Type 2 Diabetes and Subsequent Incidence of Breast Cancer in the Nurses' Health Study

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OBJECTIVE — Hyperinsulinemia may promote mammary carcinogenesis. Insulin resistance has been linked to an increased risk of breast cancer and is also characteristic of type 2 diabetes. We prospectively evaluated the association between type 2 diabetes and invasive breast cancer incidence in the Nurses' Health Study.

RESEARCH DESIGN AND METHODS — A total of 116,488 female nurses who were 30–55 years old and free of cancer in 1976 were followed through 1996 for the occurrence of type 2 diabetes and through 1998 for incident invasive breast cancer, verified by medical records and pathology reports.

RESULTS — During 2.3 million person-years of follow-up, we identified 6,220 women with type 2 diabetes and 5,189 incident cases of invasive breast cancer. Women with type 2 diabetes had a modestly elevated incidence of breast cancer (hazard ratio [HR] = 1.17; 95% CI 1.01–1.35) compared with women without diabetes, independent of age, obesity, family history of breast cancer, history of benign breast disease, reproductive factors, physical activity, and alcohol consumption. This association was apparent among postmenopausal women (1.16; 0.98–1.62) but not premenopausal women (0.83; 0.48–1.42). The association was predominant among women with estrogen receptor–positive breast cancer (1.22; 1.01–1.47).

CONCLUSIONS — Women with type 2 diabetes may have a slightly increased risk of breast cancer.

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Breast cancer incidence is higher in more affluent countries and among women with high socioeconomic status (1,2). Although lower parity, delayed childbearing, and higher alcohol consumption in high socioeconomic status populations may explain part of this observation (2), a lifestyle characterized by sedentary routines (3) and possibly a diet high in refined carbohydrates, sugars, and animal fats may also play an important role. This Western lifestyle often results in insulin resistance, a condition characterized by a decreased sensitivity of target tissues to circulating insulin and compensatory hyperinsulinemia (4). Insulin inhibits the production of sex hormone–binding globulin (SHBG) (5,6), which results in an increase in free steroid hormones, free estrogens in particular, because testosterone successfully competes with estrogen for SHBG (7).

Insulin is also a growth-promoting hormone with mitogenic effects in both normal and malignant breast tissue (8,9). Insulin suppresses IGF binding protein-1 and thus increases bioavailable IGF-1 (10). The effect of estradiol on hormone-dependent breast cancer cell proliferation may depend on the presence of insulin or IGF (9,11).

Insulin resistance coupled with an insulin secretory defect causes type 2 diabetes. Hyperinsulinemia with insulin resistance also has been postulated to increase the risk of breast cancer (12–14). Obesity is associated with type 2 diabetes and leads to a rise in endogenous estrogen levels.

With the worldwide increase in obesity and type 2 diabetes, an association between type 2 diabetes and breast cancer might have public health implications. We used data from the large ongoing Nurses' Health Study cohort to investigate whether type 2 diabetes is associated with subsequent incidence of breast cancer independent of adiposity.

RESEARCH DESIGN AND METHODS

Population

The Nurses' Health Study was established in 1976 when 121,700 female registered nurses 30–55 years of age completed a mailed questionnaire on their health status and on various potential risk factors for cancer, cardiovascular disease, and other major illnesses. Participants receive follow-up questionnaires biennially to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diseases including diabetes and breast cancer. The response rate still exceeds 90%. The Nurses' Health Study was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA).

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Abbreviations: HR, hazard ratio; SHBG, sex hormone–binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetes confirmation and validation

All women who report a physician diagnosis of diabetes on the biennial questionnaire are mailed a supplemental questionnaire requesting detailed information on diagnosis, laboratory results, and treatment. Participants who confirmed a diagnosis of diabetes on this supplementary questionnaire were considered to have "definite" type 2 (non–insulin-dependent) diabetes if they met the National Diabetes Data Group criteria for diabetes (15), did not meet criteria for type 1 (insulin-dependent and ketosis-prone) diabetes, and were diagnosed at age ≥30 years. No weight criteria were used in the type 2 classification. Only women with definite type 2 diabetes were classified as diabetic in this analysis; women who reported a diagnosis of diabetes on the main questionnaire but were classified as probable or unlikely on the basis of supplementary questionnaire information and women who were classified as having type 1 diabetes were excluded from this analysis.

The validity of supplementary questionnaires to confirm and characterize diabetes type was evaluated in a random subsample of Nurses' Health Study participants with self-reported type 2 diabetes (16). Of 84 women contacted, 71 gave permission for medical record review; records were obtained for 62 women. Self-reports of type 2 diabetes were confirmed by medical record review by an endocrinologist for 61 (98%) of the cases.

The diagnostic criteria for diabetes were changed by the American Diabetes Association in 1997 (17). Because we assessed diabetes only up to 1996 for this analysis, the change in criteria did not affect our diabetes definition.

Information on diabetes medication (insulin and sulfonylureas) was obtained from the main and supplementary questionnaires.

Identification of breast cancer

On each biennial questionnaire, participants were asked whether they had been newly diagnosed with breast cancer during the previous 2 years, and if so, what was the date of diagnosis. The National Death Index is also routinely searched for deaths among women who do not respond to the questionnaires. All women who reported breast cancer (or the next of kin for those who had died) were asked for permission to review the relevant medical records to confirm the diagnosis. Pathology reports, obtained for 93% of the cases, confirmed breast cancer in >99% of women whose reports were reviewed. Although medical records could not be obtained for 7% of the cases, analyses were based on all reports of newly diagnosed breast cancer, because the degree of accuracy of the participants' reports was extremely high among those for whom records were obtained. Cases of breast carcinoma in situ (n = 612) were censored from this analysis because we do not follow them further for the occurrence of invasive breast cancer in our cohort. Only a fraction of in situ breast cancers progresses to become invasive. We excluded ductal carcinoma in situ as end point because differential use of preventive services could lead to higher detection of carcinoma in situ and lead to spurious associations. Diabetic women see providers more often than healthy women and therefore might have greater access to screening.

Population for analysis

Women who reported cancer (except for nonmelanoma skin cancer) at baseline in 1976 were excluded from the analyses (n = 3,302), as were those who reported type 1 diabetes (n = 497) or type 2 diabetes that was not confirmed by the supplementary questionnaire (n = 1,091) or if their date of diagnosis of diabetes was missing (n = 4). Women who reported onset of diabetes before age 30 years were excluded from the study population, as they were more likely to have type 1 diabetes (n = 112). Participants also were excluded if their date of birth was missing (n = 27), if they died shortly after agreeing to participate in the study (n = 2), if they did not report their height (n = 149), or if they developed breast cancer during follow-up but their date of diagnosis was not available (n = 29). This left a study population of 116,488 women. During follow-up, women were censored from the analysis if they developed breast cancer or any other cancer, if they died, or if they were lost to follow-up.

Statistical analysis

Women were followed prospectively for the occurrence of diabetes from 1976 to 1996 and for invasive breast cancer from 1976 to 1998. Women with prevalent diabetes in 1976 were included in the analyses. When duration of diabetes was considered, self-reported date of diagnosis was used also for women who reported onset before 1976. Person-years of follow-up were calculated as the time from completion of the 1976 questionnaire at baseline to the date of return of the 1998 questionnaire or to the date of diagnosis of invasive breast cancer, breast carcinoma in situ, other cancer, death, or loss to follow-up, whichever occurred first. Women contributed person-years as diabetic subjects (exposed) from the time of diagnosis of type 2 diabetes until they reached one of the above-listed censoring points. Women with prevalent diabetes in 1976 contributed person-years as diabetic subjects from the start of follow-up. Women contributed person-years as nondiabetic subjects (nonexposed) during the time they were free of type 2 diabetes. A Cox proportional hazards model was used to calculate the hazard of developing invasive breast cancer given a history of type 2 diabetes (18). The proportional hazards model allows us to adjust simultaneously for multiple potential confounders of this association. Regression models were adjusted for age (in months), family history of breast cancer in first-degree relative(s) (dichotomous), history of benign breast disease (dichotomous), height (continuous), BMI at age 18 years (continuous), current BMI (continuous), waist-to-hip ratio (continuous), age at menarche (≤11, 12, 13, 14, ≥15 years), parity (0, 1, 2, 3, ≥4 children), age at birth of first child (<25, 25–29.9, 30–34.9, ≥35 years), menopausal status (premenopausal, postmenopausal, unknown), age at menopause (continuous), use of postmenopausal hormones (never, past user for <5 years, past user for ≥5 years, current user for <5 years, current user for ≥5 years), moderate and vigorous physical activity (<1, 1–1.9, 2–3.9, 4–6.9, ≥7 h per week), and alcohol consumption (none, 0.1–4.9, 5.0–14.9, ≥15 g per day). Covariate values were updated in the analysis whenever new information was obtained from the biennial questionnaire between 1976 and 1996. Information on alcohol consumption was first obtained in 1980 and assumed constant between 1976 and 1980. Because waist-to-hip ratio was assessed only in 1986 and 1996, we did not include this variable as a covariate in all our analytic models, but in secondary analyses we tested whether inclusion would alter the

Table 1—*Age-standardized characteristics of 116,488 participants of the Nurses' Health Study according to diabetes status*

	No diabetes*	Type 2 diabetes*
Person-years (*n*)	2,306,664	59,171
Mean age (years)	52.1	59.1
Breast cancer cases (*n*)	5,403	202
Family history of breast cancer (%)†	13.0	12.9
History of benign breast disease (%)‡	44.7	41.7
Mean height (ms)	1.64	1.63
Mean BMI at age 18 years (kg/m^2)	21.3	23.3
Mean adult BMI (kg/m^2)	25.0	30.7
Mean waist-to-hip ratio	0.80	0.86
Mean age at menarche (years)	12.5	12.1
Nulliparous women (%)	6.9	7.3
Mean number of children (among parous women)	3.2	3.3
Mean age at first birth (among parous women) (years)	24.8	24.9
Premenopausal (%)	37.2	34.7
Mean age at natural menopause (years)	52.4	52.5
Use of postmenopausal hormones (among all women)		
Current (%)	14.5	10.7
Past (%)	9.8	11.8
Physical activity (mean number of hours per week)	3.2	2.7
Alcohol consumption		
None (%)	28.3	52.0
Mean grams per day (among women who drink alcohol)	9.2	6.4

*All values presented represent average values during follow-up; †a family history of breast cancer is defined as ever reporting breast cancer in a first-degree relative; ‡a history of benign breast disease is defined as ever reporting a history of fibrocystic or other benign breast disease.

estimates. Analyses were stratified by BMI (<25, 25–29.9, ≥30 kg/m^2), menopausal status (pre- and postmenopausal), both of the above, postmenopausal hormone use, family history of breast cancer, mammography screening, use of diabetes medication (insulin, oral hypoglycemic medication, or other oral diabetes medication), and by duration of diabetes (≤5, 5.1–10, 10.1–15, 15.1–20, ≥20 years) before a diagnosis of breast cancer. Separate analyses were conducted to explore the association between a history of type 2 diabetes and estrogen receptor–positive and –negative breast cancer and fatal breast cancer.

All tests of statistical significance are two sided.

RESULTS — During 2.3 million person-years of follow-up over 22 years, 6,120 women who were cancer-free reported type 2 diabetes and 5,605 women were newly diagnosed with invasive breast cancer. Of the women with breast cancer for whom estrogen receptor status was known, 2,915 had estrogen receptor–positive and 989 had estrogen receptor–negative breast cancer. A total of 1,100 women had died from breast cancer as of June 1998.

Table 1 shows the distribution of characteristics during follow-up among participants who reported diabetes at baseline or during follow-up and among those who remained free of the disease. Women who reported type 2 diabetes had a substantially higher BMI than nondiabetic women during adult life and at age 18 years. Women with type 2 diabetes also had a somewhat higher waist-to-hip ratio, were less physically active, drank considerably less alcohol, and were less likely to use postmenopausal hormones than nondiabetic women (Table 1).

The age-adjusted hazard ratio (HR) for developing invasive breast cancer was 1.11 (95% CI 0.96–1.28) for women with type 2 diabetes compared with nondiabetic women (Table 2). After adjustment for potential confounders, family history of breast cancer, a history of benign breast disease, height, BMI at age 18 years, current BMI, age at menarche, parity, age at first child's birth, menopausal status, age at menopause, postmenopausal hormone use, physical activity, and alcohol consumption, the association between a history of type 2 diabetes and the risk of invasive breast cancer was somewhat strengthened and was modest but significant (HR = 1.17; 95% CI 1.01–1.35). BMI at age 18 years and current BMI were entered into the regression model as continuous variables to provide the most complete control for confounding by obesity possible given the observed data. Both diabetes and obesity were independently related to breast cancer in this model. The slight increase in the HR after adjustment for covariates was due to negative confounding by a number of variables, in particular menopausal status, age at menopause, and alcohol consumption. This negative confounding was stronger than the positive confounding by current BMI. A model adjusting for all covariates except current BMI resulted in an HR = 1.23 (95% CI 1.07–1.42). Adjusting for all covariates, including current BMI, but not for the menopausal variables (menopausal status, age at menopause, and postmenopausal hormone use) produced an HR for the association of diabetes and breast cancer of 1.13 (95% CI 0.98–1.31). A model, fully adjusted except for alcohol consumption, resulted in an HR = 1.15 (95% CI 0.99–1.33).

Additional adjustment for waist-to-hip ratio did not materially alter the esti-

Table 2—*History of type 2 diabetes and HRs of invasive breast cancer among 116,488 participants of the Nurses' Health Study, 1976–1998*

	No diabetes	Type 2 diabetes
Breast cancer cases (*n*)	5,403	202
Person-years	2,306,664	59,171
Age-adjusted HR (95% CI)	1.00	1.11 (0.96–1.28)
Covariate-adjusted HR (95% CI)*	1.00	1.17 (1.01–1.35)

*Hazard ratios and 95% CI adjusted for age, family history of breast cancer, history of benign breast disease, height, BMI at age 18 years, current BMI, age at menarche, parity, age at first child's birth, menopausal status, age at menopause, use of postmenopausal hormones, physical activity, and alcohol consumption.

Table 3—*History of type 2 diabetes and HRs of invasive breast cancer subtypes among participants of the Nurses' Health Study, 1976–1998*

	No diabetes			Type 2 diabetes			
Breast cancer	Breast cancer cases (*n*)	Person-years	HR	Breast cancer cases (*n*)	Person-years	Age-adjusted HR (95% CI)	Covariate-adjusted HR (95% CI)*
Estrogen receptor–positive breast cancer†	2,794	2,308,935	1.0	121	59,240	1.16 (0.97–1.40)	1.22 (1.01–1.47)
Estrogen receptor–negative breast cancer†	957	2,309,088	1.0	32	59,304	1.06 (0.74–1.51)	1.13 (0.79–1.62)
Fatal breast cancer	1,054	2,351,547	1.0	46	61,333	1.13 (0.84–1.52)	0.98 (0.72–1.32)

*HR and 95% CI adjusted for age, family history of breast cancer, history of benign breast disease, height, BMI at age 18 years, current BMI, age at menarche, parity, age at first child's birth, menopausal status, age at menopause, use of postmenopausal hormones, physical activity, and alcohol consumption; †receptor status was not known for all breast cancer cases.

mate (HR = 1.16; 95% CI 1.00–1.34). Because data on waist-to-hip ratio were not available at baseline and not available for a considerable number of participants during follow-up, results are presented without considering waist-to-hip ratio.

The association between type 2 diabetes and breast cancer was significant among women with estrogen receptor–positive tumors but not among women with estrogen receptor–negative tumors (Table 3). There were, however, fewer cases in the latter group. There was no association between a history of diabetes and fatal breast cancer (Table 3).

The association between type 2 diabetes and breast cancer incidence was not appreciably modified by BMI (Table 4). Among premenopausal women, breast cancer risk was slightly lower for diabetic than nondiabetic women, but numbers were small. The positive association between type 2 diabetes and breast cancer was restricted to postmenopausal women and was independent of their BMI (Table 4). There was no statistically significant interaction between type 2 diabetes and menopausal status (test for interaction, $P = 0.16$). The association between type 2 diabetes and breast cancer incidence was not substantially modified by a family history of breast cancer or the use of insulin or other diabetes medication. Similarly, restricting the analysis to women who never used postmenopausal hormones or to women who ever had a mammogram

Table 4—*History of type 2 diabetes and HRs of invasive breast cancer among different subgroups of the Nurses' Health Study, 1976–1998*

	No diabetes		Type 2 diabetes			
Stratum	Breast cancer cases (*n*)	Person-years	Breast cancer cases (*n*)	Person-years	Age-adjusted HR (95% CI)*	Covariate-adjusted HR (95% CI)*†
BMI (kg/m^2)						
<25	3,050	1,389,224	36	10,577	1.19 (0.86–1.66)	1.23 (0.88–1.71)
25–29.9	1,601	613,230	67	19,504	1.05 (0.82–1.34)	1.11 (0.86–1.42)
≥30	750	302,670	99	29,064	1.12 (0.90–1.39)	1.18 (0.94–1.46)
Premenopausal‡	1,455	872,564	14	8,274	0.70 (0.41–1.19)	0.83 (0.48–1.41)
BMI <30	1,305	772,757	6	3,816	0.66 (0.29–1.47)	0.70 (0.31–1.58)
BMI ≥30	150	99,807	8	4,458	0.85 (0.39–1.85)	0.88 (0.40–1.96)
Postmenopausal‡	3,391	1,126,133	171	45,015	1.13 (0.97–1.32)	1.16 (0.98–1.36)
BMI <30	2,862	960,999	89	23,564	1.13 (0.91–1.39)	1.15 (0.93–1.43)
BMI ≥30	528	164,542	82	21,431	1.11 (0.87–1.41)	1.17 (0.91–1.49)
Postmenopausal, never used postmenopausal hormones	1,065	379,188	64	16,755	1.21 (0.93–1.56)	1.16 (0.89–1.51)
Use of diabetes medication§						
Yes	—	—	171	50,783	1.08 (0.93–1.27)	1.15 (0.99–1.35)¶
No	5,403	2,306,651	31	8,400	1.24 (0.87–1.76)	1.21 (0.85–1.73)¶
Family history of breast cancer						
Yes	1,079	299,885	40	8,181	1.06 (0.76–1.46)	1.16 (0.83–1.62)
No	4,322	2,005,240	162	50,964	1.11 (0.95–1.31)	1.17 (0.99–1.37)
Ever mammogram	4,314	1,748,894	162	44,937	1.08 (0.92–1.26)	1.16 (0.99–1.37)

*The reference group for calculation of each HR is the women without diabetes in the same stratum for the given covariates; †HR and 95% CI adjusted for age, family history of breast cancer, history of benign breast disease, height, BMI at age 18 years, current BMI, age at menarche, parity, age at first child's birth, menopausal status, age at menopause, use of postmenopausal hormones, physical activity, and alcohol consumption; ‡information on menopausal status was not available for all participants; §includes insulin and sulfonylureas; ¶additionally adjusted for duration of diabetes.

Table 5—*Years since diagnosis of type 2 diabetes and HRs of invasive breast cancer among participants of the Nurses' Health Study*

Years since diagnosis of diabetes	Breast cancer cases (*n*)	Person-years	Age-adjusted HR (95% CI)	Covariate-adjusted HR (95% CI)*
No diabetes	5,403	2,306,664	1.00	1.00
≤5 years	89	24,696	1.22 (0.99–1.51)	1.27 (1.02–1.57)
5.1–10 years	48	15,645	1.02 (0.77–1.36)	1.09 (0.82–1.46)
10.1–15 years	39	9,519	1.31 (0.95–1.80)	1.39 (1.01–1.91)
15.1–20 years	16	5,169	0.94 (0.58–1.54)	1.00 (0.61–1.63)
>20 years	10	4,154	0.66 (0.35–1.22)	0.69 (0.37–1.29)
P for trend			0.69	0.33

*Hazard ratios and 95% CI adjusted for age, family history of breast cancer, history of benign breast disease, height, BMI at age 18 years, current BMI, age at menarche, parity, age at first child's birth, menopausal status, age at menopause, use of postmenopausal hormones, physical activity, and alcohol consumption.

did not appreciably change the observed association.

There was no consistent relation between duration of diabetes and breast cancer incidence (Table 5). The hazard for breast cancer was slightly higher among women who were diagnosed with diabetes between 10 and 15 years before a diagnosis of breast cancer than for women who had diabetes for <10 years or >15 years. Women who had diabetes for <20 years had a lower HR for breast cancer than women with no diabetes, but there were few cases in this group. The relation between duration of diabetes and subsequent breast cancer risk was similar when the analysis was restricted to postmenopausal women (data not shown).

CONCLUSIONS — These data from the Nurses' Health Study indicate that women with type 2 diabetes have a slightly but significantly higher risk of developing breast cancer than women with no diabetes. The elevated risk was apparent among postmenopausal women but not among premenopausal women. Although the association between type 2 diabetes and breast cancer did not appear to be explained by adiposity, residual confounding by adiposity is likely. We controlled for obesity in our analyses as well as possible, but measurement error in self-reported weight precludes achieving complete control of confounding by adiposity.

As early as 1885, hyperglycemia was described in patients with cancer (19). In the early 1920s, Warburg (20) demonstrated that tumor slices sustained higher rates of glucose utilization and lactic acid production than normal tissue sections. Women with breast cancer were noted decades ago to have higher rates of diabetes than women with benign breast disease or healthy women (21–23). Of the systematic prospective and case-control studies that followed, some reported elevated risk ratios for breast cancer among women with type 2 diabetes (24–27), but other studies indicated no association (28–36). Most studies, however, were limited in size and therefore underpowered to reveal a modest association. Furthermore, only two studies (35,36) accounted for general and/or central obesity, which is associated with both type 2 diabetes and breast cancer. Weiss et al. (35), in a large population-based case-control study in the U.S., found no significant association between a history of adult-onset diabetes and risk of breast cancer after adjusting for BMI (odds ratio = 1.13; 95% CI 0.7–1.90). The Iowa Women's Study did not reveal an overall association between type 2 diabetes and breast cancer incidence, adjusting for both BMI and waist-to-hip ratio (36).

The data from the Nurses' Health Study provide the largest population with the longest follow-up in which the association between diabetes and breast cancer has been studied. Our findings of a modest association are consistent with several previous reports of a slightly elevated risk (21–27,29,33). Most previous studies, however, did not have sufficient power to provide stable estimates.

We found the modest association between diabetes and breast cancer to be largely independent of self-reported adiposity and body fat distribution. We attempted to adjust for confounding by obesity as closely as possible using the observed data on weight and height by entering height, BMI at age 18 years, and current BMI as continuous variables into the regression model (37). Neither current adiposity nor central obesity appeared to be an important confounder of the diabetes–breast cancer association. Central obesity, which is an even stronger predictor of insulin resistance and type 2 diabetes than BMI, has been found to increase breast cancer risk among both pre- and postmenopausal women (38).

In the Nurses' Health Study, the association between type 2 diabetes and breast cancer was only apparent among postmenopausal women. Our finding that the risk for breast cancer was nonsignificantly lower in premenopausal women with diabetes than in nondiabetic women parallels the observation that obese premenopausal women have a lower risk of breast cancer than women of normal weight (39). Whereas in postmenopausal women estrogen synthesis takes place in adipose tissue, in premenopausal women estrogen synthesis is primarily gonadal and obesity is associated with reduced endogenous estrogens (40). Insulin may elevate free plasma estrogen levels through SHBG inhibition (5–7), which may be particularly relevant in women with low estrogen levels, e.g., postmenopausal women with no exogenous estrogen replacement.

We could not confirm any effect modification of the association between diabetes and breast cancer by a family history of breast cancer, as was reported from the Iowa Women's Health Study cohort (41). In that analysis, however, the only confounders considered were BMI and waist-to-hip ratio (41).

It is possible that women who are diagnosed with diabetes are more likely to be screened for breast cancer. We examined a possible detection bias by restricting our cohort to women who received mammography screening. The estimates remained unchanged.

Given the misclassification and confounding inherent in an observational study, we have to consider the possibility that the observed association was a result of such biases. Furthermore, waist-to-hip ratio measurements were not available for the entire cohort, and thus, our final results were not adjusted for central obesity. Generally, however, associations in our data were strengthened by adjustment for potential confounders, indicating that the

true association was more likely underrather than overestimated. Nevertheless, residual or unmeasured confounding has to be considered as a possible explanation for the modest increase in risk observed. One-third or more of persons with diabetes go undetected in the population and are therefore misclassified as nondiabetic (42). Diagnostic criteria for diabetes changed after the women included in this analysis were diagnosed, and some women classified as free of type 2 diabetes would be classified as having type 2 diabetes under the new criteria (17). A reduction in nondifferential misclassification would strengthen the association between diabetes and breast cancer observed.

Between 1990 and 1998, the prevalence of diagnosed diabetes increased by 33% in the U.S.(43), reflecting the rapid increase in the prevalence of obesity (44). This phenomenon may have an impact on possible late induction of tumorigenesis and on tumor growth. In 1998, the total number of U.S. adults who suffered from diabetes was estimated at 16 million (43). Thus, even a slight increase in breast cancer risk in women with diabetes would be of public health concern. If hyperinsulinemia plays a role in breast cancer pathogenesis, interventions that improve insulin sensitivity such as exercise and dietary modifications may be expected to lower associated breast cancer incidence (45), but this assumption requires further study.

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References

1. World Cancer Research Fund/American Institute for Cancer Research: *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC, American Institute for Cancer Research, 1997
2. Hulka BS, Stark AT: Breast cancer: cause and prevention. *Lancet* 346:883–887, 1995
3. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Colditz GA: A prospective study of recreational physical activity and breast cancer risk. *Arch Intern Med* 159:2290–2296, 1999
4. Kaaks R: Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control* 7:605–625, 1996
5. Plymate SR, Hoop RC, Jones RE, Matej LA: Regulation of sex hormone-binding globulin production by growth factors. *Metabolism* 39:967–970, 1990
6. Singh A, Hamilton-Fairley D, Koistinen R, Seppala M, James VH, Franks S, Reed MJ: Effect of insulin-like growth factor-type I (IGF-I) and insulin on the secretion of sex-hormone binding globulin and IGF-I binding protein (IBP-I) by human hepatoma cells. *J Endocrinol* 124:R1–R3, 1990
7. Rosner W: The functions of corticosteroid-binding globulin and sex-hormone-binding globulin: recent advances. *Endocr Rev* 11:80–91, 1990
8. Barker BE, Fanger H, Farnes P: Human mammary slices in organ culture. I. Methods of culture and preliminary observations on the effects of insulin. *Exp Cell Res* 35:437–448, 1964
9. Van der Burg BB, Rutterman GR, Blankenstein MA, de Laat SW, van Zoelen EJJ: Mitogenic stimulation of human breast cancer cells in a growth-defined medium: synergistic action of insulin and estrogen. *J Cell Physiol* 134:101–108, 1988
10. Conover CA, Lee PD, Kanaley JA, Clarkson JT, Jensen MD: Insulin regulation of insulin-like growth factor binding protein-1 in obese and nonobese humans. *J Clin Endocrinol Metab* 74:1355–1360, 1992
11. Lippman ME, Bolan G: Oestrogen responsive human breast cancer cells in long term tissue culture. *Nature* 256:592–594, 1975
12. Bruning PF, Bonfrèr JMG, van Noord PAH, Hart AAM, de Jong-Bakker M, Nooijen WJ: Insulin resistance and breast-cancer risk. *Int J Cancer* 52:511–516, 1992
13. Yang G, Lu G, Jin F, Dai Q, Best R, Shu XO, Chen JR, Pan XY, Shrubsole M, Zheng W: Population-based case-control study of blood C-peptide level and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 10:1207–1211, 2001
14. Del Giudice ME, Fantus IG, Ezzat S, McKeown-Eyssen G, Page D, Goodwin PJ: Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res Treat* 47:111–120, 1998
15. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
16. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
17. American Diabetes Association: Clinical Practice Recommendations 1998: screening for type 2 diabetes. *Diabetes Care* 21: S20–S22, 1998
18. Cox DR: Regression models and life tables. *J R Stat Soc* 32:187–220, 1972
19. Freund E: Zur Diagnose des Carcinoms. *Wiener Medizinische Bl* 8:268–269, 1885
20. Warburg O: *The Metabolism of Tumors*. London, Constable, 1930
21. Glicksman AS, Rawson RW: Diabetes and altered carbohydrate metabolism in patients with cancer. *Cancer* 9:1127, 1956
22. Muck BR, Trotnow S, Hommel G: Cancer of the breast, diabetes and pathological glucose tolerance. *Arch Gynäkol* 220:73–81, 1975
23. Muck BR, Trotnow S, Egger H, Hommel G: Altered carbohydrate metabolism in breast cancer and benign breast affections. *Arch Gynäkol* 221:83–91, 1976
24. de Waard F, Baanders-van Halewijn EA: A prospective study in general practice on breast-cancer risk in postmenopausal women. *Int J Cancer* 14:153–160, 1974
25. O'Mara BA, Byers T, Schoenfeld E: Diabetes mellitus and cancer risk: a multisite case-control study. *J Chronic Dis* 38:435–441, 1985
26. Unger C, Rageth JC, Wyss P, Spillmann M, Hochuli E: Mammakarzinom-Risikofaktoren. *Schweiz Med Wochenschr* 121: 30–36, 1991
27. Weiderpass E, Gridlkey G, Persson I, Nyren O, Ekbom A, Adami HO: Risk of endometrial and breast cancer in patients with diabetes mellitus. *Int J Cancer* 71: 360–363, 1971
28. Adami HO, Rimsten A: Prevalence of hypertension and diabetes in breast cancer: a case-control study in 179 patients and age-matched, non-hospitalized controls. *Clin Oncol* 4:243–249, 1978
29. Rgozzino M, Melton LJ, Chu CP, Palumbo PJ: Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. *J Chronic Dis* 35:13–19, 1982
30. Kopp S, Tanneberger S, Mohner M, Kieser R: Diabetes and breast cancer risk. *Int J Cancer* 46:751–752, 1990
31. Franceschi S, la Vecchia C, Negri E, Parazzini F, Boyle P: Breast cancer risk and history of selected medical conditions linked with female hormones. *Eur J Cancer* 26:781–785, 1990
32. Adami H-O, McLaughlin J, Ekbom A, Berne C, Silverman D, Hacker D, Persson I: Cancer risk in patients with diabetes mellitus. *Cancer Causes Control* 2:307–314, 1991
33. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P: A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 70:950–953, 1994
34. Hjalgrim H, Frisch M, Ekbom A, Kyvik

KO, Melbye M, Green A: Cancer and diabetes: a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med* 241:471–475, 1997
35. Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB: Breast cancer risk in young women and history of selected medical conditions. *Int J Epidemiol* 28: 816–823, 1999
36. Sellers TA, Sprafka JM, Gapstur SM, Rich SS, Potter JD, Ross JA, McGovern PG, Nelson CL, Folsom AR: Does body fat distribution promote familial aggregation of adult onset diabetes mellitus and postmenopausal breast cancer? *Epidemiology* 5:102–108, 1994
37. Michels KB, Greenland S, Rosner BA: Does body mass index adequately capture the relation of body composition and body size to health outcomes? *Am J Epidemiol* 47:167–172, 1998
38. Huang Z, Willett WC, Colditz GA, Hunter DJ, Manson JE, Rosner B, Speizer FE, Hankinson SE: Waist circumference: waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol* 150:1316–1324, 1999
39. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE, Willett WC: Dual effects of weight and weight gain on breast cancer risk. *JAMA* 278: 1407–1411, 1997
40. Gerber M: Re: Body size and breast cancer risk among women under age 45 years (Letter). *Am J Epidemiol* 145:669, 1997
41. Sellers TA, Anderson KE, Olson JE, Folsom AR: Family histories of diabetes mellitus and breast cancer and incidence of postmenopausal breast cancer. *Epidemiology* 9:102–105, 1998
42. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
43. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S. 1990–1998. *Diabetes Care* 23:1278–1283, 2000
44. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL: Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes* 22:39–47, 1998
45. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, the Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002