Cancer Causes Control (2011) 22:1163–1171
DOI 10.1007/s10552-011-9794-8

ORIGINAL PAPER

Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer

Mats Lambe · Annette Wigertz · Hans Garmo · Göran Walldius · Ingmar Jungner · Niklas Hammar

Received: 21 February 2011 / Accepted: 3 June 2011 / Published online: 19 June 2011

Abstract
Background Epidemiological evidence indicates that individuals with type 2 diabetes are at an increased risk of cancer. Elevated glucose levels, below the diagnostic threshold for diabetes, have also been suggested to be associated with increased cancer risks.
Methods We investigated possible associations between glucose levels and the risk of breast, endometrial, and ovarian cancer in a cohort of more than 230,000 women, for which information on outcome and potential confounders was obtained by record linkage to population-based registers.
Results Diabetes was associated with an increased risk of postmenopausal breast cancer (HR = 1.22, 95% CI 1.04–1.43). An indication of a slightly elevated breast cancer risk was also found in postmenopausal women with impaired glucose metabolism (HR = 1.11, 95% CI 0.96–1.28). Diabetes (HR = 1.46, 95% CI 1.09–1.96) and impaired glucose metabolism (HR = 1.41, 95% CI 1.08–1.85) were associated with an increased risk of endometrial cancer. No associations were found between glucose levels and ovarian cancer risk. Following adjustment for BMI, estimates were attenuated for endometrial cancer, while point estimates for breast and ovarian cancer remained essentially unchanged.
Conclusions Our results indicate that glucose levels below the diagnostic threshold for diabetes modify the risk not only of endometrial cancer but possibly also of postmenopausal breast cancer.

Keywords Hyperglycemia · Diabetes · Breast cancer · Endometrial cancer · Ovarian cancer

M. Lambe (✉)
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, 171 77 Stockholm, Sweden
e-mail: Mats.Lambe@ki.se

M. Lambe · A. Wigertz · H. Garmo
Regional Oncologic Centre, Uppsala, Sweden

G. Walldius
Department of Medicine, Karolinska Institutet, Stockholm, Sweden

G. Walldius · N. Hammar
Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

I. Jungner
Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet and CALAB Research, Stockholm, Sweden

N. Hammar
AstraZeneca R&D, Södertälje, Sweden

Introduction

Converging epidemiological evidence indicates that individuals with type 2 diabetes mellitus are at an increased risk of developing cancer [1, 2]. Associations with cancers of the pancreas [3], liver [4], colon [5], and endometrium [6–8] are well established.

Results from meta-analyses also suggest that diabetes is associated with an increased risk of breast cancer [9–11]. Most studies of ovarian cancer have on the other hand found no association [12–15].

Impaired glucose control and type 2 diabetes are common disorders affecting an increasing part of the adult population. Several studies have presented results suggesting that not only diabetes but also elevated glucose levels below the diagnostic threshold for diabetes may be associated with an elevated risk for cancer [16–23]. This could be expected if the risk increase associated with

diabetes is due to consequences of long-standing disturbances of glucose metabolism without clinically manifest disease. Results from previous studies to date on possible associations between glucose values in the upper normal or impaired range and breast cancer risk are conflicting [16, 19–26], and studies on endometrial and ovarian cancer are scarce [17, 20, 22, 23, 27].

To improve the understanding in this area, we investigated and contrasted in detail possible associations between glucose levels and the risk of the three major female sex hormone dependent cancers in a large cohort of more than 230,000 women, for which information on outcome (breast, endometrial and ovarian cancer) and potential confounders was obtained by means of record linkage to Swedish population-based registers.

Methods

Study population and data sources

The present study was based on the AMORIS (Apolipoprotein-related MOrtality RISk) population [28] recruited in the greater Stockholm area between 1985 and 1996. The cohort consists of individuals that took part in routine health checkups and primary care patients referred for laboratory testing. In total, the AMORIS population encompasses 689,588 individuals of which 338,101 are women. Of these women, 267,223 (79%) were classified with regard to glucose levels. Following exclusion of women younger than 25 years at index examination ($n = 27{,}636$), with a previous malignancy ($n = 7{,}551$) or with a cancer diagnosis within 6 months from the date of the index visit ($n = 1{,}299$), the final study population encompassed 230,737 women.

To obtain information about outcomes and potential confounders, the AMORIS database was linked to several other registers, including the Swedish Cancer Register, the Patient Register before and after the index date, the Multi-Generation Register, the National Population Register, and national Censuses using the individually unique national registration number, assigned to all Swedish residents at birth or at time of first permanent residency.

The study was approved by the Ethics Research Committee at Karolinska Institutet.

The Swedish cancer register The national Swedish Cancer Register was established in 1958 and is updated yearly. Clinicians and pathologists/cytologists are mandated by law to report all newly diagnosed malignant tumors. In 1998, the reporting rate to the Cancer Register was estimated to be about 96% of all diagnosed cases [29].

The Swedish patient register The Swedish Patient Register, established in 1964 and with complete national coverage from 1987 onward, includes data on individual hospital discharges. Each record corresponds to one hospital admission and contains the dates of admission and discharge. The main and as many as seven additional discharge diagnoses are recorded for each hospitalization.

The multi-generation register The Swedish Multi-Generation Register includes as index persons all Swedish residents born in 1932 or later who were alive in 1961 and all those born thereafter, with links to their parents, siblings, and offspring. Adoptions and nonbiological relations are flagged and can be identified.

The national population register The National Population Register contains information on current place of residence and vital status of all residents in Sweden. The database is continuously updated with information on dates of immigration or emigration which, for the purpose of the present study, allowed censoring of women that emigrated from Sweden during follow-up.

Census data The Census system is based on a mandatory questionnaire, to be completed and returned by every household in Sweden. The 1980 and 1990 Census were utilized in the present study and includes information on a socioeconomic index based on occupation.

Classification of exposures and outcomes

All laboratory analyses were automated and carried out at the same clinical laboratory (CALAB laboratories, Stockholm, Sweden [30]). Information is available on a broad range of biomedical factors, including glucose levels. Glucose was measured enzymatically by means of a glucose-oxidase/peroxidase method. Subjects were classified with regard to glucose levels at the first contact examination (index examination) where a glucose level below 6.1 mmol/L was classified as normal glucose metabolism (NGM), 6.1–6.9 mmol/L as impaired glucose metabolism (IGM), and 7.0 mmol/L or higher as diabetes mellitus. In addition, if a subject prior to the index examination had information about hospitalization with diabetes as discharge diagnosis in the Patient Register, this was also regarded as manifest diabetes irrespective of the recorded glucose value. The data at hand did not allow for identification of type of diabetes.

Height and weight were available for 38,065 women and were used to compute body mass index (BMI).

Information on age at first child birth and number of children (including nulliparity) was obtained from the Swedish Multi-Generation Register.

Information on socioeconomic standing was retrieved from the most recent Census prior to the index examination and was categorized into high or low based on a commonly used classification system that distinguishes between manual workers, lower nonmanual employees, and intermediate or high nonmanual employees [31].

Incident cases of breast, endometrial, and ovarian cancer in the AMORIS population were identified in the national Swedish Cancer Register.

Statistical analysis

Proportional hazards regression analysis was used to estimate relative risk of developing cancer (hazard ratios), comparing subjects with different glucose levels at the index examination. In all analyses, adjustment was made for age. Additional analyses were made to investigate possible confounding from fasting status and socioeconomic standing. In a separate analysis restricted to parous women, adjustments were also done for reproductive history (age at first birth and parity). In the subcohort of 38,065 women with BMI-measurements, the possible confounding role of obesity was assessed. Separate analyses were also performed in women known to be fasting at the time of blood sampling, as well as in subjects who we judged to have provided glucose measurements as part of a regular health check up based on the profile of the test panel.

In the analyses of breast cancer risk, stratification was made for age at diagnosis as a proxy for menopausal status and a split of follow-up was made at age 50. In the analysis of premenopausal women, individuals were followed to age 50 after which they were censored. In the assessment of postmenopausal risk individuals with glucose measurement before being 50 years of age entered the study at age 50 by means of delayed entry.

In the assessment of endometrial cancer risk, women who had a hysterectomy prior to the index examination ($n = 8474$) were excluded. Similarly, for analyses of ovarian cancer risk, women who had undergone resection of at least one ovary were excluded ($n = 7494$).

Follow-up started at the index examination and terminated at the date of the cancer diagnosis of interest (breast, endometrial, and ovarian cancer in separate analyses), date of hysterectomy (in analyses of endometrial cancer), date of oophorectomy (in analyses of ovarian cancer), death, emigration out of Sweden or 31 December 2002, whichever came first.

Results

In the study population of 230,737 women, 218,279 (94.6%) had normal glucose metabolism (NGM) at the index examination, 6,843 (3.0%) had an impaired glucose metabolism (IGM), and 5,615 (2.4%) had glucose levels above the threshold for diabetes or had a hospital discharge diagnosis of diabetes mellitus prior to the index examination. The mean follow-up time was 11.7 years. A total of 127,112 (55%) women were recorded as fasting at the time of the index examination. The proportion of glucose measurements labeled as fasting was highest in the NGM group (55.8%) compared with (43.0%) in the IGM group and (42.5%) in the group with diabetes. Younger age and nulliparity at index examination were more common among individuals with NGM. Among parous women, age at first child birth was comparable between the three groups of glucose levels. In the subcohort with information available on anthropometric measurements, the mean BMI was lowest in the NGM group (23.8 kg/m^2) and highest in the diabetes group (26.7 kg/m^2). During follow-up, 6,070 cases of breast cancer, 1,070 cases of endometrial cancer, and 783 cases of ovarian cancer were identified (Table 1).

In all analyses, adjustments were made for age at the index examination. Further adjustments for socioeconomic status did not change the results (not shown in Table), and this variable was, therefore, not kept in the models. In separate analyses restricted to subjects who provided glucose measurements as part of a regular health control estimates were practically unchanged (not shown in Table). In analyses restricted to women who were known to be fasting associations remained virtually unchanged. If anything, associations between IGM and risks of endometrial and postmenopausal breast cancer were slightly more pronounced (Tables 2, 3). To address more in detail, possible reverse causation separate analyses were also performed with lag times of 1 and 3 years, respectively. With this approach, results remained unchanged (not shown in Table).

Breast cancer

The overall risk of breast cancer in patients with diabetes was elevated (HR = 1.15, 95% CI 0.99–1.34), but no association was found for impaired glucose metabolism (Table 2). However, in an analysis stratified on age at cancer diagnosis as a proxy for menopausal status, an increased risk associated with diabetes was confined to postmenopausal breast cancer (HR = 1.22, 95% CI 1.04–1.43). A slightly elevated risk was also suggested in postmenopausal women with impaired glucose metabolism (HR = 1.11, 95% CI 0.96–1.28) (Table 3). In a subcohort of parous women adjustments for parity and age at birth of first child did not change the results (Tables 2, 3). In the subcohort of women in which BMI-measurements were available, relative risk estimates were virtually the same as in the full cohort and adjustments for BMI did not markedly change the point estimates (Table 3).

Table 1 Characteristics of women in the AMORIS population stratified on glucose levels at index examination

	NGM Glucose <6.1 mmol/L (n = 218,279)	IGM Glucose 6.1–6.9 mmol/L (n = 6,843)	Diabetes[a] Glucose ≥7.0 mmol/L (n = 5,615)	All (n = 230,737)
Age at glucose measurement, mean (sd)	46.0 (13.3)	55.3 (14.3)	58.5 (14.5)	46.6 (13.6)
Follow-up time, mean (sd)	11.8 (4.1)	10.3 (4.4)	9.4 (4.5)	11.7 (4.1)
Fasting status at index examination, *n* (%)				
Fasting	121,784 (55.8)	2,940 (43.0)	2,388 (42.5)	127,112 (55.1)
Unknown/nonfasting	96,495 (44.2)	3,903 (57.0)	3,227 (57.5)	103,625 (44.9)
Year of birth, *n* (%)				
<1920	3,104 (1.4)	339 (5.0)	355 (6.3)	3,798 (1.6)
1920–1939	34,539 (15.8)	2,192 (32.0)	2,163 (38.5)	38,894 (16.9)
1940–1949	39,332 (18.0)	1,540 (22.5)	1,303 (23.2)	42,175 (18.3)
1950–1959	64,754 (29.7)	1,643 (24.0)	1,088 (19.4)	67,485 (29.2)
1960	76,550 (35.1)	1,129 (16.5)	706 (12.6)	78,385 (34.0)
Parity, *n* (%)				
0 children	59,997 (27.5)	1,667 (24.4)	1,459 (26.0)	63,123 (27.4)
1 child	42,670 (19.5)	1,405 (20.5)	1,202 (21.4)	45,277 (19.6)
2 children	75,688 (34.7)	2,243 (32.8)	1,682 (30.0)	79,613 (34.5)
3+ children	39,924 (18.3)	1,528 (22.3)	1,272 (22.7)	42,724 (18.5)
Age at birth of first child, *n* (%)				
<20	27,903 (17.6)	896 (17.3)	742 (17.9)	29,541 (17.6)
21–25	62,901 (39.7)	1,996 (38.6)	1,619 (39.0)	66,516 (39.7)
26–30	46,492 (29.4)	1,519 (29.3)	1,183 (28.5)	49,194 (29.3)
31–34	16,262 (10.3)	559 (10.8)	440(10.6)	17,261 (10.3)
35+	4,724 (3.0)	206 (4.0)	172 (4.1)	5,102 (3.0)
Cancer diagnosis				
Breast cancer, *n* (%)	5,697 (2.6)	202 (3.0)	171 (3.0)	6,070 (2.6)
Age at breast cancer diagnosis, mean (sd)	57.8 (11.4)	65.1 (11.4)	66.0 (10.8)	58.2 (11.5)
Endometrial cancer, *n* (%)	966 (0.4)	57 (0.8)	47 (0.8)	1,070 (0.5)
Age at endometrial cancer diagnosis, mean (sd)	63.7 (10.1)	63.9 (9.3)	66.1 (8.5)	63.8 (10.0)
Ovarian cancer, *n* (%)	729 (0.3)	33 (0.5)	21 (0.4)	783 (0.3)
Age at ovarian cancer diagnosis, mean (sd)	59.8 (11.8)	63.6 (11.6)	68.6 (10.6)	60.2 (11.9)
Socioeconomic index, *n* (%)				
High	65,273 (29.9)	1,597 (23.3)	1,087 (19.4)	67,957 (29.5)
Low	118,733 (54.4)	3,472 (50.7)	2,646 (47.1)	124,851 (54.1)
Not gainfully employed	16,320 (7.5)	543 (7.9)	468 (8.3)	17,331 (7.5)
Unclassified/missing	17,953 (8.2)	1,231 (18.0)	1,414 (25.2)	20,598 (8.9)
Body mass index (BMI-kg/m^2): mean (sd)				
Measured in 16.5% of women	23.8 (3.9)	26.0 (5.1)	26.7 (5.7)	23.9 (4.0)

NGM normal glucose metabolism

IGM impaired glucose metabolism

[a] The diabetes group included individuals with glucose level ≥7.0 mmol/L at the index examination and those with a registered hospital discharge diagnosis of diabetes mellitus prior to the date of the index examination irrespective of glucose level

Endometrial cancer

Both diabetes (HR = 1.46, 95% CI 1.09–1.96) and impaired glucose metabolism (HR = 1.41, 95% CI 1.08–1.85) were associated with an increased risk of endometrial cancer. Adjustments for parity and age at birth of first child did not change the relative risk estimates (Table 2). In the subcohort of women with BMI-measurements, relative risk estimates

Table 2 Glucose levels and risk of breast, endometrial, and ovarian cancer in the AMORIS population

	Breast cancer			Endometrial cancer			Ovarian cancer		
	n (cases)	HR[a]	95% CI	*n* (cases)	HR[a]	95% CI	*n* (cases)	HR[a]	95% CI
Glucose level									
NGM[b]	5,697	Ref		966	Ref		729	Ref	
IGM[c]	202	1.05	(0.91–1.21)	57	1.41	(1.08–1.85)	33	1.23	(0.86–1.75)
Diabetes[d]	171	1.15	(0.99–1.34)	47	1.46	(1.09–1.96)	21	0.98	(0.64–1.52)
Adjusted for fasting status									
NGM[b]	5,697	Ref		966	Ref		729	Ref	
IGM[c]	202	1.05	(0.91–1.20)	57	1.43	(1.09–1.87)	33	1.24	(0.87–1.76)
Diabetes[d]	171	1.15	(0.98–1.34)	47	1.48	(1.10–1.99)	21	0.99	(0.64–1.53)
Subcohort of parous women									
Glucose level									
NGM[b]	4,445	Ref		694	Ref		518	Ref	
IGM[c]	155	1.04	(0.88–1.22)	41	1.42	(1.03–1.95)	23	1.20	(0.79–1.83)
Diabetes	120	1.07	(0.89–1.28)	36	1.61	(1.15–2.25)	18	1.20	(0.75–1.93)
Adjusted for fasting status, parity, and age at birth of first child									
NGM[b]	4,445	Ref		694	Ref		518	Ref	
IGM[c]	155	1.04	(0.89–1.23)	41	1.42	(1.03–1.95)	23	1.22	(0.80–1.86)
Diabetes[d]	120	1.08	(0.90–1.30)	36	1.61	(1.15–2.26)	18	1.23	(0.76–1.97)
Subcohort of women with BMI-measurements									
Glucose level									
NGM[b]	999	Ref		163	Ref		118	Ref	
IGM[c]	31	1.06	(0.74–1.52)	12	2.00	(1.11–3.60)	3	0.80	(0.25–2.52)
Diabetes[d]	20	1.06	(0.68–1.65)	7	1.75	(0.82–3.75)	2	0.80	(0.20–3.26)
Adjusted for fasting status and BMI									
NGM[b]	999	Ref		163	Ref		118	Ref	
IGM[c]	31	1.07	(0.75–1.53)	12	1.80	(0.99–3.25)	3	0.79	(0.25–2.50)
Diabetes[d]	20	1.07	(0.69–1.68)	7	1.48	(0.69–3.19)	2	0.79	(0.19–3.25)
Subcohort of women known to be fasting									
Glucose level									
NGM[b]	3,393	Ref		616	Ref		449	Ref	
IGM[c]	105	1.11	(0.91–1.34)	35	1.60	(1.13–2.25)	19	1.34	(0.84–2.12)
Diabetes[d]	78	1.10	(0.88–1.38)	25	1.47	(0.98–2.20)	11	1.00	(0.55–1.83)

[a] Hazard ratio—adjustments for age at index examination were done in all analyses

[b] Normal glucose metabolism—glucose <6.1 mmol/L at the index examination

[c] Impaired glucose metabolism—glucose 6.1–6.9 mmol/L at the index examination

[d] Diabetes—glucose ≥7.0 mmol/L at the index examination or with a registered hospital discharge diagnosis of diabetes mellitus prior to the date of the index examination irrespective of glucose level

were slightly more marked than in the full cohort. Following adjustment for BMI, point estimates were somewhat attenuated (Table 2).

Ovarian cancer

No clear associations were found between glucose levels and ovarian cancer risk. There were very few cases in the subcohort of women where BMI-measurements were available yielding estimates of relative risk with wide confidence intervals. Adjustments for BMI did not change the results (Table 2).

Discussion

In this large cohort of women, diabetes was associated with an increased risk of endometrial cancer and postmenopausal breast cancer. Also, increased risks were observed for endometrial cancer at glucose levels below the

Table 3 Glucose levels and risk of breast cancer in pre and postmenopausal women in the AMORIS population

	Breast cancer					
	Followed until the age of 50			Followed from the age of 50		
	n (cases)	HR[a]	95% CI	*n* (cases)	HR[a]	95% CI
Glucose level						
NGM[b]	1,425	Ref		4,272	Ref	
IGM[c]	15	0.63	(0.38–1.06)	187	1.11	(0.96–1.28)
Diabetes[d]	9	0.60	(0.31–1.16)	162	1.22	(1.04–1.43)
Adjusted for fasting status						
NGM[b]	1,425	Ref		4,272	Ref	
IGM[c]	15	0.64	(0.38–1.06)	187	1.11	(0.95–1.28)
Diabetes[d]	9	0.61	(0.31–1.17)	162	1.21	(1.04–1.42)
Subcohort of parous women						
Glucose level						
NGM[b]	1,030	Ref		3,415	Ref	
IGM[c]	12	0.66	(0.37–1.17)	143	1.09	(0.92–1.29)
Diabetes[d]	6	0.54	(0.24–1.22)	114	1.13	(0.93–1.36)
Adjusted for fasting status, parity, and age at birth of first child						
NGM[b]	1,030	Ref		3,415	Ref	
IGM[c]	12	0.66	(0.37–1.17)	143	1.10	(0.93–1.30)
Diabetes[d]	6	0.55	(0.25–1.24)	114	1.14	(0.94–1.37)
Subcohort of women with BMI-measurements						
Glucose level						
NGM[b]	277	Ref		722	Ref	
IGM[c]	3	0.65	(0.21–2.03)	28	1.14	(0.78–1.66)
Diabetes[d]	1	0.38	(0.05–2.70)	19	1.17	(0.74–1.87)
Adjusted for fasting status and BMI						
NGM[b]	277	Ref		722	Ref	
IGM[c]	3	0.67	(0.21–2.08)	28	1.15	(0.78–1.68)
Diabetes[d]	1	0.39	(0.05–2.80)	19	1.18	(0.74–1.87)
Subcohort of women known to be fasting						
Glucose level						
NGM[b]	818	Ref		2,575	Ref	
IGM[c]	5	0.57	(0.24–1.37)	100	1.16	(0.95–1.42)
Diabetes[d]	3	0.52	(0.17–1.63)	75	1.15	(0.91–1.45)

[a] Hazard ratio—adjustments for age at index examination were done in all analyses

[b] Normal glucose metabolism—glucose <6.1 mmol/L at the index examination

[c] Impaired glucose metabolism—glucose 6.1–6.9 mmol/L at the index examination

[d] Diabetes—glucose ≥7.0 mmol/L at the index examination or with a registered hospital discharge diagnosis of diabetes mellitus prior to the date of the index examination irrespective of glucose level

diagnostic threshold for diabetes. For postmenopausal breast cancer, an increased risk was suggested in women with impaired glucose metabolism, but this association did not reach statistical significance. Adjustments for possible confounding factors such as age, socioeconomic standing, BMI, parity, and age at birth of first child did not materially change the estimates. No associations were seen between glucose levels and the risk of ovarian cancer.

Several mechanisms have been postulated to contribute to an association between adult onset diabetes and cancer risk: activation of the insulin pathway, activation of the insulin-like growth factor pathway, and impaired regulation of endogenous sex hormones [9]. Both insulin and insulin-like growth factor I (IGF-I) have been shown to promote tumor development by stimulating cell proliferation, while inhibiting apoptosis [32]. Also, glucose may increase risk directly by stimulating proliferation of tumor cells acting as energy source [33]. The relative contribution from glucose, insulin, or IGF-I to the risk of cancer is unclear.

Breast cancer

The analysis of breast cancer was stratified into two age groups as a proxy for menopausal status (<50 years and ≥50 years at the time of diagnosis). Our findings of an increased risk of post, but not premenopausal breast cancer in women with diabetes are supported by the results of two meta-analyses [10, 11].

Furthermore, our results indicate an association between impaired glucose metabolism and an increased risk of postmenopausal breast cancer. As the risk associated with diabetes was only modestly increased, the risks associated with glucose levels below this threshold can be assumed to be slightly lower and thereby also more difficult to detect. Results from previous studies on nondiabetic glucose levels and breast cancer have been contradictory. Four out of nine studies reported no association [19–21, 24]. For example, one large Korean study reported an increased risk of breast cancer associated with diabetes, but found no association for fasting glucose levels below the diabetic level [19]. Five studies found evidence of an association with glucose levels below the threshold for diabetes, but with divergent results for menopausal status. Muti et al. [16] reported an association between hyperglycemia and risk of premenopausal breast cancer. Similarly, Stattin et al. [22] found elevated fasting glucose to be associated with an increased risk in women <49 years at baseline, but not in older women. In a study where the majority of cases (136 out of 187) were older than 50 years of age at the start of follow-up, Mink et al. [25] reported an association between glucose levels above the normal range and breast cancer risk, even though the associations were attenuated when BMI was considered. A large recent study based on six European cohorts found glucose levels below the diabetic level to be associated with an increased risk of breast cancer among women ≥60 years of age [34]. Based on a random sample of women from the Women's Health Initiative study, Kabat et al. [26] found no association between glucose levels and postmenopausal breast cancer risk in white women, but an increased risk for African-American women. Heterogeneity in findings across studies may at least to some extent be explained by differences in cut points for glucose levels, follow-up times, whether or not menopausal status was considered in the analyses, and statistical power issues.

Endometrial cancer

Diabetes has previously been reported to be associated with approximately a two times increased risk of endometrial cancer [6–8], findings which our results corroborate. In the present study, an increased risk was also present for individuals with impaired glucose metabolism. Similarly, three out of four earlier studies with data available on fasting glucose levels have found evidence of increased risks associated with increasing glucose levels [17, 22, 23, 27].

Ovarian cancer

Consistent with findings from earlier studies, we found no associations between diabetes [12–15] or between impaired glucose metabolism [20, 23] and risk of ovarian cancer. However, Hemminki et al. [35] observed an increased risk of ovarian cancer among patients hospitalized for type 2 diabetes.

Strengths of the present study included the size and the prospective study design with almost 100% complete coverage of incident cancers in the Swedish Cancer Register. The number of cancer cases available for analyses was considerably higher than in earlier studies in this area conducted in Western populations. The data at hand also allowed adjustments for known reproductive risk factors. Another important strength was that recorded glucose values were based on the same automated analytic methods performed in one laboratory. No patients were hospitalized at the time of blood draw.

There are some limitations that warrant consideration. First, no information was available on lifestyle factors such as physical activity, alcohol consumption, and smoking. To some extent, adjustment for BMI may reduce confounding from low physical activity. In addition, if impaired fasting glucose in part is caused by low physical activity, adjustment for this factor in the analyses could be overly conservative. While smoking is not an established risk factor for breast cancer [36, 37], it has been suggested to be associated with an increased risk of mucinous ovarian cancer [38] and a decreased risk of endometrial cancer [39]. Second, we had no information on use of exogenous female hormones or antidiabetic medication. There are reports of associations between use of antidiabetics and cancer risk and mortality, with metformin associated with a decreased risk and sulfonylurea and insulin with an increased risk [40–42]. A third potential limitation was misclassification of glucose levels, particularly in individuals with unknown fasting status. This notion was supported by our finding of a larger proportion of individuals with unknown fasting status observed in the IGM and diabetes groups. Finally, information on glucose levels was based on one blood sample only. However, it is unlikely that any such misclassification is related to the likelihood of developing cancer. If anything, a nondifferential misclassification of glucose levels would tend to underestimate the strength of observed associations. Adjustments for fasting status at the index examination did not change results. Also, when the analysis was restricted to women known to be fasting, the associations remained virtually the same.

No detailed information was available on the primary reason for the measuring of glucose. However, an estimated 80% of subjects provided measurements as part of a regular health control as indicated by the profile of the test panel. Following separate analyses of this group estimates remained virtually unchanged.

BMI-measurements were only available for a subcohort of women; nevertheless, the number of cases available for analysis in this subgroup was larger than in most previous studies. We can not exclude that this subcohort was slightly different from the full cohort, but this should not affect the relation between glucose levels and cancer incidence within the cohort, nor influence the possibility to evaluate the potential confounding effect from obesity. Following adjustments for BMI, estimates for endometrial cancer risk were somewhat attenuated, while estimates for breast and ovarian cancer remained unchanged.

In conclusion, our results based on a very large cohort of women confirm previous reports of associations not only between diabetes mellitus and endometrial cancer but also between diabetes and postmenopausal breast cancer risk. More importantly, we found evidence of risk modifying effects of glucose levels below the diagnostic threshold for diabetes. Given an expected continued increase in the prevalence of impaired fasting glucose in many populations, even small excess risks for breast cancer have important public health implications. Impaired glucose metabolism is a potentially modifiable risk factor by means of lifestyle changes such as increased physical activity, dietary habits, and weight control [43]. In a public health perspective, such changes may not only reduce the risk of developing adult onset diabetes but may also prove to be of importance to reduce the burden of cancer in women.

Acknowledgments The study was supported by grants from the Swedish Council for Working life and Social research (# 2007-214), Karolinska Institutet Funds, the Swedish Cancer Society (# 2007/0526, # CAN 2010/608), and the Gunnar and Ingmar Jungner Foundation for Laboratory Medicine (Stockholm). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest The authors declare no conflicts of interest.

References

1. Strickler HD, Wylie-Rosett J, Rohan T et al (2001) The relation of type 2 diabetes and cancer. Diabetes Technol Ther 3:263–274
2. Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. Diabetes Care 33:1674–1685
3. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M (2005) Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 92:2076–2083
4. El-Serag HB, Hampel H, Javadi F (2006) The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 4:369–380
5. Larsson SC, Orsini N, Wolk A (2005) Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 97:1679–1687
6. Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 50:1365–1374
7. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A (2008) Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 98:1582–1585
8. Saltzman BS, Doherty JA, Hill DA et al (2008) Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. Am J Epidemiol 167:607–614
9. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B (2005) Diabetes mellitus and breast cancer. Lancet Oncol 6:103–111
10. Larsson SC, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 121:856–862
11. Xue F, Michels KB (2007) Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr 86:S823–S835
12. Adler AI, Weiss NS, Kamb ML, Lyon JL (1996) Is diabetes mellitus a risk factor for ovarian cancer? A case-control study in Utah and Washington (United States). Cancer Causes Control 7:475–478
13. Parazzini F, Moroni S, La Vecchia C, Negri E, dal Pino D, Bolis G (1997) Ovarian cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer 33: 1634–1637
14. Wideroff L, Gridley G, Mellemkjaer L et al (1997) Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 89: 1360–1365
15. Weiderpass E, Ye W, Vainio H, Kaaks R, Adami HO (2002) Diabetes mellitus and ovarian cancer (Sweden). Cancer Causes Control 13:759–764
16. Muti P, Quattrin T, Grant BJ et al (2002) Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 11:1361–1368
17. Furberg AS, Thune I (2003) Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer 104:669–676
18. Saydah SH, Loria CM, Eberhardt MS, Brancati FL (2003) Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol 157:1092–1100
19. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. Jama 293:194–202
20. Rapp K, Schroeder J, Klenk J et al (2006) Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia 49:945–952
21. Dankner R, Chetrit A, Segal P (2007) Glucose tolerance status and 20 year cancer incidence. Isr Med Assoc J 9:592–596
22. Stattin P, Bjor O, Ferrari P et al (2007) Prospective study of hyperglycemia and cancer risk. Diabetes Care 30:561–567
23. Stocks T, Rapp K, Bjorge T et al (2009) Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. PLoS Med 6(12):e1000201
24. Manjer J, Kaaks R, Riboli E, Berglund G (2001) Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo preventive project. Eur J Cancer Prev 10:33–42

25. Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR (2002) Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. Am J Epidemiol 156:349–352
26. Kabat GC, Kim M, Caan BJ et al (2009) Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer 125:2704–2710
27. Cust AE, Kaaks R, Friedenreich C et al (2007) Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European prospective investigation into cancer and nutrition (EPIC). Endocr Relat Cancer 14:755–767
28. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E (2001) High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 358:2026–2033
29. Barlow L, Westergren K, Holmberg L, Talback M (2009) The completeness of the Swedish cancer register: a sample survey for year 1998. Acta oncologica (Stockholm, Sweden) 48:27–33
30. Jungner I, Marcovina SM, Walldius G, Holme I, Kolar W, Steiner E (1998) Apolipoprotein B and A-I values in 147576 Swedish males and females, standardized according to the World Health Organization-international federation of clinical chemistry first international reference materials. Clin Chem 44:1641–1649
31. Statistics Sweden (2011) Swedish socio-economic classification (SEI). http://www.scb.se/Grupp/Hitta_statistik/Forsta_Statistik/Klassifikationer/_Dokument/SEI-AGG_Eng.pdf. Accessed 2011
32. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nature Rev 8:915–928
33. Shaw RJ (2006) Glucose metabolism and cancer. Curr Opin Cell Biol 18:598–608
34. Bjorge T, Lukanova A, Jonsson H et al (2010) Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev 19:1737–1745
35. Hemminki K, Li X, Sundquist J, Sundquist K (2010) Risk of cancer following hospitalization for type 2 diabetes. Oncologist 15:548–555
36. Hamajima N, Hirose K, Tajima K et al (2002) Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 87:1234–1245
37. Magnusson C, Wedren S, Rosenberg LU (2007) Cigarette smoking and breast cancer risk: a population-based study in Sweden. Br J Cancer 97:1287–1290
38. Jordan SJ, Whiteman DC, Purdie DM, Green AC, Webb PM (2006) Does smoking increase risk of ovarian cancer? A systematic review. Gynecol Oncol 103:1122–1129
39. Zhou B, Yang L, Sun Q et al (2008) Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med 121:501–508
40. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM (2009) New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 32:1620–1625
41. Smith U, Gale EA (2009) Does diabetes therapy influence the risk of cancer? Diabetologia 52:1699–1708
42. Pollak M (2010) Metformin and other biguanides in oncology: advancing the research agenda. Cancer Prev Res 3:1060–1065
43. Misra A (2009) Prevention of type 2 diabetes: the long and winding road. Lancet 374:1655–1656