Cancer Causes & Control (2019) 30:1057–1065
https://doi.org/10.1007/s10552-019-01213-y

ORIGINAL PAPER

Type 2 diabetes and obesity in midlife and breast cancer risk in the Reykjavik cohort

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Received: 19 March 2019 / Accepted: 1 August 2019 / Published online: 10 August 2019

Abstract

Purpose As obesity and type 2 diabetes (T2D) have been increasing worldwide, we investigated their association with breast cancer incidence in the Reykjavik Study.

Methods During 1968–1996, approximately 10,000 women (mean age = 53 ± 9 years) completed questionnaires and donated blood samples. T2D status was classified according to self-report ($n = 140$) and glucose levels ($n = 154$) at cohort entry. A linkage with the Icelandic Cancer Registry provided breast cancer incidence through 2015. Cox regression with age as time metric and adjusted for known confounders was applied to obtain hazard ratios (HR) and 95% confidence intervals (CI).

Results Of 9,606 participants, 294 (3.1%) were classified as T2D cases at cohort entry while 728 (7.8%) women were diagnosed with breast cancer during 28.4 ± 11.6 years of follow-up. No significant association of T2D (HR 0.95; 95% CI 0.56–1.53) with breast cancer incidence was detected except among the small number of women with advanced breast cancer (HR 3.30; 95% CI 1.13–9.62). Breast cancer incidence was elevated among overweight/obese women without (HR 1.18; 95% CI 1.01–1.37) and with T2D (HR 1.35; 95% CI 0.79–2.31). Height also predicted higher breast cancer incidence (HR 1.03; 95% CI 1.02–1.05). All findings were confirmed in women of the AGES–Reykjavik sub-cohort ($n = 3,103$) who returned for an exam during 2002–2006. With a 10% T2D prevalence and 93 incident breast cancer cases, the HR for T2D was 1.18 (95% CI 0.62–2.27).

Conclusions These findings in a population with low T2D incidence suggest that the presence of T2D does not confer additional breast cancer risk and confirm the importance of height and excess body weight as breast cancer risk factors.

Keywords Breast cancer · Type 2 diabetes · Obesity · Anthropometry · Prospective cohort · Cox regression

Introduction

The rising incidence of obesity and type 2 diabetes (T2D) affects populations around the world but at different rates across ethnic groups and geographic locations [1, 2]. The important role of obesity in the development of postmenopausal breast cancer has been studied extensively [3–6] while the possible influence of T2D appears to be weaker and results are less consistent [7, 8]. Due to the strong influence of body mass index (BMI) on T2D as well as breast cancer development, the exploration of the combined impact of T2D and obesity on breast cancer incidence is of great interest. A worldwide modeling effort estimated attributable risks of 6.9% and 2.2% for high BMI (≥ 25 k/m^2) and T2D, respectively, with a combined risk of 8.9% [9]. Two meta-analyses reported 20% [10] and 23% [7] higher breast cancer risk for women with T2D. However, separation by

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adjustment for weight status reduced the estimated elevated breast cancer risk associated with T2D to 16% as compared to 33% in studies that did not include BMI in their models [7]. Within the Multiethnic Cohort (MEC) of African American, Native Hawaiian, Japanese American, Latino, and white participants [11], T2D was significantly associated with breast cancer (HR 1.15; 95% CI 1.07–1.23), but adjusting for BMI lowered the relative risk to 1.08 (95% CI 1.00–1.16). As many of the previous studies relied on self-reported T2D diagnoses, individuals with elevated fasting glucose levels may have been missed resulting in biased estimates for the T2D-breast cancer association. Prediabetes, either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), may also increase the risk to develop breast cancer [12, 13]. T2D incidence in Iceland is relatively low compared with other Western countries today [1] and was even lower in the Reykjavik Study initiated in 1968 when detailed information on lifestyle and anthropometric measures was collected. At the time, 12% of the female participants were in the obese category [14]. Using population data from this cohort offers a unique opportunity to examine the association of undiagnosed T2D and IFG with breast cancer risk. Therefore, the current analysis aimed to determine the independent contributions of obesity, T2D, and IFG at baseline to develop breast cancer within the Reykjavik Study and its sub-study, the Age, Gene/Environment Susceptibility (AGES)–Reykjavik Study initiated 34 years later.

Methods

Study population

The current analysis builds on a prospective cohort, the Reykjavik Study, initiated in 1967 for male participants and in 1968 for female participants by the Icelandic Heart Association. Participants were all current residents of the capital area in Iceland in 1966 and born between 1908 and 1935, and thus aged from 31 to 88 years [15, 16]. The enrollment occurred in six waves (1968–1969, 1971–1972, 1977–1979, 1981–1984, 1987–1991, and 1994–1996) when 10,049 women agreed to be part of the investigation (71% response rate). At cohort entry, information on age, year of birth, education, height, weight, parity, regular sports activity since age 20, and medical history was collected.

Detailed reproductive information was obtained through a linkage of 91% participants of the Reykjavik Study with the Cancer Detection Clinic (CDC) cohort, an investigation established in 1964 that builds on the nationwide, centralized cervical and breast cancer-screening programs [17]. It includes all women in Iceland who attend annual cervical cancer (20–69 years) and breast cancer screening (40–69 years). Information closest to study entry was obtained on age at menarche (continuous) and age at first birth (none, <25, ≥ 25 years) but not a detailed mammography screening history. To reduce the substantial number of missing values for age at first birth, women who reported no children when entering the Reykjavik Study were coded as "no birth." Women classified as nulliparous in the CDC cohort who reported a child in the Reykjavik Study were categorized as "25 and older" given that all participants were at least 33 years old at cohort entry.

AGES–Reykjavik Study

During 2002–2006, the AGES–Reykjavik Study with a focus on body composition and metabolism re-examined 5,764 participants (57% women) aged 66–96 years [15]. As described elsewhere [18], 8,030 of the 11,549 surviving cohort members of the original Reykjavik Study were randomly chosen and invited for another exam with a 71.8% response rate. Respondents had significantly lower triglycerides, fasting blood glucose, and BMI and included a smaller percentage of smokers [15]. At the exam, updated information on chronic conditions, including T2D status, as well blood samples for glucose and insulin was collected. In addition to the same questions as at the baseline exam in the Reykjavik Study, the AGES–Reykjavik Study also asked about family history of breast cancer, reproductive history, and alcohol intake allowing better adjustment for known breast cancer risk factors. In total, 3,103 women had sufficient information for the current analysis within the AGES–Reykjavik cohort. Both studies were approved by the National Bioethics Committee in Iceland (VSN-17-189). Informed consent was obtained from all participants.

Diabetes status

At entry to both the Reykjavik and the AGES–Reykjavik Study, T2D status was based on self-reports ("Do you have diabetes now or earlier?") plus age at diagnosis, diabetes diet, and diabetes medication as categories of insulin vs. tablets without specific information. Glucose levels at fasting and 90 min after a 50-g glucose load were obtained in both studies to detect undiagnosed disease [14, 19]. For both cohorts, glucose levels in a capillary blood sample were estimated by the Hoffman ferricyanide method, adapted to the Technicon-Method N-9a [15, 16]. Those with fasting glucose levels ≥ 126 mg/dL and 90-min levels > 200 mg/dL were classified as T2D and those ranging 100–125 mg/dL as IFG [20]. As oral glucose tolerance tests (OGTT) with 2-h glucose levels were not available, IGT could not be assessed [21]. A summary variable indicated abnormal glucose status, i.e., IFG, T2D, or insulin-dependent diabetes. Cases diagnosed at an early age and insulin use were classified as type 1 diabetes and not considered in the current analysis.

Diagnosis of breast cancer

For both cohorts, follow-up for first diagnosis of invasive breast cancer was done by record linkage with the population-based Icelandic Cancer Registry through 2015 [22], using the unique Icelandic identification numbers. The 118 cases of invasive breast cancer diagnosed before the baseline exam in the Reykjavik study were excluded. After removing 35 women without information on height and body weight, the dataset for analysis had 9906 women with 728 incident breast cancer cases diagnosed in the period 1969–2015. In the AGES–Reykjavik Study, 3,103 women remained in the dataset after exclusions; 93 incident breast cancer cases were detected by 2015.

Statistical analysis

The associations of T2D (self-reported and based on glucose testing), IFG, and glucose levels with breast cancer incidence were examined using Cox regression models with age as time metric and adjusted for birth cohort (1908–1914, 1915–1919, 1920–1924, 1925–1929, 1930–1936), BMI calculated from weight and height measurements at entry (<18.5, 18.5 to 25, 25 to <30, ≥ 30 kg/m^2), height (continuous), education (primary, secondary, college), regular sports since age 20 (yes/no), smoking status (never, past, current), age at menarche (9–12, 13, 14, 15–21 years), parity (none, 1–2, ≥ 3, missing), and age at first childbirth (none, <25, ≥ 25 years, missing). We also included location of early life residence as determined by classifying each woman's place of residence from birth using three categories: capital area, coastal villages, and rural areas as a lower risk of breast cancer had been observed in women who lived in coastal villages than in the capital area during early life [23]. Missing covariate information was included into the models as a separate category except for BMI, for which women with missing values had been excluded. Information on hormone therapy and diabetes medication was not available for the cohort.

An analysis restricted to postmenopausal breast cancers was performed after removing 22 cases diagnosed in women ≤ 50 years. Separate models by BMI status, as well as models with different outcomes according to stage, estrogen (ER), and progesterone (PR) receptor status were examined for effect modification. To explore if obesity and T2D are independent predictors of breast cancer risk, models with and without BMI were compared. For a closer examination of possible effect modification [24], an interaction test was performed and a combined variable incorporating BMI and T2D (BMI <25 kg/m^2/no T2D, <25 kg/m^2/T2D, ≥ 25 kg/m^2/no T2D, ≥ 25 kg/m^2/T2D) was created and modeled with BMI <25 kg/m^2/no T2D as the reference category using the same covariates as above.

Separate analyses for models with T2D, IFG, and combined T2D/IFG as exposure were conducted for the 3,103 women in the AGES–Reykjavik Study, which included information from the AGES questionnaire for age at menarche, smoking, and physical activity and, in addition, breastfeeding (yes, no), hormone therapy (never, ever, missing), and alcohol intake (<1 or ≥ 1 drink/week). Parity and age at first live birth were combined into one variable (no children, parous <25 or ≥ 25 years). Missing values were coded as a separate category for all covariates.

Results

Of the 9,606 women in the Reykjavik Study, 294 (3.1%) were classified as having T2D at study entry, based on self-report ($n = 140$) or on glucose levels ($n = 154$). For 9,587 participants, a fasting blood sample was available. Another 134 (1.4%) women were classified with IFG according to fasting glucose levels. During 28.4 ± 11.6 years of follow-up, 728 (7.8%) breast cancer cases were diagnosed resulting in 13,826 person-years for breast cancer cases as opposed to 258,935 person-years for women without breast cancer. Of all breast tumors, 51% were diagnosed at TNM stage 1, 36% at stage 2, 6% at stages 3/4, and 7% did not have stage information. The respective mean ages at cohort entry and at breast cancer diagnosis were 53.2 ± 9.0 and 69.7 ± 11.2 years. Within the study population, 2.4% were underweight (<18.5 kg/m^2), 52.6% normal weight, 33.3% overweight (25 to ≤ 30 kg/m^2), and 11.7% obese (≥ 30 kg/m^2). Women with a higher BMI were more likely to have TD2 (Table 1): the respective proportions for low, normal, overweight, and obese BMI with T2D were 2.2, 1.4, 3.5, and 9.6%. An inverse trend of birth cohort with the presence of T2D was seen; the percentage decreased from 6.7 to 1.8% from the oldest to the youngest birth cohort. The proportion of women with T2D was higher for those with early life residence in the capital (3.4%) than for those with coastal (3.0%) and rural (2.7%) residence.

No significant association of T2D with breast cancer was detected in a model adjusted for age only (HR, 1.01; 95% CI 0.62–1.67) and in fully adjusted models without and with BMI included as confounder (Table 2). The respective HRs were 0.99 (95% CI, 0.60–1.64) and 0.95 (95% CI 0.42–1.89). In stratified analyses by self-reported vs. glucose-based T2D, similar HRs were obtained (HR 0.89; 95% CI 0.57–1.56) and (HR 1.01; 95% CI 0.52–1.96). Restricting the BMI-adjusted model to the 706 breast cancer cases diagnosed >50 years showed similar results. With IFG, IFG/T2D, or fasting glucose as exposure, the respective HRs in BMI-adjusted models were 0.88 (95% CI 0.44–1.78), 0.95 (95% CI 0.64–1.42), and 1.02 (95% CI 0.96–1.08) for each increase of 10 mg/dL fasting glucose.

Table 1 Characteristics of the study population by diabetes status, Reykjavik Study, 1968–2015

Characteristic	Category	Reykjavik Study[a]				AGES Study[b]	
		No T2D	T2D	% T2D	All women	Number	% T2D
Participants	Number	9,312	294	3.1	9,606	3,103	10.1
Breast cancer cases	Number	712	16	2.2	728	93	11.8
Deaths	Number	6,544	255	3.8	6,799	1,414	12.6
Person-years	Number	266,738	6,023	2.2	272,761	30,769	9.5
Follow-up time	Mean ± SD	28.6 ± 11.5	20.5 ± 10.9	–	28.4 ± 11.6	9.9 ± 3.4	–
Age at cohort entry	Mean ± SD	53.0 ± 8.9	60.4 ± 9.2	–	53.2 ± 9.0	76.8 ± 5.9	–
Age at breast cancer	Mean ± SD	69.7 ± 11.2	73.1 ± 9.7	–	69.7 ± 11.2	82.0 ± 6.3	–
Age at diabetes	Mean ± SD	NA	56.8 ± 11.7	–	56.8 ± 11.7	75.5 ± 9.4	–
Height (cm)	Mean ± SD	163.2 ± 5.7	161.8 ± 6.0		163.1 ± 5.7	160.6 ± 5.8	–
Birth cohort	1907–1914	1,348	97	6.7	1,445	72	12.3
	1915–1919	1,636	53	3.1	1,689	298	10.5
	1920–1924	2,055	56	2.6	2,111	642	12.2
	1925–1929	2,058	48	2.3	2,106	850	10.7
	1930–1936	2,215	40	1.8	2,254	928	7.7
Location of early life residence	Reykjavik	3,282	115	3.4	3,397	1,142	12.1
	Coastal area	3,084	95	3.0	3,179	1,009	9.6
	Rural	2,445	69	2.7	2,514	796	8.0
	Missing	501	15	2.9	516	156	9.0
Education, years	Primary	5,034	190	3.6	5,224	1,367	11.1
	Secondary	3,495	88	2.4	3,583	1,396	9.2
	College	783	16	2.0	799	340	10.0
BMI, kg/m^2	< 18.5	223	5	2.2	228	56	5.4
	≥ 18.5 to < 25	4,992	69	1.4	5,061	1,012	5.6
	≥ 25 to < 30	3,083	113	3.5	3,196	1,258	9.6
	≥ 30	1,014	107	9.6	1,121	777	17.0
Smoking status	Never	4,099	134	3.2	4,223	1,624	10.8
	Past	1,418	70	4.7	1,488	993	10.0
	Current	3,795	90	2.3	3,885	377	8.8
Regular sports	No	7,249	239	3.2	7,488	1,882	10.6
	Yes	2,063	55	2.6	2,118	775	7.5
Age at menarche, years	≤ 12	1,578	61	3.7	1,639	572	11.5
	13	2,417	82	3.3	2,499	753	8.9
	14	2,710	49	1.8	2,759	972	9.4
	≥ 15	1,848	51	2.7	1,899	640	8.6
	Missing	759	51	6.3	810	166	20.5
Number of children	0	937	40	4.2	977	218	8.3
	1–2	2,452	53	2.1	2,505	661	3.3
	≥ 3	5,874	201	3.3	6,075	2,060	11.6
	Missing	49	0	0	49	164	20.7
Age at first live birth, years	< 25	4,654	137	2.9	4,792	1,788	8.3
	≥ 25	3,059	77	2.3	3,136	893	9.5
	Missing	662	40	6.5	702	204	9.5

[a]T2D diagnosis based on self-report ($n = 140$) or elevated glucose levels ($n = 154$)

[b]Values are for exams conducted among AGES participants in 2002–2006

In the subset of 3,103 women who participated in the AGES–Reykjavik Study, the mean age at study exam was 76.9 ± 5.9 years. In this group, 313 (10%) women were classified as T2D and 1,019 (33%) as IFG. After entry into AGES, 93 (3%) women were diagnosed with incident breast cancer. With additional adjustment for alcohol intake,

Table 2 Type 2 Diabetes and Breast Cancer Risk, Reykjavik and AGES Study, 1968–2015

Characteristic	Exposure category	Number of cases		Person-years		HR[a]	95% CI
		Exposed	Unexposed	Exposed	Unexposed		
Reykjavik Study (n =9,606)	T2D (model without BMI)	16	712	6,023	266,738	0.99	0.60, 1.64
	T2D (model with BMI)	16	712	6,023	266,738	0.95	0.57, 1.56
	T2D (postmenopausal)	16	690	6,023	266,480	0.95	0.58, 1.57
	IFG[b]	8	720	3,165	269,596	0.88	0.44, 1.78
	T2D and IFG[c]	26	702	9,606	269,596	0.95	0.64, 1.42
	Fasting glucose (per 10 mg/dL)	16	712	272,289		1.02	0.96, 1.08
AGES Study[d] (n =3,103)	T2D (model without BMI)	11	82	2,912	27,857	1.24	0.66, 2.36
	T2D (model with BMI)	11	82	2,912	27,857	1.18	0.62, 2.27
	IFG	35	58	10,243	20,526	1.19	0.78, 1.82
	T2D and IFG	46	47	13,155	17,614	1.26	0.83, 1.92
	Fasting glucose (per 10 mg/dL)	11	82	30,752		0.97	0.87, 1.09
Stratified models for Reykjavik Study							
Hormone receptors[d]	ER+/PR+	4	264	5,915	259,410	0.69	0.25, 1.87
	ER−/PR−	3	95	5,894	254,971	1.22	0.38, 3.93
	ER+/PR− and ER−/PR+	1	133	5,877	255,751	0.28	0.04, 2.03
Tumor stage[e]	TNM 1	9	363	5,966	259,869	1.05	0.54, 2.05
	TNM 2	2	258	5,880	258,439	0.31	0.08, 1.24
	TNM 3/4	4	43	5,893	253,918	3.30	1.13, 9.62

[a]Hazard ratios (HR) and 95% confidence intervals (CI) obtained by Cox regression with age as time metric and adjusted for BMI (except when noted), height, birth cohort, education, place of residence, smoking status, physical activity, age at menarche, parity, and age at first live birth

[b]Presence of impaired fasting glucose (100–125 mg/dL)

[c]Presence of impaired fasting glucose (100–125 mg/dL) or T2D based on self-report of fasting glucose

[d]Women in AGES study (n =3,103); models also include alcohol intake, hormone treatment, and breast feeding. Parity and age at first live birth were combined into one variable (no children, parous < 25 or ≥ 25 years)

[e]Values were missing on hormone receptors for 228 cases and on tumor stage for 49 cases

ER estrogen receptor, *PR* progesterone receptor, *TNM* tumor, nodes, metastasis classification, *BMI* body mass index

menopausal hormone therapy, and breast feeding (Table 2), the HRs for T2D at baseline of AGES were 1.24 (95% CI 0.66–2.36) and 1.18 (95% CI 0.62–2.27) before and after adjustment for BMI. Although the risk estimate was elevated when the women with T2D and IFG were combined and adjusted for BMI (HR 1.26; 95% CI 0.83–1.92), it did not reach statistical significance. The HR per 10 mg/dL fasting glucose was 0.97 (95% CI 0.87–1.09).

Within the Reykjavik Study cohort, stratification by ER/PR status showed slightly elevated HRs for ER−/PR− tumors but no statistically significant association. On the other hand, findings differed by stage at diagnosis. Whereas the incidence of tumors diagnosed at stage I and II was not associated with T2D status, the risk estimate for TNM stages 3/4 tumors among women with T2D was significantly elevated (HR 3.30; 95% CI 1.13–9.62), although the number of breast cancer cases with and without T2D was small (n =4 and 43).

Of the covariates, height and BMI were the most significant predictors of breast cancer after adjustment for all the covariates in the overall model (Table 3). Every 1 cm of additional height predicted a 3% (95% CI 1.02–1.05) or every 10 cm a 37% (95% CI 1.19–1.57) higher breast cancer risk. Compared to normal weight women, the respective HRs of underweight, overweight, and obese women were 0.86 (95% CI 0.48–1.53), 1.15 (95% CI 0.97–1.36), and 1.38 (95% CI 1.09–1.75). After removing the 22 cases diagnosed < 50 years, these HRs strengthened to 0.82 (95% CI 0.45–1.49), 1.18 (95% CI 1.00–1.39), and 1.41 (95% CI 1.10–1.79).

A formal interaction test between BMI and T2D was not significant ($p = 0.74$). Results from the analysis of the combined BMI and T2D variable, using low BMI and no TD2 as reference (Fig. 1), showed that having normal BMI and T2D did not predict higher breast cancer incidence (HR 0.46; 95% CI 0.11–1.83). However, breast cancer incidence was significantly elevated for women with high BMI and no T2D (HR 1.18; 95% CI 1.01–1.37). Participants with high BMI (≥ 25 kg/m^2) and T2D had a non-significant 35% increased risk of breast cancer (95% CI 0.71–2.58). When using the combined BMI/T2D variable within the AGES–Reykjavik Study, no breast cancers

Table 3 Anthropometric Risk Factors and Breast Cancer Risk, Reykjavik and AGES Study, 1968–2015

Study	Risk factor	Categories	Number of cases		Person-years		HR[a]	95% CI
			Exposed	Unexposed	Exposed	Unexposed		
Reykjavik Study (*n* =9,606)	Height	Per cm	16	712	6,023	266,738	1.03	1.02, 1.05
	BMI	< 18.5	0	12	74	5,604	0.86	0.48, 1.53
		≥ 18.5– < 25	2	380	1,595	148,077	1.00	Ref
		≥ 25– < 30	6	238	2,307	86,525	1.15	0.97, 1.36
		≥ 30	8	82	2,046	26,531	1.38	1.09, 1.75
AGES Study[b] (*n* =3,103)	Height	Per cm	11	82	2,912	27,857	1.02	0.98, 1.06
	BMI	< 18.5	0	1	18	432	0.82	0.11, 6.13
		≥ 18.5– < 25	0	26	532	9,168	1.00	Ref
		≥ 25– < 30	5	33	1,130	11,602	1.06	0.64, 1.76
		≥ 30	6	22	1,231	6,654	1.28	0.73, 2.23

[a]Hazard ratios (HR) and 95% confidence intervals (CI) obtained by Cox regression with age as time metric and adjusted for birth cohort, education, place of residence, smoking status, physical activity, age at menarche, parity, age at first live birth, and BMI or height

[b]Women in AGES study; models also include alcohol intake, hormone treatment, and breast feeding. Parity and age at first live birth were combined into one variable (no children, parous < 25 or ≥ 25 years)

T2D type 2 diabetes, *BMI* body mass index

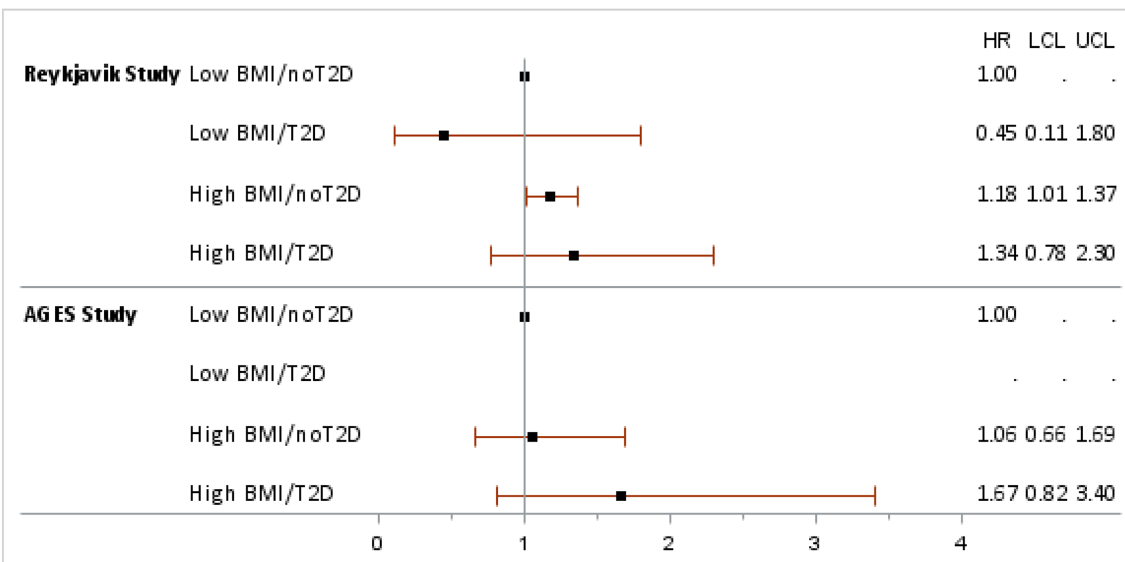

Fig. 1 Breast Cancer by Type 2 Diabetes and BMI Status, Reykjavik and AGES–Reykjavik Study, 1968–2015. Low BMI = < 25 kg/m^2, High BMI = ≥ 25 kg/m^2 and no type 2 diabetes, T2D = Presence of type 2 diabetes[2]. Hazard ratios (HR) and 95% confidence intervals (CI) obtained by Cox regression with age as time metric and adjusted for birth cohort, height, education, place of residence, smoking status, physical activity, parity, age at menarche, and first live birth. Women in AGES study (*n* =3,103); models also include alcohol intake, hormone treatment, and breast feeding. Parity and age at first live birth were combined into one variable (no children, parous < 25 or ≥ 25 years)

were diagnosed in the low BMI/no T2D group while the respective risk estimates for the high BMI group without (HR 1.06; 95% CI 0.66–1.69) and with T2D (HR 1.67; 95% CI 0.82–3.40) were not significant although the HR for the high BMI women with T2D was higher than for those without.

Discussion

Over a follow-up time of close to 30 years, women with T2D and/or IFG who participated in the Reykjavik Study did not experience a higher breast cancer risk than those without T2D, previously known or undiagnosed cases based on abnormal glucose values, but excess body weight and height were associated with breast cancer incidence independent of T2D status. The higher incidence of postmenopausal breast cancer among participants with excess body weight [25] and height [26] was comparable to reports from other white populations. In a secondary analysis stratified by stage at diagnosis, the risk for advanced breast cancer was elevated in women with T2D, but this may be a chance finding due to the small number of women in this group. Despite the smaller sample size of the AGES–Reykjavik Study, its confirmatory results were important because of the adjustment for additional known risk factors.

The current results agree with a worldwide study showing that BMI contributes more to the burden of breast cancer than T2D [9] but disagrees with several meta-analyses showing a 20% higher risk [7, 10]. It is worth noting that despite the overall significant summary risk estimate in a large meta-analysis with 40 studies (SRR = 1.27, 95% CI 1.12–1.39), nearly half (19 vs. 21) of the studies reported null findings. Except for the importance of including BMI as a covariate, the divergent results are not well understood. The null finding for IFG parallels a summary report indicating a small risk of breast cancer associated with pre-diagnostic elevated glucose levels [27].

One possibility for the conflicting results is that the metabolic consequences of elevated BMI and T2D vary across populations. The concept of metabolically healthy obesity hypothesizes that some individuals with excess body weight remain free of metabolic consequences, such as insulin resistance or chronic inflammation as indicated by C-reactive protein [28]. Possible reasons may be differences in the distribution of body fat and the relative proportion of visceral fat, individual variation in coping with a positive energy balance, or a higher-quality diet. As a result of these observations, it was proposed that the risk associated with cardiovascular disease might be lower among metabolically healthy obese individuals than for obese individuals with metabolic disturbances [29, 30]. This idea is supported by an evaluation of T2D incidence within the AGES–Reykjavik Study showing no difference in cardiovascular mortality rate by T2D status [31]. Based on information from the original Reykjavik Study, high BMI, family history of T2D, elevated triglycerides, and high systolic blood pressure at cohort entry were identified as predictors of T2D in later in life but a large proportion of participants with overweight/obesity had not developed T2D or other cardiovascular conditions [19]. Another interesting finding from the Reykjavik Study and the AGES–Reykjavik Study showed that the decline in all-cause mortality observed from 1993 to 2004 was 50% greater among participants with T2D than those without T2D [31]. This observation supports the hypothesis that Icelanders with T2D experience less serious consequences than individuals in some other geographic locations, possibly due to better treatment and control in a country with equal access to health care or to an overall healthier metabolic status [32].

The most serious limitations of the current analysis are the lack of information on T2D cases diagnosed after cohort entry and the small sample size of only 16 women with T2D and breast cancer resulting in low statistical power. Self-reports can be a problem but the availability of fasting glucose levels allowed the detection of undiagnosed cases and IFG despite the known low sensitivity (mean 0.25; range 0.19 to 0.32) and specificity (mean 0.94; range 0.92 to 0.96) of one fasting glucose measurement [33]. Although not likely, misclassification of type 1 diabetes as T2D may have added to the problem. Thus some non-differential misclassification with respect to exposure status can be expected, which is likely to move the hazard ratios towards unity. Using prevalent T2D as exposure adds to the problem that management and drug treatment of the disease may have affected BMI levels. As no OGTTs were available, only IFG and not IGT could be assessed; the two conditions do not always overlap [20]. Missing values for known confounders and the fact that information on alcohol intake, hormone therapy, and breast feeding was not available for the Reykjavik Study may have biased the risk estimates. Also, the lack of detailed information on diabetes medication may have affected the results [34]. Despite the confirmation of our results within the AGES–Reykjavik Study with updated glucose levels and T2D reports, the null findings may not be conclusive given the limited sample sizes and power of the entire cohort and its sub-study.

Strengths of the current analysis include the long follow-up period, the glucose measurements at cohort entry, low rates of loss-to-follow-up, and the linkage with the Icelandic Cancer Registry with complete and countrywide follow-up [22]. The fact that the elevated breast cancer risk associated with obesity in the Reykjavik Study is comparable to published reports [25] also indicates the general validity of the study. The analysis is unique in that it is based on a population with relatively low T2D incidence, partly due to low prevalence of obesity at the time of recruitment for the Reykjavik Study [14, 35]. Even today, the age-adjusted prevalence of T2D in Iceland in 2017 was only 5.3% as compared to 6.8% for all of Europe, 10.8% in the Middle East, and 11.0% In North America according to the International Diabetes Federation [1].

In conclusion, our results from women with low obesity rates and T2D incidence suggest that a diagnosis of T2D may only confer a very small, if any, additional breast cancer risk beyond the elevated risk associated with obesity and height among participants of the Reykjavik Study. Possible reasons for the differences in comparison with other populations include speculations about better metabolic health and equal access to health care and treatment among Icelanders.

Acknowledgments The AGES–Reykjavik Study was funded by NIH contract N01-AG-12100, the Intramural Research Program of the National Institute on Aging, the Icelandic Heart Association, and the Icelandic Parliament. This work was also supported by the Icelandic Centre for Research, RANNIS Grant Number: 152495051, https://en.rannis.is/ (to AH), and the Public Health Fund of the Icelandic Directorate of Health (to AH). GM was funded by a Fulbright Global Scholar Award (2017–2018).

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