cancer in European women may be more closely related to shared lifestyle factors and residual confounding than to a direct association (46).

Strengths of the current review include the geographic diversity, the high percentage of prospective designs, the generally sound procedures for the ascertainment of diabetes and breast cancer diagnoses, and the adjustment for many relevant confounders in a large proportion of the studies (Figure 2). Nevertheless, a number of limitations need to be mentioned. The number of epidemiologic studies

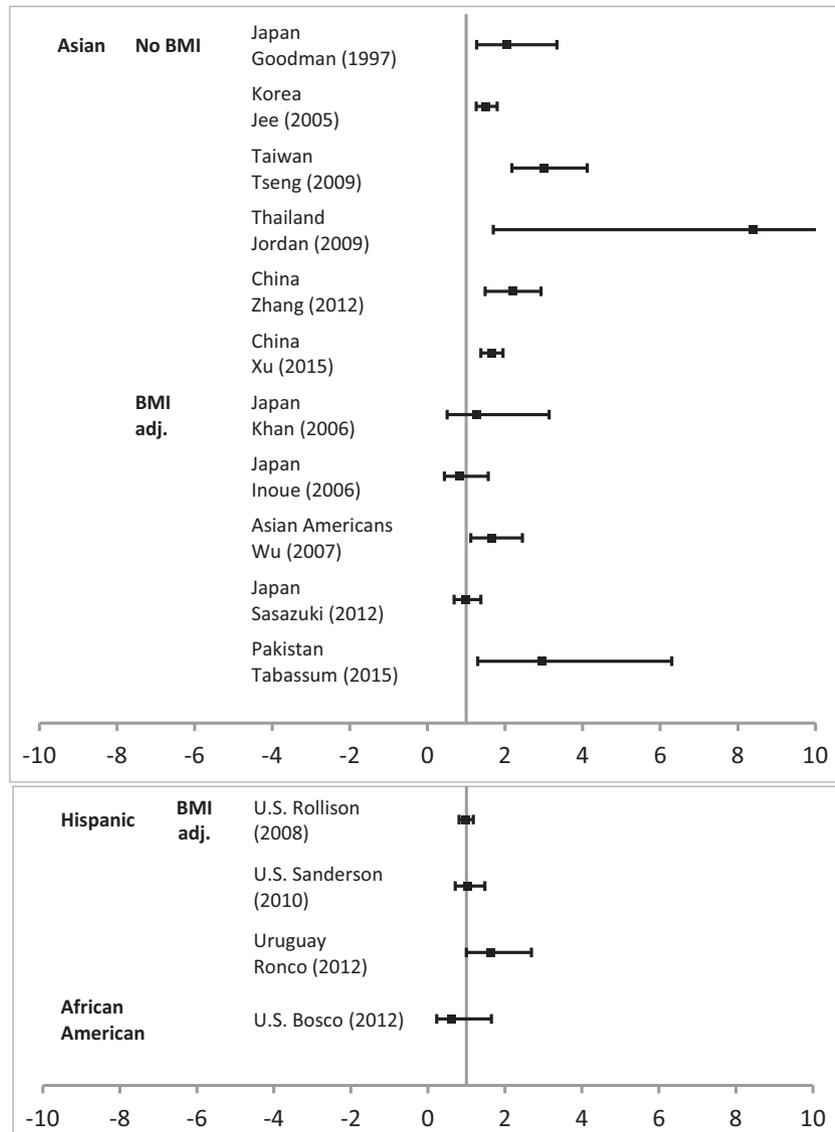


Figure 2. Risk estimates for the association of type 2 diabetes and breast cancer for 3 ethnic groups. *adj.*, adjusted body mass index; *BMI*, body mass index.

investigating the relationship between diabetes and breast cancer risk in these ethnic groups is small. Methodologic concerns include diverse study designs and control populations, small numbers of cases, differences in the definition of diabetes, and uncontrolled confounding factors, e.g., physical activity, diet, family history of breast cancer and reproductive characteristics in some reports. With only 3 studies in Hispanic women (29,36,37) and 1 in African Americans (38), no definite conclusions are possible for those 2 groups, in particular, given the young age distribution in the African American study (38). Significantly elevated risk estimates were detected only for Asian women, but caution is necessary because some of these reports are based on small numbers of cases (23,32) and lack adjustment for BMI (23,27,28,30–32); they compare risk with the general population instead of with appropriately selected controls (27,28,31) or have case-control study designs that involve the well-known problems of recall bias (32–34). There is some suggestion that risk maybe confined to postmenopausal women (18,34), but the mortality investigation in Taiwan indicated a stronger association in younger women (27).

Although the influence of diabetes diagnoses on survival in women with breast cancer was not part of the formal review, the limited evidence is worth mentioning; some results indicate an

adverse impact of diabetes on outcomes. Patients with breast cancer and with preexisting diabetes were found to be at higher risk for long-term all-cause mortality in 2 systematic reviews involving primarily Caucasian women (47,48); the respective pooled HRs of 4 and 6 studies of breast cancer patients were 1.61 (95% CI 1.46 to 1.78) and 1.49 (95% CI 1.35 to 1.65). The results for breast cancer-specific mortality suggest a modestly elevated risk but are inconclusive due to the limited evidence (49,50). In the California Breast Cancer Survivorship Consortium (49), the mortality of 8952 women with breast cancer was investigated using information from 2187 deaths. The findings indicated that breast cancer-specific mortality was higher in women with a history of diabetes (HR 1.48; 95% CI 1.18 to 1.87) than in those without diabetes. The association was statistically significant for Caucasians (HR 1.63; 95% CI 1.10 to 2.43); similar in magnitude but not statistically significant for Asian Americans (HR 1.43; 95% CI 0.84 to 2.44), Hispanic women (HR 1.50; 95% CI 0.71 to 3.17) or African American women (HR 1.17; 95% CI 0.72 to 1.90). A study of 1180 Hispanic patients with breast cancer and 1298 non-Hispanic white women (50) showed a nearly 2-fold higher mortality in Hispanic women with diabetes (HR 1.85; 95% CI 1.11 to 3.09) after adjustment for BMI, whereas the comparable HR in Caucasians was 1.33 (95% CI 0.67 to 2.62).

Conclusions

To disentangle the complicated interactions between obesity, development of diabetes and breast cancer risk, more comprehensive data collection and analysis will be necessary because residual confounding and effect modification in many of the studies that were included may be responsible for the observed ethnic differences. The potential importance and implications of finding ethnic-based differences include more intensive breast cancer screening in women with diabetes from certain ethnic populations that are at high risk.

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