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Metabolic disorders and breast cancer risk (United States)

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Abstract

Objective: To clarify the hormonal context of breast cancer etiology we used data from a large, population-based case–control study to investigate the relationship between breast cancer risk and a history of diabetes mellitus, disorders associated with estrogen stimulation (uterine fibroids, endometriosis, gallstones), and disorders associated with androgen stimulation (acne, hirsutism, and polycystic ovaries).

Methods: Breast cancer patients between 50 and 75 years old were identified from state-wide tumor registries in Wisconsin, Massachusetts, and New Hampshire; controls were randomly selected from drivers' license lists (age less than 65) or Medicare enrollment files (age 65–74). Information on reproductive history, medical history, and personal habits was obtained by telephone interview. A total of 5659 cases and 5928 controls were interviewed and provided suitable data.

Results: There was no overall association between breast cancer risk and reported history of diabetes mellitus, endometriosis, uterine fibroids, gallstones, or cholecystectomy. However, the disorders with androgenic associations all conferred an increased risk: the overall odds ratio (OR) for a history of acne was 1.4 (95% CI 1.0–1.9), that for hirsutism was 1.2 (95% CI 0.81–1.8), and that for polycystic ovaries 1.6 (95% CI 0.8–3.2). Diabetes mellitus diagnosed before age 35 conferred an odds ratio of 0.52 (95% 0.25–1.1), while diabetes diagnosed at a later age was associated with an increased risk (OR = 1.2, 95% CI 1.0–1.4).

Conclusions: Androgen-related phenomena are likely to be important in the etiology of breast cancer.

Introduction

Steroid hormones are important in the etiology of breast cancer: reproductive events are risk factors for this cancer, and oophorectomy before natural menopause clearly reduces risk [1]. These relationships are often interpreted to imply that estrogens are the dominant hormone in breast cancer development, although other hormones have also been implicated, including progestins, androgens, insulin, and insulin-like growth factors [2]. However, the role of all these hormones in breast cancer etiology is not clear, in part because of difficulties characterizing long-term hormonal patterns in women.

Several non-malignant disorders in women are affected by a woman's hormonal status, and thus can be considered "biomarkers" of long-term hormonal tendencies. Estrogens are permissive for uterine fibroids and endometriosis, in the sense that these disorders seem to require some level of estrogen stimulation and often improve after menopause or after treatments that reduce steroid hormone stimulation [3, 4]. There is also evidence that estrogens exacerbate a tendency to form

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gallstones [5]. On the other hand, acne, polycystic ovaries, and hirsutism have all been associated with high circulating levels of androgens and with increased sensitivity of skin appendages to androgens [6, 7]. Finally, early-onset diabetes mellitus implies profoundly low insulin levels, while adult-onset diabetes is associated with hyperinsulinemia and insulin resistance in the early phases of the disease, and relative insulin deficiency thereafter [8].

To clarify the relationship between breast cancer risk and endogenous hormones we studied several "metabolic" disorders in a large, population-based breast cancer case–control study.

Materials and methods

This study was conducted in Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, and used state cancer registries to identify female residents newly diagnosed with invasive breast cancer during January 1990 through December 1994. We attempted to contact all cases, except those diagnosed more than 2 years prior to the registry report or those whose physicians refused permission for contact. Female controls were randomly selected in each state from two sources: drivers' license lists (women under age 65) and Medicare enrollment lists (women aged 65–74). Computer listings of eligible controls were obtained annually, and controls were chosen randomly to have an age distribution similar to that of the cases. Women without a listed telephone number, or who were unable to participate in an English-language interview, were ineligible. For comparability to controls we also excluded cases without a driver's license (if under age 65), not enrolled in Medicare (if age 65 or older), or without a listed telephone number.

After sending potential subjects a letter describing the study, we attempted a telephone interview requesting information regarding reproductive history, hormone use, personal habits, occupation, demographic data, medical history, and occurrence of breast cancer in first-degree relatives. Each subject was asked whether she had ever been told by a physician that she had diabetes mellitus, acne, gallstones, cholecystectomy, uterine fibroids, endometriosis, hirsutism, or polycystic ovaries. Because questions regarding cholecystectomy, acne, hirsutism, and polycystic ovary were not included in the questionnaire for all subjects, variable numbers are included in the analyses regarding these disorders, as indicated in Table 1.

All analyses were based on exposures that occurred prior to a reference date: for case subjects, the date of diagnosis; for controls, the date of interview minus the average time interval between case diagnosis and interview in the corresponding state. Subjects were deemed postmenopausal if they reported a natural menopause (no menstrual periods for at least 6 months), or a bilateral oophorectomy before the reference date. Women with a history of hysterectomy without bilateral oophorectomy were considered to be premenopausal if their reference age was in the first decile of age at natural menopause among controls (<42 years of age for current smokers and < 43 years of age for nonsmokers), to be postmenopausal if the reference age was in the highest decile for age at natural menopause among controls (>55 years of age), and otherwise to have an unknown age at menopause. Subjects who had started hormone replacement therapy before cessation of menses were deemed postmenopausal with unknown age of

Table 1. Characteristics of subjects

	Percent of subjects reporting disorder				Percent of subjects reporting disorder with onset < age 35			
	Cases		Controls		Cases		Controls	
	No.[a]	Percent	No.[a]	Percent	No.[b]	Percent	No.[b]	Percent
Diabetes	5564	8.4	5841	7.2	463	2.4	411	6.1
Gallstones	5556	21.4	5831	19.8	1135	21.9	1112	25.1
Cholecystectomy	3453	19.2	3883	17.7	630	20.0	669	19.1
Endometriosis	5550	4.3	5816	5.2	234	41.5	295	38.0
Uterine fibroids	5514	17.9	5797	16.9	957	20.5	955	21.4
Acne	4558	2.2	4750	1.6	97	88.7	77	87.0
Hirsutism	4557	1.3	4750	1.1	49	40.8	50	50.0
Polycystic ovaries	4548	0.5	4747	0.3	22	54.5	14	71.4

[a] Numbers of subjects providing information regarding history of the indicated disorder.
[b] Numbers of subjects reporting the indicated disorder and providing information regarding age of onset.

menopause. Interviewers remained unaware of the case–control status of the subjects until the end of the interview for 87% of cases and 96% of controls. Subjects judged to be unreliable by the interviewers were excluded from the analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs) computed with unconditional logistic regression were used as the measure of association. Covariates included were age (continuous term), state, menopausal status (two categories) age at first term birth (five categories), parity (three categories), lactation history (three categories), body mass index – BMI (four categories), hormone replacement therapy – HRT use (never, former current use), age of menopause, oral contraceptive – OC use (never, ever use), family history of breast cancer (present or absent), history of benign breast disease (present or absent), and alcohol intake (six categories). Subjects with missing values for any of the variables in a regression model could not be included in such analyses unless an ''unknown'' category was incorporated, which was done for all factors except parity. In subgroup and interaction analyses the ORs were computed within groups above and below the median BMI of controls, and for never and ever users of HRT. The significance of the interactions was assessed using likelihood ratio tests distinguishing models with, and without, product terms for the relevant variables. In some analyses ORs were computed separately for disease onset before age 35 and age 35 or later.

Results

A total of 6839 eligible cases were identified; physicians refused contact for 158 (2.3%), 293 (4.3%) were dead, 83 (1.2%) could not be contacted, 620 (9.1%) declined participation, and 5685 (83.0%) were interviewed. Of these, 5659 were considered reliable by the interviewer, and are included in the analysis. Of 7655 potential controls, 183 (2.4%) had died, 124 (1.6%) could not be found, 1397 (18.2%) declined participation, and 5951 (77.7%) were interviewed. Of these, 5928 were considered reliable and are included in the analysis. The mean age was 65.3 ± 8.0 for cases and 64.1 ± 8.0 for controls. Differences between cases and controls generally corresponded to known epidemiological associations (data not shown).

There was no overall association between breast cancer risk and history of uterine fibroids, gallstones, or cholecystectomy (Tables 1 and 2). Subjects who reported endometriosis had a modest reduction in risk (OR 0.8, 95% CI 0.7–1.0).

In contrast, subjects who reported acne, hirsutism, or polycystic ovary disease had increased relative risks (Table 2). The most commonly reported of these, acne, was associated with an OR of 1.4 (95% CI 1.0–1.9). Similarly increased relative risks were associated with hirsutism and polycystic ovary disease, although with the smaller numbers these estimates were compatible with chance effects. BMI and HRT use did not modify these associations (data not shown).

Table 2. Odds ratios of breast cancer for history of various metabolic disorders

	Number of controls/cases	Multivariate OR (95% CI)[a]	*p* for interaction[b]
Diabetes mellitus	468/422	1.1 (1.0–1.3)	0.02
Estrogen-related disorders			
Uterine fibroids	985/979	1.1 (1.0–1.2)	0.83
Endometriosis	237/303	0.8 (0.7–1.0)	0.31
Gallstones	1187/1155	1.0 (0.9–1.1)	0.43
Cholecystectomy	663/686	1.1 (1.0–1.2)	0.33
Androgen-related disorders			
Acne	100/78	1.4 (1.0–1.9)	0.47
Hirsutism	60/52	1.2 (0.8–1.8)	0.38
Polycystic ovaries	22/14	1.6 (0.8–3.2)	0.40

[a] Adjusted for age, state, age at first birth, BMI, family history of breast cancer, HRT use, menopausal status, age at menopause, OC use, parity, alcohol use.

[b] *p* for interaction between age groups.

There was no overall association between diabetes mellitus and breast cancer risk (OR 1.1, 95% CI 1.0–1.3). However, the OR for diabetes diagnosed before age 35 was 0.5 (95% CI 0.3–1.1), while a later onset conferred an OR of 1.2 (95% CI 1.0–1.4) (p for interaction $= 0.02$). BMI and HRT use did not modify this association (data not shown).

Discussion

In this large, population-based case–control study, a history of disorders associated with androgenic effects (hirsutism, polycystic ovaries, acne) was associated with an increased risk of breast cancer, but disorders usually considered estrogen-related (endometriosis, uterine fibroids, gallstones) were unassociated with risk. Early-onset diabetes conferred a reduced risk of breast cancer, while diabetes with later onset was associated with a modestly increased risk.

Endometriosis, uterine fibroids, and gallbladder disease are all disorders for which estrogens have a permissive or exacerbating role [3, 4, 9]. Endometriosis and fibroids tend to regress after menopause [3, 4], and gallbladder disease [10] and perhaps fibroids [11] are more common in obese women. Cigarette smoking, thought to have an ''anti-estrogenic effect,'' is inversely

associated with endometriosis and uterine fibroids [12]. Exogenous estrogens have a lithogenic effect on bile [5]. There are also suggestions that uterine fibroids, endometriosis, and gallbladder disease are all associated with an increased risk of endometrial cancer [13–16], a neoplasm with strong estrogenic determinants.

Although some previous studies have reported a modest relation between breast cancer risk and previous hospitalization for endometriosis [17, 18] or surgery for fibroids [18, 19], other studies have failed to find a substantial association with either condition [20–23]. There also seems to be no relation of gallbladder disease with breast cancer risk [20–22, 24–26], despite one report to the contrary [27]. These findings contrast with those for low bone density or hip fracture; both are linked to relative estrogen deficiency [28] and have been associated with a decreased risk of breast cancer [29–31].

There is emerging evidence that high levels of free estradiol are associated with an increased risk of postmenopausal breast cancer [32–34]. Nonetheless, the lack of clear association of breast cancer risk with estrogenic disorders suggests that estrogens may not dominate the etiology of breast cancer; their effect on breast cancer is certainly less marked than for endometrial cancer [35].

Women with acne, hirsutism, and polycystic ovaries all have higher levels of circulating androgens than women without these disorders [6, 7], and women with acne and hirsutism may also have enhanced dermal sensitivity to androgens [36, 37]. Embryologically, the breast is closely related to accessory skin structures such as sweat glands, so such local androgen sensitivity may be relevant to breast cancer [38]. Thus our epidemiological findings are consistent with data indicating an association between high serum androgen levels and breast cancer risk [32, 39–42].

There has been relatively little investigation of the implications of acne, hirsutism, and polycystic ovaries for breast cancer risk. In three studies, women with breast cancer had higher sebum secretion than controls [43–45]. Since sebum secretion is an important predisposing factor for acne, these findings suggest that acne could be a marker of increased breast cancer risk. One study reported increased risks in women with self-reported hirsutism, particularly among those who also reported adult acne [22]; another investigation reported higher breast cancer risks in subjects with acne [46]. Previous investigation of the association between polycystic ovaries and breast cancer risk has been conflicting, showing no association [23, 47], an inverse association (among women 20–54 years old) [48], or a direct relation (among postmenopausal women) [49].

Hyperinsulinemia is a risk factor for adult-onset diabetes mellitus, and some diabetics retain high insulin levels [8, 50]. Since insulin can have important effects on the levels and activity of insulin-like growth factors [51] and also affects sex hormone metabolism [2, 52], an association of clinical diabetes with risk of postmenopausal breast cancer is plausible. Indeed, diabetes is a clear risk factor for endometrial cancer [53, 54]. The association of hyperinsulinemia with hyperandrogenism in women, particularly in the polycystic ovary syndrome [2, 55, 56], is also relevant and suggests shared effects with sex hormones.

Studies that have investigated the overall relationship between diabetes mellitus and breast cancer have generally not found an association (summarized in ref. [23]). However, in agreement with our data, other studies have also reported lower relative risks with early-onset diabetes mellitus and higher relative risks with later-onset diabetes mellitus [23, 53, 54]. These data could reflect the relative insulin-deficiency of early-onset diabetics, and the high insulin levels of late-onset diabetics.

It is possible that the treatments for some of the disorders we studied affected the odds ratios we observed. Surgery is often used to treat uterine fibroids and gallstones, but such treatment is unlikely to affect breast cancer risk. However, hormonal treatments for endometriosis, hirsutism, and polycystic ovary disease have been used, and such therapy could affect breast cancer risk. Use of OCs to ameliorate acne is unlikely to have affected our findings since we adjusted for OC use. As noted, the treatment of diabetes with insulin could well affect the associations we observed.

The population-based design of our study, together with a high response rate, make major response biases unlikely. The lack of public discussion of the relationship between the disorders we studied and breast cancer also reduces the possibility of response bias. However, our questionnaire did not deal in detail with these medical problems, and the reported medical history we obtained may not be completely accurate. While it seems unlikely that subjects would overlook a serious diagnosis such as diabetes, some of the conditions (*e.g.* acne, hirsutism, gallstones) may have been unnoticed or forgotten. On the other hand, subjects may have misinterpreted their own medical history in reporting entities such as polycystic ovaries. The impact of this lack of accuracy on our relative risk estimates is not entirely predictable. If the misclassification was similar in cases and controls, the net effect would have been a conservative bias [57]. Some of the disorders we studied may be asymptomatic; if health-conscious controls were particularly likely to participate, then enhanced diagnosis among them could have introduced a downward bias in the relative risk estimates. In any case the over-

whelming majority of our subjects were postmenopausal, and the relationships we identified may not pertain to premenopausal breast cancer.

In summary, we found that breast cancer risk was associated with a history of androgen-related – but not estrogen-related – disorders. Early-onset diabetes was inversely related to risk, while later-onset diabetes conferred a small increase in risk. These data suggest a role for androgen-related phenomena and perhaps insulin-mediated processes in the etiology of breast cancer.

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