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Breast Cancer In Men: Risk Factors with Hormonal Implications

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Cases included in a population-based case-control study of breast cancer in men were recruited from 10 geographic areas of the United States from 1983 to 1986. Controls, matched to cases on age and geographic area, were selected by random digit dialing for men under age 65 years and from Health Care Financing Administration files for older men. Results are based on responses from 227 cases and 300 controls to questions asked in a standardized personal interview. An increased risk of breast cancer was most strongly associated with undescended testes and was also related to orchiectomy, orchitis, testicular injury, late puberty, and infertility; and a decreasing trend in risk was observed with an increasing number of children. Relative risk estimates were also elevated in relation to a history of high blood cholesterol, rapid weight gain, benign breast conditions, and possibly obesity. These findings suggest that breast cancer in men develops in response to androgen deficiency associated with testicular dysfunction and under conditions associated with excess estrogen. Risk was also found to be elevated in men with a history of amphetamine use, diabetes, and cigar smoking and reduced in men with prior head trauma. *Am J Epidemiol* 1992;135:734–48.

breast neoplasms; cryptorchism; testicular diseases

Although breast cancer rarely occurs in men, the histologic, clinical, and epidemiologic similarities between breast cancer in men and in women strongly suggest that this disease in the two sexes is a single etiologic entity. Most breast cancers in both sexes are ductal carcinomas (1, 2), and individual tumors arising in men are histologically indistinguishable from those that develop in women. Like breast cancers in women, many of those in men have estrogen and progesterone receptors (3), which are predictive of response to hormone therapy. In both sexes, rates of breast cancer are higher in Jews than in non-Jews (4–6) and show similar variations among various countries (7, 8). In addition, as with breast cancer in women, risk of this disease in men has been

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Abbreviation: CI, confidence interval.

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associated with a family history of breast cancer in both male (9–13) and female (12–16) first-degree relatives, exposure of the chest to ionizing radiation (13–15, 17, 18), a history of benign breast disease (6, 13–15, 19, 20), and possibly obesity (15).

Additional risk and protective factors for breast cancer in women strongly implicate an etiologic role for endogenous gonadal or pituitary hormones. Risk is increased in nulliparous women and in those with an early age of menarche and late ages at menopause and first-term pregnancy (21), and risk is decreased in women with a premenopausal oophorectomy and possibly in women with high parity and prolonged lactation (21). A similar or analogous role for endogenous hormones in the etiology of breast cancer in men is suggested by observed relations with testicular atrophy associated with Klinefelter's syndrome (22–25), orchitis (6, 13, 26), and testicular trauma (6, 14), as well as by associations with liver disease (15, 16, 27).

Because breast cancer in men is rare, previous investigations in males have been of the descriptive type (based only on incidence and mortality rates) or were individual clinical reports, uncontrolled case series, or case-control studies of relatively small size, and in some instances were based only on reviews of existing records. The putative risk factors for breast cancer in men have therefore not been firmly established. To our knowledge, this investigation is the largest case-control study of breast cancer in men that has been conducted to date. It was initiated both to confirm or refute results of prior investigations and to identify new risk factors that may provide clues to the etiology of breast cancer in either sex.

This paper is a report of results from this study that provide further insights into possible hormonal factors of etiologic importance. Separate communications have dealt with the etiologic roles of heredity (28) and nonionizing radiation (29).

MATERIALS AND METHODS

Cases eligible for inclusion in this study were all noninstitutionalized male residents of 10 geographic areas covered by population-based registries of the Surveillance, Epidemiology, and End Results program of the United States National Cancer Institute, who were diagnosed as having a primary breast carcinoma from October 1983 through September 1986. The 10 geographic areas constituted approximately 15 percent of the US population and included the states of Connecticut, Hawaii, Iowa, New Jersey, New Mexico, and Utah and the metropolitan areas and nearby counties surrounding San Francisco, California; Detroit, Michigan; Atlanta, Georgia; and Seattle, Washington. Cases were identified through the reporting system of each cancer registry.

For each interviewed case, a search was alternately made for one or two noninstitutionalized controls (30) to maintain an overall control-to-case ratio of 1.5:1. Controls were matched to cases on age (same 5-year age group) and geographic area. Controls for men under age 65 years were selected by random digit dialing. Primary sampling units were generated from the area codes and three-digit prefixes used in each area. Four-digit suffixes were randomly selected and randomly assigned to primary sampling units. Each resultant telephone number was called up to six times, including two daytime, two evening, and two weekend calls, to obtain a household census and identify men eligible as controls. Controls for men age 65 years and older were selected from randomly generated samples of individuals in each area supplied by the Health Care Financing Administration.

Interviews were conducted with all subjects in their homes by specially trained interviewers who were not told whether each man was a case or a control. Responses were recorded on standardized forms which were forwarded to the coordinating center in Seattle for editing, data processing, and analysis. Information ascertained included indicators of socioeconomic status, history of medical conditions possibly indicative of hormonal aberrations (e.g., liver disease, testicular pathology, indices of fertility and infertility, delayed onset of puberty, prostatic and thyroid diseases, diabetes, head injury, and benign breast conditions), other chronic

medical conditions, body size, periods of rapid weight gain, exposure to exogenous hormones and gynecomastogenic drugs, use of alcohol and tobacco, the two occupations held the longest, exposure to ionizing radiation, and family history of breast and other neoplasms. Dietary habits were also obtained by means of a self-administered food frequency questionnaire.

Information was also abstracted from medical records on selected clinical characteristics of the cases and their tumors, and histologic slides were sent to a single reference pathologist for diagnostic confirmation and uniform histologic classification (31).

Conditional logistic regression techniques (32) were used to calculate odds ratios, as estimates of relative risks, and their 95 percent confidence intervals. The strata utilized consisted of all subjects in the same 5-year age group and geographic area, rather than the original matched pairs or triplets. To assess confounding effects, we estimated relative risks with and without the inclusion of potential confounders in multivariate logistic models. All estimates presented are controlled for age and geographic area.

RESULTS

Response rates

Of the 320 cases that were initially identified as eligible for this study, 240 (75.0 percent) were interviewed (84 percent of those under age 65 years and 62 percent of those who were older). Of these, three were later found not to have primary mammary carcinomas, one was of unknown race, and nine had no corresponding controls, leaving 227 cases for inclusion in the analyses. Of 259 controls selected from Health Care Financing Administration roles, 160 (61.8 percent) were interviewed. A household census was obtained for 65.3 percent of the residences identified by random digit dialing, and 166 (69.2 percent) of the 240 eligible controls in these dwellings were interviewed, giving an estimated overall response rate of 45.2 percent ($0.653 \times 0.692 \times 100$). Five controls of Asian or unknown race (there were no Asian cases) and 21 controls who were matched to a case who was eliminated from the study were excluded, leaving 300 controls in the analyses.

Fifty-six cases came from New Jersey, and 42, 36, 28, 23, 17, 12, 8, 3, and 2 came from Connecticut; Detroit, Michigan; Seattle, Washington; San Francisco, California; Iowa; Atlanta, Georgia; New Mexico; Hawaii; and Utah, respectively. The median age of the cases was 63 years, and only 27 (11.9 percent) were under age 50. A total of 198 cases were white, 25 were black, and four were of other races. Cases and controls were comparable with respect to age, race, and geographic area of residence.

Histologic slides for review by the reference pathologist were obtained from the tumors of 211 of the cases. Of these, 158 (74.9 percent) were invasive ductal carcinomas, and the remaining 53 were one of nine additional histologic types of carcinomas.

Socioeconomic and demographic factors

Risk of breast cancer was not found to be strongly or significantly related to years of education or to an index of socioeconomic status based on occupation (33), although relative risk estimates were lowest for men in the lowest occupational quartile and highest for men with a postgraduate degree.

Cases and controls did not vary significantly by religion, except for a disproportionate number of Jews among the cases (10.6 percent vs. 5.3 percent of controls). Risk in Jews relative to non-Jews was estimated to be 2.1 (95 percent confidence interval (CI) 1.1–4.2), and this value was not altered by controlling for education, number of children, marital status, relative age at voice change, weight for height, exposure to ionizing radiation, or testicular abnormality.

Relative to currently married men, the risk in men who had never been married (based on 17 cases and nine controls) was estimated to be 2.8 (95 percent CI 1.1–6.9). However, more single than married cases (but not more single than married controls) gave a history of several other risk factors, including multiple chest radiographic ex-

aminations, a weight gain of more that 50 pounds (22.70 kg) during a 6-month period, and a history of both undescended testes and orchiectomy, which at least in part explains the observed increase in risk in single men.

Testicular abnormalities

As shown in table 1, risk of breast cancer was significantly elevated in men with a history of undescended testes. Two of the seven cases with this condition, but not the single control, had bilateral cryptorchism. Three of the cases had their condition surgically corrected, at ages 10, 16, and 41 years. Only one of the seven cases gave a history of infertility; none had a delayed puberty, had never married, or was unusually tall. Buccal smears were not taken from these individuals, and height was considered as a crude indicator of the possibility of Klinefelter's syndrome. Risk of breast cancer was also increased, although not significantly so, in men with a history of congenital inguinal hernia. Although none of the men with this condition reported that they had an undescended testis, varying degrees of cryptorchism are frequently observed in conjunction with congenital hernia, and one man with a hernia reported removal of a testicle at the time of his hernia repair.

TABLE 1. Relative risk estimates of breast cancer in men with various types of testicular and inguinal abnormalities, 10 United States populations, 1983–1986

Condition*	No. with condition		Relative risk estimate	95% CI†
	Cases	Controls		
None	217	295	1.0	Reference
Undescended testis	7	1	11.6	1.4–95.2
Congenital inguinal hernia	6	4	2.3	0.6–8.1
Removal of one or both testes	4	3	2.1	0.4–9.9
Injury to testis	7	6	1.6	0.5–5.0
Mumps infection of testis	6	10	0.7	0.2–2.0
Other infection of testis	5	4	2.0	0.5–7.7

* These conditions are not mutually exclusive.
† CI, confidence interval.

Removal of a testis was also weakly associated with risk of breast cancer (table 1). However, two of the four cases, but none of the three controls who had had their testes removed had this procedure because of a cryptorchid condition, and no increase in risk (estimated relative risk (RR) = 1.0; 95 percent CI 0.2–6.3) was observed for men with orchiectomy for other reasons (based on two cases and three controls). On the other hand, the cases tended to have had their testes removed at an earlier age than did the controls, regardless of the reason. The procedure was performed at ages of less than 1 and of 16 years on the cases with cryptorchism and at 17 and 32 years on the cases with other indications; orchiectomies were performed on the controls at ages 28, 41, and 59 years.

Moderately elevated relative risk estimates, with 95 percent confidence intervals that include one, were also observed in men with testicular injury and infections of the testes other than mumps. The men with injuries were not those with orchiectomies or cryptorchism, and those with testicular infections did not have a history of mumps. No increase in risk was observed in relation to self-reported mumps orchitis. However, as shown in table 2, among men who were infected after age 14 years, risk of breast cancer was found to increase with the age at which a man reported having had mumps. Although the observed trend with age at infection could have occurred by chance (p value of test for trend = 0.19), it could also indicate an association with either unrecog-

TABLE 2. Relative risk estimates of breast cancer in men by age at mumps infection, 10 United States populations, 1983–1986

Age at mumps infection (years)	No. of subjects*		Relative risk estimate†	95% CI‡
	Cases	Controls		
No mumps	117	158	1.0	Reference
≤14	70	103	0.9	0.6–1.4
15–19	11	12	1.6	0.6–3.9
≥20	10	5	2.5	0.8–7.6

* Excluding 19 cases and 22 controls with unknown history of mumps.
† p value of test for trend = 0.19.
‡ CI, confidence interval.

nized or unreported mumps orchitis, since the incidence of orchitis in persons with mumps increases after puberty (34).

No associations were observed between risk of breast cancer and such nontesticular inguinal-genital conditions as hydrocele (five cases and eight controls), varicocele (five cases and eight controls), and hypospadias (one case and two controls), suggesting that the above associations (table 1) are probably not a result of selective recall by the cases. An association was also not observed with vasectomy. Fourteen (6.2 percent) of the cases and 26 (8.7 percent) of the controls had had this procedure.

Using the same scheme that was developed for a study of testicular cancer (35), we classified all occupations, without knowledge of the subjects' status as a case or control, as likely, possibly, or unlikely to result in exposure of the testicular area to heat. No evidence of an increase in risk of breast cancer was found in men whose longest or second longest job was in either the likely or the possibly exposed category.

To estimate the onset of puberty, we asked all subjects to indicate whether they stopped growing, began shaving, and noted a change in their voice, earlier, about the same time as, or later than their childhood peers. As shown in table 3, there is weak evidence of an association between risk of breast cancer and time of puberty as measured by two of these three indices. Men with later puberty had not had undescended testes.

Infertility and fertility

As one measure of infertility, the men were asked whether they and their wife had failed to conceive a child after attempting to do so for 2 or more years. They were also asked whether this condition was attributable to the man or to his wife. As shown in table 4, relative risk estimates are greater than unity if the infertility involved the man or was of unknown cause, but not if it was due to only the wife. Since men may be more reluctant than women either to admit to an infertility problem or to be evaluated for one, the infertility of unknown cause may reflect a male etiology. A combined relative risk estimate is therefore provided for infertility of male, both male and female, and unknown cause. The 95 percent confidence intervals of all estimates in the table include one. Time from first marriage to first pregnancy was used as a crude, inde-

TABLE 3. Relative risk estimates of breast cancer in men who reached developmental landmarks, in relation to the time of their peers, 10 United States populations, 1983–1986

Time developmental landmark was reached in relation to peers	No. of subjects		Relative risk estimate	95% CI*
	Cases	Controls		
Stopped growing†				
Earlier	21	39	1.0	Reference
Same	162	208	1.6‡	0.9–2.9
Later	37	46	1.5‡	0.7–3.1
Voice changed§				
Earlier	18	33	1.0	Reference
Same	160	208	1.4‖	0.7–2.6
Later	23	23	1.8‖	0.8–4.2
Began shaving regularly¶				
Earlier	24	32	1.0	Reference
Same	137	184	0.9	0.5–1.6
Later	57	75	0.8	0.4–1.6

* CI, confidence interval.
† Seven cases and seven controls with unknown time growth stopped excluded.
‡ Adjusted for time voice changed.
§ Two cases and four controls who claimed their voice did not change and 24 cases and 32 controls with unknown time of voice change excluded.
‖ Adjusted for time stopped growing.
¶ Nine cases and nine controls with unknown time when shaving began excluded.

TABLE 4. Relative risk estimates of breast cancer in married men with a history of infertility, 10 United States populations, 1983–1986

Type of infertility	No. of subjects*		Relative risk estimate	95% CI†
	Cases	Controls		
None	190	269	1.0	Reference
Wife only	8	14	0.9	0.3–2.1
Husband or both	7	6	1.7	0.5–5.3
Unknown	5	2	4.3	0.8–22.9
Husband, both, or unknown	12	8	2.3	0.9–6.0

* Excluding 17 cases and nine controls who had never married.
† CI, confidence interval.

pendent indicator of infertility. Although a significant trend of increasing risk with years to first conception was initially found (p value of test for trend = 0.049), the strength of this trend was reduced (p = 0.20) after controlling for number of pregnancies. Relative risks were estimated to be 1.0 (reference category), 1.2 (95 percent CI 0.7–1.9), 2.1 (95 percent CI 1.1–3.7), and 0.9 (95 percent CI 0.4–2.1) in men whose wives conceived less than 2, 2–3, 4–8, and 9 or more years after marriage, respectively. No associations were found between risk of breast cancer and having been married to a woman at the time she had a stillbirth or miscarriage.

Table 5 shows a strong trend of decreasing risk with the number of live children that a man had fathered. After this variable and interval from marriage to first pregnancy were controlled for, no significant trend in risk was observed in relation to the age at which a man fathered his first child. Relative risks were estimated to be 1.0 (reference category), 0.7 (95 percent CI 0.4–1.2), 0.8 (95 percent CI 0.4–1.5), and 1.3 (95 percent CI 0.6-2.6) in men who were less than 25, 25–27, 28–31, and 32 years or older when their first child was conceived.

Prior neoplasms and exogenous hormones

Twenty-six (11.5 percent) of the cases and 32 (10.6 percent) of the controls had a history of cancer. The types of neoplasms were also similar in cases and controls. One case and four controls had been diagnosed with prostate cancer, giving an estimated relative risk of 0.4 (95 percent CI 0.04-3.4). None of these men, or any other cases in the study, had been treated with estrogens; only one control in the study had received estrogens. Three cases and six controls had received androgens, giving an estimated relative risk of 0.7 (95 percent CI 0.2–2.8). One of the exposed controls, but none of the exposed cases, had been treated with androgens for undescended testis. Similar proportions of cases and controls had ever received oral, parenteral, or topical cortisone (31.6 vs. 28.1 percent) and had worked at a job with a probable exposure to hormones (7.9 vs. 6.3 percent).

TABLE 5. Relative risk estimates of breast cancer in married men by number of children that they fathered who were born alive, 10 United States populations, 1983–1986

No. of children born alive	No. of subjects*		Relative risk estimate†	95% CI‡
	Cases	Controls		
None	38	31	1.0	Reference
1	34	38	0.8	0.4–1.6
2–3	105	143	0.6	0.4–1.1
4	17	35	0.3	0.1–0.7
≥5	16	44	0.3	0.1–0.7

* Excluding 17 cases and nine controls who had never married.
† p value of test for trend = 0.002.
‡ CI, confidence interval.

Liver diseases and alcoholism

Nearly equal proportions of cases and controls gave a history of hepatic cirrhosis (0.4 vs. 0.7 percent), hepatitis (3.1 vs. 2.3 percent), jaundice (3.5 vs. 4.0 percent), and other liver conditions (0.9 vs. 0.7 percent).

A variety of indices of alcohol intake were developed, and none were associated with risk of breast cancer, including total lifetime number of drinks, the number of drinks per week that the man currently drank, the number of drinks per week during the period of his life when he drank the most, the number of drinks per week when he first started drinking, and the age at which he first started drinking.

Head injury

Table 6 shows that risk of breast cancer was significantly lower in men with a history of hospitalization for a head injury, particularly if the injury was of sufficient severity to require hospitalization for more than 1 day and if it was incurred after age 29 years. The types and causes of the head injuries were similar in the cases and the controls, but information on these features of the trauma was imprecise. The observed association was not altered by controlling for years of education.

Other diseases and conditions

As shown in table 7, a small and not statistically significant increase in risk of breast cancer was observed in men with a history of diabetes, and risk was found to increase with duration of the diabetic condition. The estimates of the relative risks were not altered by controlling for quartile of weight for height at age 35 years or when weighed least after attaining full height. All diabetics except one of the controls had non-insulin-dependent disease.

Ten cases and eight controls gave a history of prior thyroid disease, resulting in an estimated relative risk of 1.6 (95 percent CI 0.6–4.2). Two cases and one control specifically reported hyperthyroidism, three cases and three controls reported hypothyroidism, and the remaining subjects with thyroid disease reported a variety of ill-defined conditions. Affected cases and controls did not differ significantly by the year in which their thyroid condition was diagnosed or treated, or by type of treatment. Four cases and one control reported being treated with thyroid hormone for their thyroid disease.

Thirty-one cases and 16 controls gave a history of elevated blood cholesterol, giving an estimated relative risk of breast cancer of 2.9 (95 percent CI 1.5–5.6). This value was not appreciably altered by controlling for diabetes, hypertension, or weight for height at age 35 years or when a man weighed the least. A history of elevated levels of other blood lipids was elicited from nearly equal proportions of cases (3.1 percent) and controls (3.4 percent).

After controlling for history of elevated cholesterol, a relative risk of 1.0 (95 percent CI 0.7–1.5) was estimated for men with a history of high blood pressure. The estimates for hypertensive men who were treated and those who were not treated for hypertension were 1.2 (95 percent CI 0.8–1.8) and 0.8 (95 percent CI 0.4–1.4), respectively. The slight

TABLE 6. Relative risk estimates of breast cancer in men with a history of head injuries, 10 United States populations, 1983–1986

Variable	Level	No. of subjects		Relative risk estimate	95% CI*
		Cases	Controls		
Head injury	None	214	268	1.0	Reference
	Any	13	32	0.4	0.2–0.8
Age at head injury (years)	<11	2	4	0.5	0.1–2.8
	11–29	9	12	0.6	0.3–1.6
	≥30	2	16	0.2	0.03–0.7
Days in hospital	1	5	7	0.7	0.2–2.5
	2–7	4	14	0.3	0.1–0.9
	≥8	4	11	0.4	0.1–1.2

* CI, confidence interval.

TABLE 7. Relative risk estimates of breast cancer in men with diabetes, 10 United States populations, 1983–1986

Years since diabetes diagnosed	No. of subjects*		Relative risk estimate†	95% CI‡
	Cases	Controls		
None	199	276	1.0	Reference
Ever	28	23	1.6	0.9–2.8
1–5	10	11	1.2	0.5–2.8
6–10	7	5	1.9	0.6–6.2
≥11	10	5	2.5	0.8–7.6

* One case and two controls with unknown date of onset of diabetes were excluded from analyses by years since diagnosis. One control with unknown history of diabetes was excluded.
† p value of test for trend = 0.05 if nondiabetics were included and 0.67 if nondiabetics were excluded.
‡ CI, confidence interval.

TABLE 8. Relative risk estimates of breast cancer in men in four quartiles of weight for height at various times in life, 10 United States populations, 1983–1986

Time in life	Quartile of weight for height*			
	1 (lowest)	2	3	4 (highest)
At age 35 years	1.0	1.1	1.2	1.2
At usual weight	1.0	1.3	1.0	1.4
When weighed least	1.0	1.6	1.4	1.6
When weighed most	1.0	1.1	1.0	1.4

* Weight (kg)/height $(m)^2$; quartiles based on distribution of controls. 95% confidence interval of all estimates include one.

TABLE 9. Relative risk estimates of breast cancer in men who gained 30 or more pounds (13.62 kg) in 6 months, 10 United States populations, 1983–1986

Weight gain (pounds)*	No. of subjects		Relative risk estimate	95% CI†
	Cases	Controls		
None	213	288	1.0	Reference
>30	14	12	1.8	0.8–4.1
30	3	6	0.8	0.2–3.1
31–49	4	4	1.8	0.4–8.4
≥50	7	2	5.0	1.0–24.4

* Metric equivalents: >30 pounds, >13.62 kg; 30 pounds, 13.62 kg; 31–49 pounds; 14.07–22.25 kg; ≥50 pounds, ≥22.70 kg.

increase in estimated relative risk among treated men was not restricted to men who received antihypertensive drugs that have been reported to be gynecomastogenic.

Nearly equal proportions of cases and controls gave a history of acne (8.0 vs. 8.3 percent), varicose veins (6.2 vs. 8.7 percent), and hot flushes or night sweats (13.7 vs. 13.0 percent). Only one case and one control had a history of osteoporosis.

Body size and weight gain

No trend of increasing risk with height was observed, although compared with men in the lowest quartile of height (based on the distribution of the controls) those in the highest quartile (over 1.83 m) had an estimated relative risk of 1.3 (95 percent CI 0.7–2.3). Table 8 similarly shows no trends of increasing risk with weight for height at age 35 years, at the man's usual weight, or when he weighed the most or least. However, the relative risk estimates tended to be highest in the upper quartiles and lowest in each first quartile of height for weight. Similar, but even less striking, findings were observed for weight uncorrected for height.

As shown in table 9, a relative risk of 1.8 was estimated in men who reported gaining over 30 pounds (13.62 kg) during a 6-month period. Risk also was seen to increase with the number of pounds gained, although this trend is based on small numbers of individuals and could readily have occurred by chance. Only the estimated relative risk in men who gained over 50 pounds (22.70 kg) was of borderline statistical significance.

Gynecomastogenic drugs

A variety of drugs have been reported to cause gynecomastia (36, 37). The possible associations between those used by men in this study and breast cancer are shown in table 10. Cimetidine, aldactone, spirolactone, and possibly the cardiac glycosides (Lanoxin and Digoxin (Burroughs Wellcome Co., Research Triangle Park, NC in this study) are thought to cause gynecomastia by competing with endogenous dihydrotestosterone for intracellular receptors (37). The remaining drugs shown in the table are either neurotransmitter agonists or antagonists; their most likely gynecomastogenic mechanism is stimulation of prolactin production, but other mechanisms may also be involved (37). Drugs in no specific mode of action category are consistently associated

TABLE 10. Relative risk estimates of breast cancer in men who used various gynecomastogenic drugs, 10 United States populations, 1983–1986

Drug	No. of exposed subjects		Relative risk estimate	95% CI*
	Cases	Controls		
Amphetamines				
Any type	14	7	2.9	1.1–7.9
Amphetamine (Benzedrine)†	7	2	4.4	0.9–21.7
Dextroamphetamine (Dexadrin)†	6	4	2.0	0.6–7.2
Phenylpropanolamine (Dexatrim)†	3	1	5.5	0.5–58.0
Tranquilizers and antidepressants				
Any tranquilizer	50	62	1.1	0.7–1.7
Any antidepressant	9	20	0.6	0.3–1.5
Benzodiazepines	34	41	1.2	0.7–2.0
Diazepan (Valium)†	27	33	1.0	0.6–2.0
Meprobamate	4	4	1.1	0.2–4.5
Phenothiazines	3	2	2.3	0.4–14.4
Tricyclic antidepressants	3	9	0.4	0.1–1.6
Medications for ulcers				
Cimetidine (Tagament)†	9	14	0.9	0.4–2.1
Antihypertensive agents				
Aldactone or spirolactone	3	1	3.4	0.3–33.4
Sympatholytic agents	13	16	1.2	0.6–2.6
Clonidine	3	4	1.0	0.2–4.5
Methyldopa (Aldomet)†	10	13	1.2	0.5–2.8
Respirine				
Alone	0	6	0.0	
Alone or in combination	13	19	0.9	0.4–1.9
Cardiac glycosides	1	1	1.1	0.1–18.9

* CI, confidence interval.
† Benzedrine: Smith, Kline, and French, Philadelphia, Pennsylvania; Dexadrin: SmithKline Beecham, Pittsburgh, Pennsylvania; Dexatrim: Thompson Medical Co., Inc., New York, New York; Valium: Roche Laboratories, Nutley, New Jersey; Tagamet: SmithKline Beecham; Aldomet: Merck, Sharp, & Dohme, West Point, Pennsylvania.

with an increased risk of breast cancer. However, a significantly increased risk was observed in men who took amphetamines, and this association is evident for all three drugs in this category. Most of these drugs were taken for weight reduction, but the relative risk estimates shown in the table were not altered by controlling for any of the indices of obesity considered (table 8).

Isoniazid and the cardiac glycosides may cause gynecomastia by the refeeding mechanism (37), but neither of these drug types were used by sufficient numbers of study subjects for meaningful analysis.

Gynecomastia has also been reported in users of marijuana, but use of this drug was not reported by a higher proportion of cases (3.1 percent) than controls (4.7 percent).

Benign breast conditions

Forty-four cases and 25 controls gave a history of one or more benign breast conditions, resulting in an estimated relative risk of 2.5 (95 percent CI 1.5–4.3). Table 11 shows relative risk estimates of breast cancer to be significantly increased in men with previous breast swelling, nipple discharge, and cysts. Risk in relation to swelling was only elevated in men whose swelling occurred at least 20 years previously, and the five cases with nipple discharge reported that

TABLE 11. Relative risk estimates of breast cancer in men with a history of benign breast conditions, 10 United States populations, 1983–1986

Breast condition	Years since condition	No. of subjects*		Relative risk estimate	95% CI†
		Cases	Controls		
None		183	274	1.0	Reference
Swelling‡	<20	4	6	0.9	0.3–3.3
	≥20	11	3	5.4	1.4–20.2
	Total	16§	9	2.5	1.0–5.8
Discharge	Total	5	0	∞	1.6–
Cyst‖	<20	8	2	5.5	1.1–26.4
	≥20	3	2	1.4	0.2–8.9
	Total	11	4	3.3	1.0–10.8
Injury	<20	3	2	2.5	0.4–15.1
	≥20	4	3	1.5	0.3–6.9
	Total	8§	5	2.2	0.7–6.9

* Excludes men with breast conditions other than those shown in the table.
† CI, confidence interval.
‡ Includes swelling with or without cyst.
§ Includes one case with unknown years since breast condition.
‖ Includes cysts with or without swelling.

their problem occurred between 7 and 50 years prior to diagnosis of their carcinoma. On the other hand, relative risk estimates were greater in men with a breast cyst or injury within the previous 20 years than in men with these conditions in the more distant past. Seven of the eight cases, but neither of the two controls, with breast cysts within the previous 20 years had had their condition within the past 10 years; and all three cases, but neither of the two controls, with a breast injury in the previous 20 years had experienced their trauma within the previous 5 years.

Tobacco

Relative risks of breast cancer were estimated to be 1.7 (95 percent CI 1.1–2.6), 1.3 (95 percent CI 0.8–1.9), 0.9 (95 percent CI 0.6–1.3), and 1.0 (95 percent CI 0.5–2.0) in men who had smoked cigars, pipes, and cigarettes for over 6 months and who had ever used smokeless tobacco, respectively. No trends of increasing risk with amounts consumed per year or per lifetime or of decreasing risks with cessation of exposure were observed in relation to use of pipes, cigarettes, or smokeless tobacco. A trend of increasing risk with amount smoked was observed in cigar smokers, but no decline in risk with cessation of use was found. This association was not altered by adjustment for use of other tobacco products, history of elevated blood cholesterol, education, marital status, age at voice change relative to peers, religion, weight for height, weight gain of over 30 pounds (13.62 kg) in 6 months, number of children, radiation exposure of the chest, or testicular pathology. The relative risk in men who smoked cigars exclusively was estimated to be 2.5 (95 percent CI 0.7–8.8), based on 10 exposed cases and six exposed controls.

DISCUSSION

This study has a number of strengths. It has greater statistical power than previous case-control studies (6, 13–16), which included from 52 (6) to 95 (14) cases. Only one prior case-control study (15) was population based with controls selected from the same population from which the cases arose; others were either population- (14) or hospital- (6, 13, 16) based investigations that used hospitalized men with other cancers (13, 14, 16) or nonneoplastic diseases (6) as

controls. In two of the previous studies (14, 16), information was obtained only from medical records.

We also have evidence that information obtained from the study subjects was of reasonable reliability and of comparable quality in cases and controls. All interviewers were asked to judge the cooperativeness of the subject and the reliability of the information obtained. Cooperativeness was recorded as "very good" for 78.0 percent of the cases and 83.1 percent of the controls and as "good" for 18.0 percent of the cases and 14.9 percent of the controls, and the information was judged to be "very reliable" and "generally reliable" from 64.3 and 33.5 percent of the respective cases and from 65.6 and 32.7 percent of the respective controls. In addition, after the interviews were completed, 87 cases and 86 controls were contacted by telephone and asked nine questions from the questionnaire. Levels of concordance were similar for cases and controls, above 80 percent for seven of the nine questions, and ranged among these questions from 65.1 to 98.8 percent. In addition, similar proportions of subjects in each group were interviewed by men (28.6 vs. 25.6 percent), and at home (83.6 vs. 82.4 percent), at work (6.7 vs. 10.6 percent), or elsewhere.

Although bias may result from more accurate recall of past events by cases than by controls, particularly when controls are not diseased individuals, there is evidence that this is not a likely explanation for the findings in this study. Risk of breast cancer was found to be associated with testicular conditions, but not with nontesticular inguinal or genital problems, which one would expect to be equally well remembered. In addition, the associations between risk of breast cancer and both number of children and age at mumps infection are biologically consistent with the findings based on direct questions regarding testicular pathology. Furthermore, since little is generally known about the etiology of breast cancer in men, it is unlikely that the cases were more aware than the controls of the possible role of any of the risk factors observed in this study.

The major weakness of this study is the low response rate among the controls. This situation would yield spurious results if respondents and nonrespondents differed with regard to one or more of the variables contributing to the positive findings. Although we have no evidence that this did or did not occur, it seems unlikely that factors related to testicular abnormalities and function would be associated with determinants of participation.

The major findings in this study suggest a protective role against breast cancer for adequate testicular function and an etiologic role for testicular dysfunction. Since the main source of androgens in men is the testis, these findings suggest that breast cancer may develop in men in response to an androgen deficiency. Other observations from this study, although based on small numbers and not statistically significant, are consistent with this interpretation. Estimated relative risks were less than unity in men with prostate cancer, which has been associated with elevated levels of endogenous androgens in some studies (38), and in those who received exogenous androgens. In addition, studies by others have found evidence for an increased risk in relation to testicular pathology (6, 13–15) and hypogonadism of Klinefelter syndrome (22, 39), and a reduced risk associated with prostatic disease (6).

Relative risk estimates were somewhat greater than one in men with conditions that have been associated with increased estrogen production such as obesity (40), elevated cholesterol (41), rapid weight gain (20), and breast swelling (20). Studies by others have also provided results supportive of these observations, including associations between breast cancer in men and prior breast diseases (6, 13–15, 19), weight at age 30 years (15), hyperthyroidism (16), exposure to exogenous estrogens (14), alcoholism (14), and liver disease (15, 16, 27).

Although the associations described in the preceding two paragraphs have not been observed in all case-control studies, and in many instances are not statistically significant at the conventional probability level of 0.05, this lack of consistency is readily ex-

plainable on the basis of small sample size and low statistical power. None of the prior studies produced results that are inconsistent with the hypothesis that estrogens and androgens are of etiologic and protective importance, respectively. Three case reports of breast cancer developing in transsexual individuals who were castrated and given high doses of exogenous estrogens (42, 43) provide additional anecdotal, but dramatic, support for this hypothesis.

Results of studies of endogenous hormones in men with breast cancer are also generally consistent with this hypothesis. Urinary estrogen excretion (44) and serum estradiol levels (45–47) have been found to be higher in men with than in those without breast cancer in some small clinical investigations, but not in a larger population-based case-control study (15). However, serum estrogen levels in the latter study were correlated with body weight in the controls, and obesity at age 30 years was found to be a risk factor, suggesting an etiologic role for elevated estrogens early in life.

In some previous studies, serum testosterone levels have actually been found to be higher in cases than in controls (15, 45–47), but the difference in each study was small and could readily have been due to chance. In addition, estrogens in men are derived from conversion of testosterone (of testicular origin) to estradiol and of androstenedione (of adrenal origin) to estrone in adipose tissue, and normal androgen levels could result in enhanced estrogen production in the presence of obesity. Altered estrogen metabolism, as reported in one early study of men with breast cancer (48), although not confirmed by a subsequent investigation (49), would also provide a mechanism for an enhanced risk in the presence of normal androgen levels. Further studies of this possibility are warranted. None of these endocrinologic studies included cases with testicular abnormalities, and it has been well documented that cases with various testicular lesions excrete low levels of androgens (26, 50, 51).

In a recent review, Zumoff (52) provided strong evidence that enhanced ovarian androgen production may be a risk factor for breast cancer in women under some circumstances. However, cohort studies of normal women in general populations have not consistently shown prediagnostic androgen levels to be predictive of subsequent breast cancer development (52, 53). The results of our study suggest that the role of androgens should be considered in further endocrinologic studies of breast cancer in either sex.

Trauma to the head was associated with an increased risk of breast cancer in men in one prior investigation (14), but in our study head injury was associated with a reduced risk of this disease. No obvious reason for this discrepancy is evident, but the more detailed information obtained directly from the subjects of this study would be expected to be more valid than the data from medical records that were utilized in the previous investigation. The previous investigators hypothesized that their findings could have resulted from enhanced prolactin production due to a reduction in hypothalamic inhibition of pituitary function, but this now seems less likely. The findings of our study might be explained by a reduction in production of gonadatropins, and possible prolactin, due to a direct effect of trauma on the pituitary, although this is conjectural. If additional studies confirm an association between head trauma and risk of breast cancer in either sex, then studies of the long-term endocrinologic consequence of such injury might provide useful clues to the etiology of breast cancer.

Additional evidence for a possible etiologic role of the pituitary is provided by the association noted in this study between risk of breast cancer and use of amphetamines, which are known to cause gynecomastia, probably by stimulation of prolactin production (37), and by a relationship noted in one previous study (14) between drugs as a group that cause prolactin elevation and breast cancer in men. On the other hand, in the present study, risk of breast cancer was not consistently associated with other drugs that are thought to have a gynecomastogenic mechanism similar to that of the amphetamines (37). The observed association with

amphetamine use could have another mode of action, could have been a result of incomplete control of confounding by weight, or could have resulted from an unrecognized nonbiologic mechanism.

Our finding of an increase in risk in relation to duration of diabetes has not been observed in other investigations of breast cancer in men, and in one prior study (16), a slight reduction in risk in diabetics was found. Studies have also generally not revealed a relationship between breast cancer in women and diabetes. The association between cigar smoking and risk observed in this study has also not been reported previously, although a weak association with pipe smoking was noted in one prior investigation (6). Neither of these observed associations resulted from analyses to test prior hypotheses, and both could have occurred by chance as a result of the large number of variables that were considered in this study. Biologic interpretations of these findings are thus not warranted unless they are confirmed by others.

Preston-Martin et al. (54) have recently summarized the evidence from studies in humans that risks of many neoplasms are increased by factors that enhance rates of cell division; and Moolgavkar et al. (55) have developed a quantitative model for breast cancer that includes the same concept. Stalsberg et al. (2) have shown that hormonally related, socioeconomic, and geographic risk factors for breast cancer in women are more strongly related to lobular and tubular carcinomas than to other histologic types and have hypothesized that these risk factors exert their effect by selectively increasing the number of lobular cells at risk, and therefore the number of cells susceptible to malignant transformation. Observations from this study and other investigations are supportive of the hypothesis that risk of breast cancer is a function of the number of susceptible cells. Men have little breast epithelium and are at very low risk of breast cancer; men with risk factors likely associated with elevated estrogen or reduced androgen levels are at greater risk than other men, and such hormonal aberrations would be expected to enhance growth of the mammary epithelium. Risk is similarly elevated in men with prior benign breast conditions, some of which probably are associated with increased epithelial proliferation; and men with Klinefelter's syndrome, who have more overt gynecomastia, low levels of endogenous androgens, and elevated estrogen levels, are at even higher risk, although their risk is not as high as that in women (22).

To estimate the proportion of all cases in this study that are attributable to observed risk factors, we assumed that causal mechanisms are operative in the associations with the following variables: undescended testis, removal of testis, congenital inguinal hernia, mumps after age 14 years, other infections of the testis, voice change at an older age than one's peers, infertility, no live children, high blood cholesterol, weight gain of more than 50 pounds (22.70 kg) in 6 months, use of thyroid hormone or amphetamines, any type of prior benign breast condition, exposure to ionizing radiation (results not presented), worked for 10 or more years in any metal industry (results not presented), and family history of breast cancer in any first- or second-degree relative (28). Exposure to one or more of these factors was reported by 78 percent of the cases and 55 percent of the controls. From these percentages, it was estimated (56) that approximately 50 percent of the cases could be attributed to one or more of these risk factors.

This low value for the population-attributable risk, although undoubtedly imprecise, serves to demonstrate the failure of this study to identify possible causes of many of the cases. Many women with breast cancer also have none of the generally recognized risk factors for this disease. One purpose of this study was to identify variables that might be new risk factors for breast cancer in women. Although some new associations were observed and additional information was accrued on the possible role of hormonal factors in the etiology of breast cancer, few new causal agents were identified, and in this respect, this study failed to achieve one of its main purposes. Given the rarity of carcinomas of the male breast, ad-

ditional case-control studies of breast cancer in men would seem warranted only if new hypotheses emerge that would focus future studies on areas of possible relevance to breast cancer in women that were not considered in this investigation.

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