Cancer Epidemiology 60 (2019) 179–184

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Type 2 diabetes, obesity, and breast cancer risk among Japanese women of the atomic bomb survivor cohort

Gertraud Maskarinec[a,*], Atsuko Sadakane[b], Hiromi Sugiyama[b], Alina Brenner[b], Yoshimi Tatsukawa[b], Eric Grant[b]

[a] University of Hawaii Cancer Center, 701 Ilalo Street Honolulu, HI 96813, USA
[b] Radiation Effects Research Foundation, 5-2 Hijiyama-koen, Minami-ku Hiroshima, 732-0815, Japan

ARTICLE INFO

Keywords:
Breast cancer
Obesity
Type 2 diabetes
Japan
Cohort study
Longitudinal analysis

ABSTRACT

Background: Much less is known about diabetes than obesity as a predictor of breast cancer incidence and most previous studies have been conducted in white populations. Therefore, this project within the Radiation Effects Research Foundation's cohort of Japanese atomic bomb survivors aimed to determine the independent contributions of obesity and diabetes to develop breast cancer.
Methods: After excluding women with unknown A-bomb radiation dose, a radiation dose of ≥100 mGy, a preexisting history of breast cancer, and missing body mass index (BMI), the analysis included 29,818 women. Breast cancer status and deaths until 2009 were identified from cancer registries and vital records. Cox regression with age as the time metric was applied to estimate hazard ratios (HR) and 95% confidence intervals (CI) for BMI and diabetes status as time-varying exposures alone and in combination while adjusting for known confounders.
Results: Diabetes prevalence increased from 2.6% to 5.3% and 7.5% from the first to the second and third data collection. During 27.6 ± 12.2 years of follow-up, 703 women had developed breast cancer (mean age of 66.0 ± 12.9 years) and 31 (4.4%) had been diagnosed with diabetes. A diagnosis of diabetes was not significantly associated with breast cancer incidence without (HR 1.12, 95% CI 0.77–1.64) and with BMI (HR 1.01, 95% CI 0.69–1.49) as a covariate. The respective HRs for overweight and obesity were 1.61 (95% CI 1.34–1.93) and 2.04 (95% CI 1.40–2.97).
Conclusions: Among a long-time Japanese cohort, excess body weight but not a diabetes diagnosis was significantly associated with breast cancer risk.

1. Introduction

Obesity is considered the most important modifiable risk factor for postmenopausal breast cancer and type 2 diabetes [1–3] and its prevalence is increasing rapidly in all parts of the world [4,5]. Thus, the burden of type 2 diabetes has soared not only in Western but also Asian countries [6,7]. Despite the traditionally lower breast cancer incidence in Asia than in Europe, North America, and Australia, breast cancer rates in Japan have also been increasing [8], possibly due to changes in lifestyle. The association between diabetes and breast cancer has been examined primarily in white populations indicating a 20–23% higher incidence for women with than without diabetes [9,10]. Yet, adjustment of the diabetes - breast cancer association for body mass index (BMI) reduced the risk estimate from 1.33 (95% confidence interval [CI] 1.18–1.51) to 1.16 (95%CI 1.08–1.24) in a large meta-analysis [10]. Several plausible biologic mechanisms and metabolic pathways have been suggested to link diabetes and breast cancer [11]. The worldwide population attributable risk for diabetes as a contributor to breast cancer incidence has been estimated as 2.2% with wide variations by geographic area [12,13]. In the Multiethnic Cohort (MEC) [14], diabetes was significantly associated with breast cancer incidence before (HR 1.15, 95%CI 1.07–1.23) and after adjustment for BMI (HR 1.08, 95%CI 1.00–1.16), but the associations of obesity with diabetes [15] and with breast cancer [1,16] differed by ancestry; elevated risks for diabetes were only seen in Latinas but not among Japanese and other ethnic groups. In contrast, women with a history of diabetes were at a 2-fold higher risk of breast cancer in a 1997 report from the Radiation Effects Research Foundation's (RERF) cohort of Japanese atomic bomb survivors [17]. Hypothesizing that type 2 diabetes is a risk factor for breast cancer independent of obesity, the current project

* Corresponding author.
E-mail address: gertraud@cc.hawaii.edu (G. Maskarinec).

https://doi.org/10.1016/j.canep.2019.04.009
Received 12 December 2018; Received in revised form 6 April 2019; Accepted 24 April 2019
Available online 02 May 2019

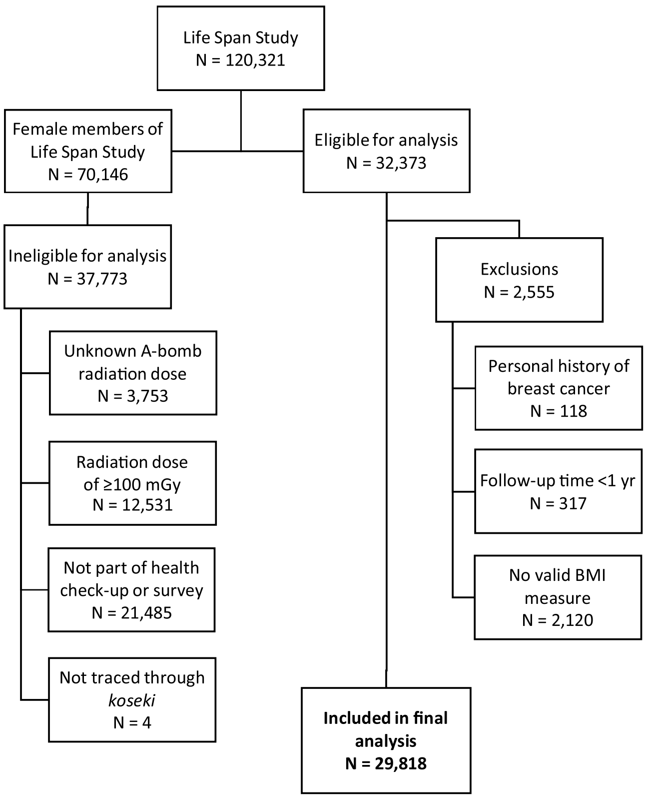

Fig. 1. Flow Diagram of Eligibility and Exclusions for Participants in the LSS Study.

aimed to determine the independent contributions of obesity and diabetes to the development of breast cancer within the RERF cohort.

2. Materials and methods

2.1. Study population

The Life Span Study (LSS) was designed to determine the long-term health effects of exposure to atomic bomb (A-bomb) radiation and has demonstrated a strong association between A-bomb radiation and breast cancer incidence [18,19]. Among the 120,321 LSS individuals, 93,741 were in Hiroshima and Nagasaki at the time of the bombings and resided in one of the cities in 1950 at the time of the first postwar national census and 26,580 were not in either city at the time of the bombings (not-in-city: NIC). Detailed methods of the LSS have been described previously [20,21]. In brief, cancer incidence was ascertained through linkages with two population-based cancer registries in Hiroshima and Nagasaki operational since 1957 and 1958, respectively. Vital status and causes of death were ascertained through the nationwide family registration system.

For the current diabetes-breast cancer analysis (Fig. 1), the following exclusion criteria were applied to the 70,146 female cohort members: unknown A-bomb radiation dose (n = 3,753), radiation dose of ≥ 100 mGy (n = 12,531) to minimize potential confounding and the number of cases attributable to radiation (estimated 4.3% for doses 5- < 100 mGy) [22], no participation in a health check-up or mail survey (n = 21,485), or could not be traced through *koseki*, Japan's national family registry (n = 4). Among the remaining 32,373 women, we excluded 118 women with a personal history of breast cancer, 317 with < 1 year of follow-up after the first survey due to uncertainty that diabetes was diagnosed before breast cancer, and 2,120 women without valid BMI measures due to missing height (n = 1,940) or invalid body weight (outside 30–100 kg; n = 960, overlap of n = 780) resulting in a final data set of 29,818 women.

2.2. Follow-up and data collection

After initial enrollment into the LSS, repeated surveys were mailed to the study participants in 1969, 1978, and 1991. For the current analysis, we used information about BMI, history of diabetes, education, reproductive factors, physical activity, smoking behavior, and alcohol intake [23]. For women from the Adult Health Study (AHS), an LSS sub-cohort that undergoes biennial clinical examinations, interviews were conducted in 1963, 1965, and 1968 as part of the check-ups. In the current study, 15.7% (4,670 out of 29,818) women were part of the AHS. Missing or incomplete information on height, weight, and diabetes was supplemented by clinical data derived from examinations conducted at the same time of the interviews.

The 1969 survey did not specifically ask about diabetes but included an open-ended question about history of any serious condition including diabetes, which were coded according to the International Disease Classification (version 8). In the 1978 and 1991 questionnaires, medical history was self-reported in response to the question "Have you ever been told that you have any of the following diseases?" The 1991 survey also asked about reproductive history. As age at the diabetes diagnosis was not recorded, age at data collection was considered as time of onset. Assuming that diabetes is rarely cured, a woman who once reported diabetes was classified as case at all future time points even if she did not report diabetes in a later survey. Current weight and height were collected in all questionnaires. Two categorical BMI variables were created: one with the World Health Organization (WHO) cut-points of 18.5, 25, and 30 kg/m^2 and one proposed for Asian populations with cut-points of 18.5, 23, and 27.5 kg/m^2 to classify BMI into underweight, normal weight, overweight, and obesity [24].

The Institutional Review Board of the RERF and the Cancer Registries of Hiroshima and Nagasaki approved the study protocol. The study was performed with a waiver of informed consent because the participants, except for a subset of the AHS participants, have not been notified that they are part of ongoing analyses within the LSS although they had agreed to complete surveys in the past; also their contact information (e.g., address) was not available anymore. Instead, the purpose and methods of this study were posted on the RERF web page according to the current ethical guidelines.

2.3. Statistical analysis

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary NC). The association of self-reported diabetes status with breast cancer incidence was examined using Cox proportional hazards regression models with age as the time metric and diabetes status and BMI as time-varying exposures. Follow-up for each woman started at the age when information on BMI and medical conditions was collected for the first time, either as part of an AHS check-up or a mailed questionnaire with the following number of women: 3,114 (10%) in 1963, 1,456 (5%) in 1965, 100 (< 1%) in 1968, 15,768 (53%) in 1969, 5,477 (18%) in 1978, and 3,903 (13%) in 1991. Follow-up continued until the earliest of the following events: diagnosis of the first primary invasive, but not in situ, breast cancer, death, or December 31, 2009. As dates of migration out of areas covered by the cancer registries were unknown, we retained breast cancer patients diagnosed outside of Hiroshima and Nagasaki prefectures in the main analysis. For cases with multiple primary cancers, follow-up continued until the earliest diagnosis of primary breast cancer, irrespective of the cancer sequence.

To model the time-varying variables, a programming statement in the proportional hazards regression procedure defined the value for diabetes status and BMI at each specific point of time (up to three per woman) in the modeling process rather than using the initial values. Because of their known association with diabetes and/or breast cancer [25], all models were adjusted for birth cohort, education, city, NIC status, height, age at menarche, number of children, age at first live birth, physical activity, smoking status, and alcohol intake. Women without any valid BMI information had been excluded from the analysis, a lack of response to the diabetes question was considered as no diabetes diagnosis, but missing values for other covariates were coded as a separate category. When BMI information at one of the 3 time points was missing, the value from the previous time point was used instead. Family history of breast cancer, menopausal status, and hormone treatment were not consistently available. Although there is an ongoing effort at the RERF to determine the hormone receptor status of breast tumors, these data are currently unavailable.

To explore if BMI and diabetes are independent predictors, diabetes models with and without BMI were compared. The models for the entire study population (Table 3) were refitted using BMI categories suggested for Asians. Stratified analyses of the diabetes-breast cancer associations by stage of breast cancer at diagnosis according to the definition of the Surveillance, Epidemiology, and End Results (SEER) program [26] and city of residence were performed to explore effect modification by these factors. In sensitivity analyses, breast cancers identified by death certificate only (n = 28), women with NIC status (N = 7,146), < 20 years at the time of the bombing (N = 13,493), and with any missing values for covariates (N = 21,185) were excluded. Graphs of the log (-log (survival)) versus log of survival time indicated that the proportional hazards assumption was met.

To evaluate the joint effect of diabetes and BMI, a combined 4-level variable (BMI < 25 or ≥25 kg/m^2 - no diabetes or diabetes) was created for each time point and modeled by regression with 'BMI < 25 kg/m^2 - no diabetes' as reference category. We also repeated this analysis using BMI and diabetes collected at the earliest survey without considering updated data.

3. Results

Among the study population of 29,818 women, 12,714 women participated in one health check-up or survey only, 11,073 women provided information at a second point in time, and 6,031 women were also part of a third data collection. The first data collection occurred as part of AHS during 1963-68 for 4,670 women, while 15,768, 5,477, and 3,903 women completed their first survey in 1969, 1978, and 1991. The mean ages (± standard deviation, SD) in 1969, 1978, and 1991 were 50.9 ± 14.9, 58.5 ± 13.4, and 65.1 ± 11.7 years. By city, 20,898 (70%) of women were residents of Hiroshima and 8,920 (30%) of Nagasaki. A total of 7,146 (24%) women had been classified as NIC with 5,562 (27%) from Hiroshima and 1,584 (18%) from Nagasaki. Overall, 1,732 (5.8%) women reported a history of diabetes and 28,086 did not (Table 1). The prevalence of diabetes was 2.6% at the time of first data collection increasing to 5.3% and 7.5% at the second and third time point. By birth cohort (1880-1915, 1916-25, 1926-35, and 1936-45), a history of diabetes was reported by 6.4, 7.9, 5.4, and 3.4% of participants, respectively.

During the 27.6 ± 12.2 years of follow-up, 703 women had developed breast cancer at a mean age of 66.0 ± 12.9 years; of these, 31 (4.4%) had been previously diagnosed with diabetes. Approximately 70% of women resided in Hiroshima and 30% in Nagasaki. More than half of participants (52%) had died by the end of 2009. The overall distribution by WHO BMI categories (underweight, normal, overweight, and obese) was 14, 69, 15, and 2%, but women with diabetes history were more likely to be overweight (29 vs. 14%) or obese (5 vs. 2%) than those without diabetes. Using Asian BMI categories, 40 vs. 26% and 15 vs. 5% of women with and without diabetes were overweight and obese, respectively.

In the entire study population (Table 2), pre-existing diabetes was not significantly associated with breast cancer risk regardless of whether or not BMI was included as a covariate. The respective hazard ratios (HRs) were 1.12 (95%CI 0.77–1.64) and 1.01 (95%CI 0.69–1.49). Exclusion of 28 women with breast cancer diagnosed by death certificate only or 7146 NIC women also did not change the results in BMI-adjusted models. After removing all participants with missing values for one or more covariates, i.e., a complete case analysis, the results did not change substantially (HR = 0.89; 95% CI 0.50–1.61). Also, no association was observed when 13,493 women who were younger than 20 years at the time of the bombing in 1945 were excluded (HR = 0.99; 95%CI 0.59–1.69). Stratification by stage at breast cancer diagnosis did not indicate major differences in strength of the diabetes-breast cancer associations; however, for 138 cases no clinical stage at diagnosis was available. The associations were also similar in Hiroshima and Nagasaki survivors.

In the joint BMI-diabetes analysis (Fig. 2), the risk estimates were elevated in all 3 categories although only statistically significant for women in the high (≥25 kg/m^2) BMI category and no diabetes category. The findings were similar when only considering information from the first survey (HR 1.93, 95%CI 1.61–2.30) and in the time-varying model based on all available surveys for each woman (HR 1.80, 95%CI 1.50–2.15). The higher risk estimates for women with both conditions were not significant in either model; the HRs were very similar: 1.59 (95%CI 0.71–3.58) based on the first survey data only and 1.29 (95%CI 0.66–2.50) based on the analysis with time-varying exposures.

As to other known risk factors that were significant predictors of breast cancer incidence in the current study population (Table 3), overweight and obesity both were associated significantly with elevated breast cancer incidence in models that included diabetes. The respective HRs for overweight and obesity were 1.61 (95%CI 1.34–1.93) and 2.04 (95%CI 1.40–2.97). Using the Asian BMI definition, the respective HRs were 1.33 (95%CI 1.12–1.57) and 2.11 (95%CI 1.62–2.76). Breast cancer incidence increased substantially with later birth cohorts; women born in 1936–1945 as compared to those born in 1880–1915 experienced a HR of 2.17 (95%CI 1.58–2.96). Having 1–2 children was associated with a 30% lower risk (HR 0.71, 95%CI 0.51–1.00) and having ≥3 children with a 40% lower risk (HR 0.61, 95%CI 0.43 – 0.87) compared to nulliparous women. Breast cancer risk increased suggestively by 2% per 1 cm of additional height. By location status at the time of the bombings, breast cancer incidence was 22% lower in Nagasaki survivors than in Hiroshima survivors (HR 0.78, 95% 0.65 – 0.94) and 26% lower in NIC women than in-city women (HR 0.74, 95% 0.57 – 0.96). Although included in all models, education, smoking status, physical activity, alcohol intake, age at menarche, and age at first live birth were not significantly associated with breast cancer incidence.

4. Discussion

Although the mean BMI of the Japanese women in this population was much lower than in Western study populations, the women with overweight or obese were at an increased risk of developing breast cancer but a history of diabetes did not affect breast cancer incidence. Birth cohort, parity, city of residence, and NIC status were also significantly associated with breast cancer incidence. It is possible that the observed city and NIC differences in breast cancer incidence are due to uncontrolled confounding by lifestyle factors and socioeconomic status in urban and rural areas. As participants in the present study were exposed to < 100 mGy of radiation, they were in distal (relative to the hypocenter) areas at the time of the bombings, i.e., in rural areas in Hiroshima and urban areas in Nagasaki [27].

The higher risk by birth cohort may be partially a result of secular increases in breast cancer incidence over time [28] due to the rising prevalence of overweight and obesity in Japan [29] and other lifestyle changes but could also be related to the younger age at the time of the radiation exposure, which is known to be a predictor of breast cancer incidence [18], but given our exclusion criteria, the exposure to radiation would have been very low. A "period effect" can be observed since approximately 2004 after the introduction of fine-needle biopsies and the pink ribbon campaign, both leading to higher breast cancer detection rates despite relatively low screening rates for breast cancer

Table 1
Characteristics of the Study Population.

Characteristic	Category	No diabetes	Type 2 diabetes	All women
Participants	Number	28,086	1,732	29,818
Women with breast cancer	Number	672	31	703
Deaths	Number	14,430	1,162	15,592
BMI at 1st data collection, kg/m^2	< 18.5	4,109 (14%)	118 (7%)	4,227 (14%)
	18.5– < 25.0	19,670 (70%)	1,017 (59%)	20,684 (69%)
	25.0– < 30.0	3,850 (14%)	499 (29%)	4,349 (15%)
	≥30	457 (2%)	99 (5%)	558 (2%)
BMI at 1st data collection (Asian categories), kg/m^2	< 18.5	4,109 (15%)	118 (7%)	4,227 (14%)
	18.5– < 23.0	15,123 (54%)	657 (38%)	15,780 (53%)
	23.0– < 27.5	7,384 (26%)	701 (40%)	8,085 (27%)
	≥27.5	1,470 (5%)	256 (15%)	1,726 (6%)
Year of birth	1880–1915	8,844 (31%)	603 (35%)	9,447 (32%)
	1916–1925	5,886 (21%)	505 (29%)	6,391 (21%)
	1926–1935	6,970 (25%)	401 (23%)	7,371 (25%)
	1936–1945	6,386 (23%)	223 (13%)	6,609 (22%)
City of residence	Hiroshima	19,623 (70%)	1,275 (74%)	20,898 (70%)
	Nagasaki	8,463 (30%)	457 (26%)	8,920 (30%)
Not-in-city	No	22,672 (76%)	1,682 (97%)	20,990 (75%)
	Yes	7,146 (24%)	50 (3%)	7,096 (25%)
Children[a]	None	2,221 (8%)	127 (7%)	2,348 (8%)
	1–2	11,002 (39%)	586 (34%)	11,588 (39%)
	≥3	12,203 (43%)	876 (51%)	13,079 (44%)
Age at first live birth[a]	No births	2,221 (8%)	127 (7%)	2,348 (8%)
	< 25 years	12,316 (44%)	868 (50%)	13,184 (44%)
	≥25 years	9,128 (33%)	503 (29%)	9,636 (32%)
Follow-up time	Mean ± std	27.8 ± 12.3	25.0 ± 11.2	27.6 ± 12.2
Age at first survey	Mean ± std	50.6 ± 14.9	54.7 ± 13.3	50.9 ± 14.9
Age at breast cancer	Mean ± std	65.9 ± 13.0	67.7 ± 9.3	66.0 ± 12.9
Age at diabetes diagnosis	Mean ± std	NA	63.9 ± 11.7	NA
Height, cm	Mean ± std	151.6 ± 6.2	151.2 ± 6.3	151.5 ± 6.2

[a] Missing values: 2,803 for number of children and 4,650 for age at first live birth.

in Japan.

These results disagree with the 1997 publication from the same cohort reporting a higher breast incidence among women with diabetes [17], but the analysis was based on few cases, a short follow-up time, and was not adjusted for BMI. The presence of diabetes predicted breast cancer mortality (HR 1.72, 95%CI 1.34–2.19) within the Asia Cancer Consortium [30] and breast cancer incidence (HR 1.71, 95%CI 1.15–2.54) among Asian Americans in California [31]. In contrast, the results agree with null findings in studies conducted in Japan [32–34] and among Japanese Americans [14]. Among six Japanese cohorts (182,542 women and 1,380 breast cancer patients) [34], the risk estimate for breast cancer associated with diabetes was 0.98 (95%CI 0.69–1.38) despite a significantly elevated risk for all cancers (HR 1.19, 95%CI 1.12–1.25). Similarly, no association was seen among 28,012 Japanese American women in the MEC, many of whom are descendants from migrants around Hiroshima [35,36], whereas obesity predicted breast cancer incidence to a similar degree as in the current study [14]. Studies from China [37,38], Korea [39], Taiwan [40], Thailand [41], and Pakistan [42] reported significantly elevated risks of developing breast cancer, ranging from 1.5 to 8.4-fold, in women with a history of diabetes than in those without diabetes, but many studies did not include BMI [37–41] or had a small sample size [42]. The findings among

Table 2
Diabetes, Obesity, and Breast Cancer Incidence in the Study Population.[a]

Characteristics	Category	Number of cases with/without diabetes	HR	95% CI
Diabetes	Unadjusted for BMI	31/672	1.12	0.77, 1.64
	Adjusted for BMI	31/672	1.01	0.69, 1.49
	DCO cases excluded[b]	30/645	1.02	0.69, 1.51
	Not-in-city residents excluded[c]	31/507	1.05	0.72, 1.55
	Complete case analysis[d]	13/241	0.89	0.50, 1.61
	Women ≥20 years in 1945	16/312	0.99	0.59, 1.69
Stage at breast cancer diagnosis[e]	Localized	21/338	1.17	0.72, 1.89
	Regional	5/180	0.63	0.26, 1.55
	Distant	1/20	1.15	0.15, 8.91
City of residence	Hiroshima	23/504	0.97	0.63, 1.52
	Nagasaki	8/168	1.11	0.51, 2.40

[a] Hazard ratios (HR) and 95% confidence intervals (CI) were obtained by Cox regression with age as time metric and BMI and diabetes status as time-varying variables plus adjusted for education, birth cohort, city, NIC, smoking status, physical activity, alcohol intake, age at menarche, number of children, and age at first live birth.

[b] Excludes 28 women with breast cancer obtained from death certificates only.

[c] Excludes 7,146 women (165 with breast cancer) classified as not-in-city at the time of the bombings.

[d] Excludes all women with at least one missing value for a covariate.

[e] For 138 breast cancer patients, the stage at diagnosis was unknown. The stage definition according to the Surveillance, Epidemiology, and End Results (SEER) program was adopted [26].

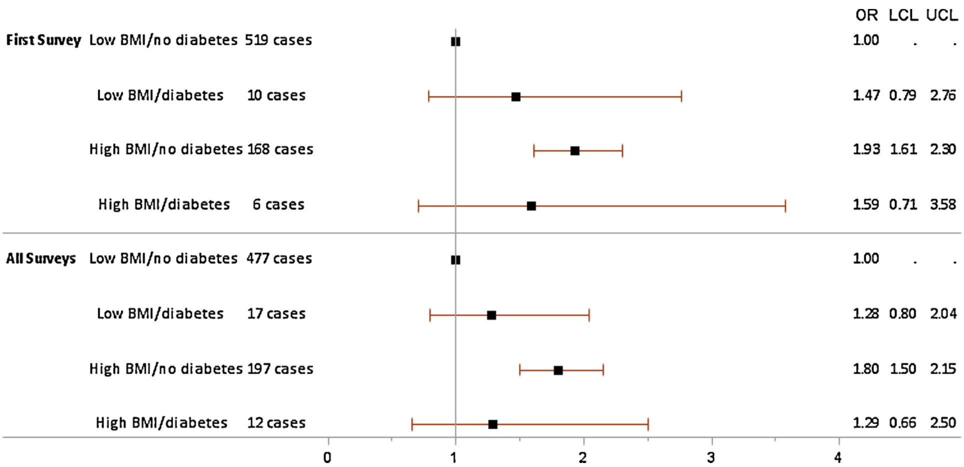

Fig. 2. BMI Status and Diabetes in Combination as Predictors of Breast Cancer Incidence[a].

[a]Hazard ratios (HR) and 95% confidence intervals (CI) were obtained by Cox regression with age as time metric and BMI/diabetes status as time-varying variables plus adjusted for education, birth cohort, city, NIC, smoking status, physical activity, alcohol intake, age at menarche, number of children, and age at first live birth.

The cut-off for low vs. high BMI was 25 kg/m^2.

Table 3
Additional Predictors of Breast Cancer Incidence in the Study Population.[a]

Characteristic	Category	Women with/without incident breast cancer	HR	95% CI
BMI, kg/m^2	< 18.5	69/4,158	0.69	0.52, 0.91
	≥18.5 to < 25	460/20,224	1.00	
	≥25 to < 30	156/4,193	1.61	1.34, 1.93
	≥30	18/537	2.04	1.40, 2.97
BMI, kg/m^2 (Asian categories)	< 18.5	69/4,158	0.72	0.54, 0.95
	18.5– < 23.0	349/15,428	1.00	
	23.0– < 27.5	216/7,869	1.33	1.12, 1.57
	≥27.5	69/1,657	2.11	1.62, 2.76
Height	1 cm	703/29,110	1.02	1.00, 1.03
Years of birth	1880–1915	132/9,315	1.00	
	1916–1925	165/6,226	1.31	1.02, 1.68
	1926–1935	219/7,152	1.61	1.23, 2.10
	1936–1945	187/6,422	2.17	1.58, 2.96
City of residence	Hiroshima	527/20,371	1.00	
	Nagasaki	176/8,744	0.78	0.65, 0.94
Not-in-city	No	538/22,134	1.00	
	Yes	165/6,981	0.74	0.57, 0.96
Parity[b]	No children	90/2,258	1.00	
	1–2 children	303/11,285	0.71	0.51, 1.00
	≥3 children	238/12,841	0.61	0.43, 0.87

[a] Hazard ratios (HR) and 95% confidence intervals (CI) were obtained by Cox regression with age as time metric and BMI and diabetes status as time-varying variables plus adjusted for education, birth cohort, smoking status, physical activity, alcohol intake, age at menarche, number of children, and age at first live birth.

[b] Missing values: 2,803 for parity.

Asian women disagree with meta-analyses among primarily white women reporting a 20% higher breast cancer incidence in women with diabetes [9,13] and relative risks of 1.16 (95%CI 1.08–1.24) for BMI-adjusted studies and 1.33 (95%CI 1.18–1.51) in studies without BMI [10].

The current findings related to BMI agree with previous reports of an elevated breast cancer incidence associated with overweight/obesity among Asian women despite having lower mean BMI levels than white women [1,16]. It has been proposed that higher proportions of visceral fat in Asians than whites are partly responsible for this observation [43]. A worldwide report recently estimated that having a high BMI was responsible for a larger proportion of the breast cancer burden (6.9%) than for diabetes (2.2%) with a combined attributable risk of 8.9% [12].

Strengths of the current analysis include the long-term follow-up of the cohort, the complete follow-up information, the repeated questionnaires, and the availability of many covariates. Changes in lifestyle risk factors and breast cancer risk we addressed by including birth cohort into the models. However, the assessment of BMI and diabetes status had a number of problems. Information was collected at different ages from the participants and varying frequency (1–3 times). New diabetes cases after 1991, the last survey date, were not captured resulting in possible under-ascertainment. Self-reports without information on glucose status may have underestimated the true prevalence of diabetes although the validity of self-reports on diabetes has been shown to be fairly high [44]. The term “diabetes” in the questionnaires does not allow differentiation between the wide spectrum of clinical conditions, including type 1 and 2 diabetes. However, the number of participants with type 1 diabetes would be extremely small as insulin was not available during the childhood of the first two birth cohorts, i.e., 1871–1925, and survival for children with type 1 diabetes born during 1926-45 would remain low.

Misclassification of diabetes status was even more likely for the 7,146 NIC cohort members who did not complete surveys after 1969. Yet, the findings in models using only the first data collection as compared to the time-varying models were very similar. With changing diabetes criteria over time and increased screening efforts leading to rising diabetes incidence [45], undiagnosed diabetes cases likely introduced misclassification bias. However, as part of a clinical study within the AHS, diabetes prevalence was similar to those derived from the surveys (1978: 5.9% and 1991: 7.6%). In addition, the fact that some participants may have moved out of the catchment area of the cancer registries might have introduced misclassification bias as the relatively large migration rates especially in younger generations may have been associated with diabetes status [46,47]. Information on hormone treatment, was not available, but the low use of in Japan makes it unlikely that major bias was introduced. Finally, we were not able to consider the impact of treatment for diabetes although the study participants (certified atomic bomb survivors) were eligible for free health check-ups and medical care.

5. Conclusions

Among a long-time cohort of Japanese women, excess body weight was an important predictor of breast cancer incidence but a diagnosis of diabetes was not. It is possible that the adverse metabolic effects of diabetes vary across populations due to different lifestyle habits and treatment approaches explaining the elevated breast cancer risk associated with diabetes in some but not all populations.

Author contributions

The authors’ responsibilities were as follows: GM, AS, and EG designed the study to address the research question; YT and HS were involved in data collection; GM and AS analyzed the data; EG provided expertise on the different data elements and statistical advice; GM, AS, and AB wrote the paper; HS, YT, AB, and EG provided critical review; GM and AS had primary responsibility for final content. All authors read and approved the final manuscript.

Declarations of interest

None of the authors has a conflict of interest to declare.

Acknowledgments

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the US Department of Energy (DOE) through DOE award DE-HS0000031 to the National Academy of Sciences. This publication was supported by RERF Research Protocol RP S1-18. The views of the authors do not necessarily reflect those of the two governments. GM was funded by a Fulbright Global Scholar Award. The authors thank Mrs. Hiroko Moriwaki for the preparation of the dataset for analysis.

References

[1] K.K. White, S.Y. Park, L.N. Kolonel, B.E. Henderson, L.R. Wilkens, Body size and breast cancer risk: the Multiethnic Cohort, Int. J. Cancer 131 (5) (2012) E705–E716.
[2] G. Maskarinec, E. Erber, A. Grandinetti, et al., Diabetes incidence based on linkages with health plans: the multiethnic cohort, Diabetes 58 (8) (2009) 1732–1738.
[3] J.J. Miao, J. Cederholm, S. Gudbjornsdottir, Excess body weight and cancer risk in patients with type 2 diabetes who were registered in Swedish National Diabetes Register–register-based cohort study in Sweden, PLoS One 9 (9) (2014) e105868.
[4] W.P. James, The epidemiology of obesity: the size of the problem, J. Intern. Med. 263 (4) (2008) 336–352.
[5] M. Arnold, M. Leitzmann, H. Freisling, et al., Obesity and cancer: an update of the global impact, Cancer Epidemiol. 41 (2016) 8–15.
[6] A. Ramachandran, C. Snehalatha, A.S. Shetty, A. Nanditha, Trends in prevalence of diabetes in Asian countries, World J. Diabetes 3 (6) (2012) 110–117.
[7] International Diabetes Federation, IDF Diabetes Atlas, IDF, Bruxelles, Belgium, 2014 (Accessed 3-2-2015), www.idf.org/diabetesatlas.
[8] J. Ferlay, I. Soerjomataram, M. Ervik, D. Forman, Bray F. Globocan, Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012, International Agency for Cancer Research, Lyon, 2012 2014, (Accessed 9-3-2014) http://globocan.iarc.fr/Default.aspx.
[9] S.C. Larsson, C.S. Mantzoros, A. Wolk, Diabetes mellitus and risk of breast cancer: a meta-analysis, Int. J. Cancer 121 (4) (2007) 856–862.
[10] P. Boyle, M. Boniol, A. Koechlin, et al., Diabetes and breast cancer risk: a meta-analysis, Br. J. Cancer 107 (9) (2012) 1608–1617.
[11] Z. Zelenko, E.J. Gallagher, Diabetes and cancer, Endocrinol. Metab. Clin. North Am. 43 (1) (2014) 167–185.
[12] J. Pearson-Stuttard, B. Zhou, V. Kontis, J. Bentham, M.J. Gunter, M. Ezzati, Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment, Lancet Diabetes Endocrinol. 6 (2) (2018) 95–104.
[13] S. Liao, J. Li, W. Wei, et al., Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature, Asian Pac. J. Cancer Prev. 12 (4) (2011) 1061–1065.
[14] G. Maskarinec, S. Jacobs, S.Y. Park, et al., Type 2 diabetes, obesity, and breast cancer risk: the multiethnic cohort, Cancer Epidemiol. Biomarkers Prev. (2017).
[15] W.C. Hsu, E.J. Boyko, W.Y. Fujimoto, et al., Pathophysiologic differences among Asians, native Hawaiians, and other Pacific Islanders and treatment implications, Diabetes Care 35 (5) (2012) 1189–1198.
[16] E.V. Bandera, G. Maskarinec, I. Romieu, E.M. John, Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective, Adv. Nutr. 6 (6) (2015) 803–819.
[17] M.T. Goodman, J.B. Cologne, H. Moriwaki, M. Vaeth, K. Mabuchi, Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors, Prev. Med. 26 (1997) 144–153.
[18] C.E. Land, M. Tokunaga, K. Koyama, et al., Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990, Radiat. Res. 160 (6) (2003) 707–717.
[19] A.V. Brenner, D.L. Preston, R. Sakata, et al., Incidence of breast cancer in the life span study of atomic bomb survivors: 1958-2009, Radiat. Res. 190 (4) (2018) 433–444.
[20] G.W. BEEBE, M. ISHIDA, S. JABLON, Studies of the mortality of A-bomb survivors. I. Plan of study and mortality in the medical subsample (selection 1), 1950–1958, Radiat. Res. 16 (1962) 253–280.
[21] K. Ozasa, E.J. Grant, K. Kodama, Japanese legacy cohorts: the life span study atomic bomb survivor cohort and survivors' offspring, J. Epidemiol. 28 (4) (2018) 162–169.
[22] D.L. Preston, E. Ron, S. Tokuoka, et al., Solid cancer incidence in atomic bomb survivors: 1958–1998, Radiat. Res. 168 (1) (2007) 1–64.
[23] E.J. Grant, A. Brenner, H. Sugiyama, et al., Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009, Radiat. Res. 187 (5) (2017) 513–537.
[24] WHO expert consultation, Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies, Lancet 363 (9403) (2004) 157–163.
[25] A. Steinbrecher, Y. Morimoto, S. Heak, et al., The preventable proportion of type 2 diabetes by ethnicity: the multiethnic cohort, Ann. Epidemiol. 21 (7) (2011) 526–535.
[26] National Cancer Institute: Surveillance EaERP, Cancer Stat Facts: Female Breast Cancer, US National Institutes of Health, Bethesda, MD, 2018 (Accessed 3-15-2019), https://seer.cancer.gov/statfacts/html/breast.html.
[27] B. French, S. Funamoto, H. Sugiyama, et al., Pre-bombing population density in Hiroshima and nagasaki: its measurement and impact on radiation risk estimates in the life span study of atomic bomb survivors, Am. J. Epidemiol. (2018).
[28] Y. Minami, A. Takano, Y. Okuno, A. Fukao, M. Kurihara, S. Hisamichi, Trends in the incidence of female breast and cervical cancers in Miyagi Prefecture, Japan, 1959–1987, Jpn. J. Cancer Res. 87 (1) (1996) 10–17.
[29] N. Yoshiike, F. Seino, S. Tajima, et al., Twenty-year changes in the prevalence of overweight in Japanese adults: the National Nutrition Survey 1976–95, Obes. Rev. 3 (3) (2002) 183–190.
[30] Y. Chen, F. Wu, E. Saito, et al., Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium, Diabetologia 60 (6) (2017) 1022–1032.
[31] A.H. Wu, M.C. Yu, C.C. Tseng, F.Z. Stanczyk, M.C. Pike, Diabetes and risk of breast cancer in Asian-American women, Carcinogenesis 28 (7) (2007) 1561–1566.
[32] M. Khan, M. Mori, Y. Fujino, et al., Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study, Asian Pac. J. Cancer Prev. 7 (2) (2006) 253–259.
[33] M. Inoue, M. Iwasaki, T. Otani, S. Sasazuki, M. Noda, S. Tsugane, Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan, Arch. Intern. Med. 166 (17) (2006) 1871–1877.
[34] S. Sasazuki, H. Charvat, A. Hara, et al., Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan, Cancer Sci. 104 (11) (2013) 1499–1507.
[35] R. Kawate, M. Yamakido, Y. Nishimoto, P.H. Bennett, R.F. Hamman, W.C. Knowler, Diabetes mellitus and its vascular complications in Japanese migrants on the Island of Hawaii, Diabetes Care 2 (2) (1979) 161–170.
[36] E.C. Nordyke, The Peopling of, University of Hawaii Press, Hawaii. Honolulu, 1989.
[37] P.H. Zhang, Z.W. Chen, D. Lv, et al., Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China, BMC Public Health 12 (2012) 567.
[38] H.L. Xu, H. Fang, W.H. Xu, et al., Cancer incidence in patients with type 2 diabetes mellitus: a population-based cohort study in Shanghai, BMC Cancer 15 (2015) 852.
[39] S.H. Jee, H. Ohrr, J.W. Sull, J.E. Yun, M. Ji, J.M. Samet, Fasting serum glucose level and cancer risk in Korean men and women, JAMA 293 (2) (2005) 194–202.
[40] C.H. Tseng, C.K. Chong, T.Y. Tai, Secular trend for mortality from breast cancer and the association between diabetes and breast cancer in Taiwan between 1995 and 2006, Diabetologia 52 (2) (2009) 240–246.
[41] S. Jordan, L. Lim, D. Vilainerun, et al., Breast cancer in the Thai Cohort Study: an exploratory case-control analysis, Breast 18 (5) (2009) 299–303.
[42] I. Tabassum, H. Mahmood, M. Faheem, Type 2 diabetes mellitus as a risk factor for female breast cancer in the population of Northern Pakistan, Asian Pac. J. Cancer Prev. 17 (7) (2016) 3255–3258.
[43] U. Lim, T. Ernst, S.D. Buchthal, et al., Asian women have greater abdominal and visceral adiposity than Caucasian women with similar body mass index, Nutr. Diabetes 1 (2011) e6.
[44] A.L. Schneider, J.S. Pankow, G. Heiss, E. Selvin, Validity and reliability of self-reported diabetes in the Atherosclerosis Risk in Communities Study, Am. J. Epidemiol. 176 (8) (2012) 738–743.
[45] A. Goto, M. Goto, M. Noda, S. Tsugane, Incidence of type 2 diabetes in Japan: a systematic review and meta-analysis, PLoS One 8 (9) (2013) e74699.
[46] R. Sposto, D.L. Preston, Y. Shimizu, K. Mabuchi, The effect of diagnostic misclassification on non-cancer and cancer mortality dose response in A-bomb survivors, Biometrics 48 (2) (1992) 605–617.
[47] R. Sposto, D.L. Preston, Correcting for Catchment Area Nonresidency in Studies Based on Tumor-Registry Data. RERF CR 1-92, Radiation Effects Research Foundation, Hiroshima, 1992 (Accessed 10-11-2018), https://www.rerf.or.jp/en/library/list-e/scientific_pub/crlist-en/1992-en/cr9201-en/.