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ARTICLE

Anthropometric and Hormonal Risk Factors for Male Breast Cancer: Male Breast Cancer Pooling Project Results

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Background The etiology of male breast cancer is poorly understood, partly because of its relative rarity. Although genetic factors are involved, less is known regarding the role of anthropometric and hormonally related risk factors.

Methods In the Male Breast Cancer Pooling Project, a consortium of 11 case–control and 10 cohort investigations involving 2405 case patients (n = 1190 from case–control and n = 1215 from cohort studies) and 52 013 control subjects, individual participant data were harmonized and pooled. Unconditional logistic regression generated study design–specific (case–control/cohort) odds ratios (ORs) and 95% confidence intervals (CIs), with exposure estimates combined using fixed effects meta-analysis. All statistical tests were two-sided.

Results Risk was statistically significantly associated with weight (highest/lowest tertile: OR = 1.36; 95% CI = 1.18 to 1.57), height (OR = 1.18; 95% CI = 1.01 to 1.38), and body mass index (BMI; OR = 1.30; 95% CI = 1.12 to 1.51), with evidence that recent rather than distant BMI was the strongest predictor. Klinefelter syndrome (OR = 24.7; 95% CI = 8.94 to 68.4) and gynecomastia (OR = 9.78; 95% CI = 7.52 to 12.7) were also statistically significantly associated with risk, relations that were independent of BMI. Diabetes also emerged as an independent risk factor (OR = 1.19; 95% CI = 1.04 to 1.37). There were also suggestive relations with cryptorchidism (OR = 2.18; 95% CI = 0.96 to 4.94) and orchitis (OR = 1.43; 95% CI = 1.02 to 1.99). Although age at onset of puberty and histories of infertility were unrelated to risk, never having had children was statistically significantly related (OR = 1.29; 95% CI = 1.01 to 1.66). Among individuals diagnosed at older ages, a history of fractures was statistically significantly related (OR = 1.41; 95% CI = 1.07 to 1.86).

Conclusions Consistent findings across case–control and cohort investigations, complemented by pooled analyses, indicated important roles for anthropometric and hormonal risk factors in the etiology of male breast cancer. Further investigation should focus on potential roles of endogenous hormones.

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Male breast cancer is uncommon, with an occurrence less than 1% that of female breast cancer (1), resulting in a paucity of identified etiologic predictors. Descriptive studies document that, unlike female breast cancer, there is no plateauing of rates after 50 years of age (and thus relatively late average ages at onset) and a higher incidence in the United States for blacks than whites (2,3). Reports of rising incidence of male breast cancer (4,5) have raised concern, although it is unclear whether changes are real or reflect enhanced detection (6). Epidemiologic studies of male breast cancer are uncommon, and most to date have been small case–control studies, raising the possibility that identified risk factors could reflect the influence of chance or selection and recall biases.

Similar to female breast cancers, many of the postulated risk factors for male breast cancer suggest the importance of anthropometric and hormonal factors. Notable is a consistent relation between obesity and male breast cancer (7–12), with obesity also linked with an increased risk of postmenopausal female breast cancer risk (13). Studies of male breast cancer in relation to hormonally related medical conditions have shown strong associations with Klinefelter

syndrome (14), a condition characterized by a rare chromosomal abnormality of 47,XXY karyotype and notable hormonal alterations (15). Male breast cancer has also been associated with gynecomastia (10), a condition linked with estrogen excesses, as well as less consistently with diabetes (9,16), liver cirrhosis (17,18), hyperthyroidism (17), gallstones (17), and bone fractures (7). However, the extent to which these associations reflect the influence of concomitant conditions (eg, obesity) remains unresolved.

As with female breast cancer, reproductive history may also be associated with risk; several studies have shown higher risks of male breast cancer with late puberty (16); being single, infertile, or childless (8,10,11,16,17,19); and having undescended testes, testicular trauma, or infections causing orchitis or epididymitis (10,20,21), conditions often associated with gynecomastia.

Several lines of evidence support further pursuit of anthropometric and hormonal factors in the etiology of male breast cancers. However, many exposures of interest have low prevalences, requiring evaluation of associations by data pooling efforts. We therefore conducted a pooled analysis of individual participant data in an international collaboration, the Male Breast Cancer Pooling Project.

Methods

Study Population

For the Male Breast Cancer Pooling Project, we identified all case–control or cohort studies with 10 or more cases of this rare malignancy. Studies were identified from literature searches in PubMed, citations within published manuscripts, and advertisement at the National Cancer Institute Cohort Consortium meetings (http://epi.grants.cancer.gov/Consortia/cohort.html). Although three case–control studies (17,22,23) could not contribute because data were no longer available, we secured the contribution of data from 11 case–control (8,9,11,12,16,19,24–28) and 10 cohort (7,20,29–36) investigations. These studies contributed deidentified data following approved data sharing agreements, as well as National Cancer Institute and study center institutional review board clearances. The case definition was any male breast cancer (*International Classification of Diseases, 10th edition*: C50; www.cdc.gov/nchs/icd/icd10.htm) reported by a cancer registry, medical record, or self-report. Cancers were required to be incident (ie, diagnosed after exposure ascertainment) for cohort studies and with exposure ascertainment near diagnosis for case–control studies. To maximize the number of case patients, we included all male breast cancers, regardless of whether they were diagnosed as a first cancer or not. For cohort studies, we created nested case–control studies with a 40:1 control-to-case ratio using incidence-density matching to retain balance between analytic efficiency and strong statistical power, especially for analyses of less common exposures (37). Control subjects were matched to case patients on sex (male), race (study-specific categories), study center (for multicenter cohorts), date of birth (±1 year), date of entry (±1 year), and exit date (date last known alive and free of cancer, excluding nonmelanoma skin cancer) greater than or equal to date of diagnosis of case patient. When matching control subjects to male breast cancer case patients that were not first cancers, potential control subjects were not right-censored at diagnosis of cancer, as per the above exit date criterion. Matching for date of entry and of birth was relaxed in increments of ±1 year until ±3 years was reached. We followed these procedures in all but the Kaiser Permanente Multiphasic Health Checkup Cohort (31), where a 10:1 control-to-case ratio was used. Follow-up ended at date of diagnosis of cancer, death, loss to follow-up, or end of follow-up, whichever occurred first.

Exposures

Exposures harmonized across studies included body mass index (BMI; kg/m^2; current/recent [usually obtained at study entry for cohort studies] and at 18–21 and 30–35 years of age), height (cm), weight (kg; current/recent and at 18–21 and 30–35 years of age), Klinefelter syndrome, gynecomastia, diabetes mellitus, osteoporosis, fractures, liver disease, thyroid disease, gallbladder disease, benign prostate disease, cryptorchidism, orchitis, testicular trauma, use of exogenous estrogens/androgens, onset of puberty, ever had children, number of children, and history of infertility. These exposures, usually self-reported, were variously defined. For instance, liver disease in some studies was restricted to cirrhosis, whereas other studies also inquired about liver cysts, hepatitis, or jaundice. Gallbladder disease was usually restricted to information on gallstones. Only a few studies inquired about benign thyroid and prostate diseases, with the information being fairly nonspecific about the types of diseases diagnosed.

Statistical Analysis

To standardize the methods and models for separate pooled analyses of case–control studies and cohort studies (nested case–control studies), we used unconditional logistic regression that adjusted for age (in tertiles based on combined control subjects across studies) and study (categorical) to generate study design–specific odds ratios (ORs) and 95% confidence intervals (CIs). We assessed whether case–control or cohort estimates (betas) deviated by more than 10% when adjusted for education, marital status, race, family history of breast cancer, and status and pack-years of tobacco smoking. None of these factors altered beta coefficients to any appreciable extent. Therefore, the main results presented herein are adjusted only for study and age. The study design-specific odds ratios and 95% confidence intervals were combined using fixed effects meta-analysis to generate overall summary estimates of association (38). Modeling age as a continuous, instead of categorical, variable did not materially affect the risk estimates. *P* values for heterogeneity were derived using an interaction term of exposure and study, within each of the pooled analyses of case–control studies and of cohort studies. Additional sensitivity analyses included adjustment for BMI in analyses of gynecomastia, fractures, and Klinefelter syndrome; exclusion of individuals with gynecomastia in analyses of BMI and vice versa; stratification of the main results by median age of diagnosis; reanalysis of all exposures with exclusion of the National Mortality Follow-back Survey (11) because age was age at death rather than at breast cancer diagnosis; and analyses focusing only on male breast cancers occurring as a first primary cancer. All analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC) and STATA 11.2 (StataCorp LP, College Station, TX). All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

Table 1. Characteristics of the investigations included in the Male Breast Cancer Pooling Project

Case–control studies					
Study (reference)	**Location**	**Period of recruitment**	**No. of case patients***	**No. of control subjects***	**Type of control subjects**
Los Angeles County Study (19)	Los Angeles County, United States	1978–1985	75	75	Neighborhood
Swedish Study (26)	Southern Sweden	1970–1986	93	455	Lung cancer and lymphoma patients
U.S. National Follow-up Back Survey (11)	United States, nationwide	1986	178	512	Men dying of causes other than male breast cancer
U.S. Multi-center Study (16)	United States, multicenter	1983–1986	227	301	Random digit dialing and Medicare
JANUS Serum Bank Nested Case-Control Study (25)	Norway	1973–2005	27	54	Volunteers providing blood samples to the JANUS serum bank
Italian Study (8)	Milan, Italy	1988–1994	26	90	Patients admitted to hospital for acute, non-neoplastic, non-hormone-related disease
Greek Study (27)	Greece	1996–1997	23	76	Hospital visitors
Scandinavian Case-control Study (9)	Denmark, Norway, and Sweden	1987–1991	156	468	Population register
Canadian Multi-site Study (12)	Canada, multiple sites	1994–1998	81	399	Population-based sample
European Multi-center Study (28)	Denmark, France, Germany, Italy, Latvia, Portugal, Spain, and Sweden	1995–1997	104	1,901	Primarily population control subjects, although also some colon and stomach cancer patients
United Kingdom Study (24)	England and Wales	2005–ongoing	200	200	Male nonblood relatives of case patients and husbands of women without breast cancer participating in the Breakthrough Generations Study, a large national cohort study
Total			1190	4531	

Cohort studies					
Study (reference)	***Location***	***Period of recruitment/ follow-up***	***No. of case patients****	***Size of cohort*†***	***Special Cohort Characteristics***
Cancer Prevention Study II (29)	United States, nationwide	1992/2007	46	73487 (1840)	General population recruited by American Cancer Society volunteers
European Prospective Investigation in Cancer and Nutrition (EPIC) (34)	23 centers located in 10 European countries	1992–2000/ 2005–2009	30	147992 (1200)	
Health Professional Follow-up Study (HPFS) (30)	United States, nationwide	1986/ 2008	39	49239 (1560)	US male health professionals who responded to a mailed questionnaire on lifestyle and medical history
Kaiser Permanente Multiphasic Health Checkup Cohort (31)	Oakland and San Francisco, CA Kaiser Permanente HMO	1964–1968/ 2009	40	(482)	Individuals receiving health checkup examinations, primarily for routine purposes, within Kaiser Permanente
Multi-ethnic Cohort Study (32)	Hawaii and California (mainly Los Angeles County)	1993–1996/ 2008	32	79953 (1280)	General population sample identified primarily through drivers' license files in Hawaii and California, supplemented with Health Care Financing Administration files in California and Voters Registration files in Hawaii
Netherlands Cohort Study (NLCS) (36)	Netherlands	1986 2006	27	58279 (1080)	Representative sample of residents in the Netherlands

(Table continues)

Table 1 (Continued).

Study (reference)	Location	Period of recruitment/ follow-up	No. of case patients*	Size of cohort*†	Special Cohort Characteristics
		Cohort studies			
NIH–AARP Diet and Health Study (7)	United States, multiple states	1995–1996/ 2006	151	307 742 (6040)	AARP members
Physicians' Health Study I (PHS-I) (35)	United States, nationwide	1981–1984 / 2010	24	28 418 (960)	Male physicians agreeing to be enrolled in a randomized trial of aspirin and beta-carotene
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Follow-up Study (33)	United States, multiple study centers	1993–2001/ 2010	42	71 729 (1680)	Individuals willing to be randomized for various cancer screening modalities
US Veterans Affairs Medical Care System Database (20)	United States, multiple sites	1969–1996	784	4 500 803 (31 360)	Veterans with hospitalizations for conditions other than male breast cancer
Total			1215	5 260 925 (47 482)	

* Numbers shown represent contributions to this pooling project rather than those reported in the designated publications. For most cohort studies with a greater than 40:1 control-to-case ratio, we used incidence density matching to select 40 control subjects for each case patient.

† Numbers in parentheses represent the control subjects used in the analyses for the cohort investigations.

Results

The study design, study location, and numbers of study subjects for the 21 participating studies are described in Table 1. A total of 2405 case patients and 52,013 controls subjects were assembled (1190 patients and 4531 control subjects from case–control studies and 1215 patients and 47 482 control subjects from cohort studies). The median age of the case patients was 66.0 years (standard deviation [SD] = 10.8): 64.1 (SD = 11.0) for the case–control studies and 68.0 (SD = 10.2) for the cohort studies. The majority of subjects were white (85.7% overall, 95.8% in the case–control studies, and 84.5% in the cohort studies).

The relation of anthropometric variables with male breast cancer risk is shown in Table 2. Risk increased statistically significantly with adult weight (OR per 5 kg = 1.07; 95% CI = 1.04 to 1.09). When assessed according to tertiles, those in the highest tertile of weight had an odds ratio of 1.36 (95% CI = 1.18 to 1.57) compared with those in the lowest tertile. The risk associated with weight was more evident in case–control studies than in cohort studies. Height also was statistically significantly positively related to risk (OR = 1.18; 95% CI = 1.01 to 1.38 for the highest vs lowest tertile). When weight and height were simultaneously assessed through the derivation of BMI, men in the highest tertile had an odds ratio of 1.30 (95% CI = 1.12 to 1.51), with somewhat stronger relations observed in case–control studies (OR = 1.39) than cohort studies (OR = 1.16). We also assessed risk in relation to World Health Organization definitions of obesity (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html). In comparison with healthy weight individuals (BMI = 18.5–24.9 kg/m^2), those considered obese (BMI ≥30 kg/m^2) showed a risk comparable with that based on a tertile comparison (OR = 1.35; 95% CI = 1.12 to 1.62).

Among a limited number of studies, we also assessed BMI at two earlier age ranges (18–21 and 30–35 years of age). These measures did not appear to predict cancer risk as strongly as BMI ascertained closer to the time of diagnosis, although the estimates for these time periods were less precise given the fewer studies involved.

Evaluation of medical histories in relation to male breast cancer risk revealed statistically significant associations with Klinefelter syndrome (OR = 24.7; 95% CI = 8.94 to 68.4) and gynecomastia (OR = 9.78; 95% CI = 7.52 to 12.70) (Table 3). A history of diabetes, assessed in most investigations, was related to a modest but statistically significant risk increase (OR = 1.19; 95% CI = 1.04 to 1.37). Although adult fractures were associated with a slight increase in risk (OR = 1.18; 95% CI = 0.97 to 1.42), based on quite discrepant questions [including skull fractures in one study (26)], a prior diagnosis of osteoporosis was not associated with any risk elevation (OR = 0.76; 95% CI = 0.45 to 1.28), albeit based on small numbers. Male breast cancer risk was unrelated to a history of liver, thyroid, gallbladder, or prostate diseases from the few studies among which data were available but was associated with a history of cryptorchidism (OR = 2.18; 95% CI = 0.96 to 4.94; based on data only from case–control studies) and orchitis (OR = 1.43; 95% CI = 1.02 to 1.99). Testicular trauma and use of exogenous estrogens/androgens were unrelated to risk, although data were sparse for both exposures.

Although relationships with the aforementioned medical conditions were adjusted only for the effects of study and age, the odds

Table 2. Relationship of anthropometric factors to male breast cancer risk

	Meta-analysis					Case–control studies					Cohort studies				
Factors	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***
Adult weight, kg	19					10				.09†	9				.35†
Continuous, per 5 kg		1481	19760	1.07 (1.04 to 1.09)	<.001		1059	3949	1.09 (1.06 to 1.12)	<.001		422	15811	1.04 (1.00 to 1.08)	.06
Lowest tertile, ≤76.4‡		525	6718	1.00 (referent)			390	1739	1.00 (referent)			135	4979	1.00 (referent)	
Middle tertile, 76.5–86.3		444	6492	1.04 (0.90 to 1.20)	.60		313	1279	1.09 (0.91 to 1.30)	.37		131	5213	0.96 (0.75 to 1.23)	.74
Highest tertile, >86.3		512	6550	1.36 (1.18 to 1.57)	<.001		356	931	1.54 (1.29 to 1.85)	<.001		156	5619	1.09 (0.86 to 1.39)	.49
P_{trend}									<.001					.48	
Height, cm	19					10				.40†	9				.17†
Continuous, per 5 cm		1493	19863	1.06 (1.02 to 1.11)	<.01		1068	3980	1.07 (1.02 to 1.13)	.01		425	15883	1.05 (0.98 to 1.13)	.20
Lowest tertile, ≤173.0		511	6648	1.00 (referent)			382	1682	1.00 (referent)			129	4966	1.00 (referent)	
Middle tertile, 173.1–180.3		570	8072	0.99 (0.86 to 1.14)	.87		394	1486	0.96 (0.81 to 1.14)	.62		176	6586	1.05 (0.83 to 1.33)	.68
Highest tertile, >180.3		412	5143	1.18 (1.01 to 1.38)	.03		292	812	1.22 (1.00 to 1.48)	.05		120	4331	1.12 (0.87 to 1.45)	.38
P_{trend}									.07					.38	
Adult BMI, kg weight/ m height^2	19					10				.09†	9				.86†
Continuous, per 5 kg/m^2		1469	19631	1.19 (1.10 to 1.30)	<.001		1048	3910	1.24 (1.12 to 1.38)	<.001		421	15721	1.11 (0.97 to 1.28)	.13
Lowest tertile, ≤24.6		496	6538	1.00 (referent)			368	1484	1.00 (referent)			128	5054	1.00 (referent)	
Middle tertile, 24.7–27.4		479	6568	1.15 (1.00 to 1.33)	.06		340	1290	1.22 (1.02 to 1.46)	.03		139	5278	1.04 (0.81 to 1.32)	.77
Highest tertile, >27.4		494	6525	1.30 (1.12 to 1.51)	<.001		340	1136	1.39 (1.16 to 1.67)	<.01		154	5389	1.16 (0.91 to 1.49)	.23
P_{trend}									<.01					.22	
Body mass index 18–21 y											6				.48†
Continuous, per 5 kg/m^2												189	7540	1.05 (0.80 to 1.38)	.71
Lowest tertile, ≤21.2												60	2513	1.00 (referent)	
Middle tertile, 21.3–23.4												63	2518	1.05 (0.73 to 1.50)	.80
Highest tertile, >23.4												66	2509	1.11 (0.78 to 1.60)	.56
P_{trend}														.56	
Body mass index 30–35 y						3				.43†					
Continuous, per 5 kg/m^2							386	2092	1.11 (0.93 to 1.33)	.24					
Lowest tertile, ≤23.0							147	698	1.00 (referent)						
Middle tertile, 23.1–25.4							131	708	1.22 (0.90 to 1.64)	.20					
Highest tertile, >25.4							108	686	0.89 (0.65 to 1.22)	.47					
P_{trend}									.53						

* Odds ratios (ORs) were adjusted for study and age and estimated with unconditional logistic regression. All statistical tests were two-sided. CI = confidence interval.

† *P* values for heterogeneity across individual studies within each category of study (case–control or cohort).

‡ Ranges of control values across studies are shown in parentheses.

Table 3. Relationship of selected medical diagnoses to male breast cancer risk

	Meta-analysis					Case–control studies					Cohort studies				
Factors	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***
Klinefelter syndrome	3					2				NC†	1				
No		973	33706	1.00 (referent)			194	2354	1.00 (referent)			779	31 352	1.00 (referent)	
Yes		8	9	24.73 (8.94 to 68.38)	<.001		3	1	22.30 (1.98 to 251.70)	.01		5	8	25.28 (8.24 to 77.54)	<.001
Gynecomastia	8					7				<.001†	1				
No		1488	34507	1.00 (referent)			736	3356	1.00 (referent			752	31 151	1.00 (referent)	
Yes		164	268	9.78 (7.52 to 12.71)	<.001		132	59	14.57 (10.13 to 20.96)	<.001		32	209	6.34 (4.34 to 9.27)	<.001
Diabetes mellitus	17					7				<.01†	10				.23†
No		1809	44039	1.00 (referent)			781	3079	1.00 (referent			1028	40 960	1.00 (referent)	
Yes		285	6516	1.19 (1.04 to 1.37)	.01		105	297	1.22 (0.94 to 1.58)	.13		180	6219	1.18 (1.01 to 1.39)	.04
Osteoporosis	6					1					5				NC†
No		1251	41 145	1.00 (referent)			225	295	1.00 (referent			1026	40 850	1.00 (referent)	
Yes		15	743	0.76 (0.45 to 1.28)	.31		1	1	1.09 (0.07 to 17.90)	.95		14	742	0.75 (044 to 1.28)	.29
Fractures	5					2				<.001†	3				.15†
No		1032	37298	1.00 (referent)			152	1680	1.00 (referent)			880	35618	1.00 (referent)	
Yes		137	4002	1.18 (0.97 to 1.42)	.09		43	660	1.32 (0.89 to 1.96)	.18		94	3342	1.14 (0.92 to 1.41)	.24
Liver disease	13					7				NC†	6				.79†
No		1865	39468	1.00 (referent)			938	3624	1.00 (referent)			927	35 844	1.00 (referent)	
Yes		93	2110	0.89 (0.71 to 1.13)	.35		47	103	0.89 (0.61 to 1.29)	.53		46	2007	0.90 (0.66 to 1.21)	.48
Thyroid disease	9					5				.60†	4				.12†
No		1362	36 180	1.00 (referent)			503	2709	1.00 (referent)			859	33 471	1.00 (referent)	
Yes		44	925	1.11 (0.79 to 1.55)	.55		20	87	1.17 (0.65 to 2.11)	.60		24	838	1.08 (0.72 to 1.63)	.71
Gallbladder disease	11					2				.48†	9				.85†
No		1223	45144	1.00 (referent)			123	1840	1.00 (referent)			1100	43 304	1.00 (referent)	
Yes		82	2577	1.17 (0.93 to 1.47)	.17		7	138	0.72 (0.33 to 1.59)	.41		75	2439	1.22 (0.97 to 1.55)	.10
Benign prostate disease											5				.99†
No												730	28 998	1.00 (referent)	
Yes												155	6254	0.98 (0.82 to 1.17)	.81
Cryptorchidism						3				.01†					
No							392	2204	1.00 (referent)						
Yes							12	31	2.18 (0.96 to 4.94)	.06					
Orchitis	6					5				.62†	1				
No		1311	33783	1.00 (referent)			546	2849	1.00 (referent)			765	30 934	1.00 (referent)	
Yes		49	508	1.43 (1.02 to 1.99)	.04		30	82	1.11 (0.69 to 1.79)	.67		19	426	1.80 (1.13 to 2.87)	.01
Testicular trauma						3				<.01†					
No							433	1118	1.00 (referent)						
Yes							23	70	1.05 (0.63 to 1.74)	.85					
Use of exogenous estrogens/ androgens						3				.36†					
No							250	2323	1.00 (referent)						
Yes							21	73	0.96 (0.55 to 1.69)	.90					

* Odds ratios (ORs) were adjusted for study and age and estimated with unconditional logistic regression. All statistical tests were two-sided. CI = confidence interval.

† *P* values for heterogeneity across individual studies within each category of study (case–control or cohort). NC = not calculable.

ratios were little impacted with further adjustment for BMI. This included little alteration in the risks associated with gynecomastia and diabetes. As an additional means of controlling for BMI, given that obese individuals tend more frequently to have either diabetes or gynecomastia, we examined whether these conditions persisted as risk factors among nonobese individuals. Gynecomastia was statistically significantly related to risk even among men in the lowest BMI tertile. Diabetes was somewhat more strongly related to risk among heavier than thin individuals (OR = 1.16 vs 1.08), but the difference was not statistically significant. The relation between BMI and male breast cancer persisted among those without diabetes or gynecomastia.

There was no statistically significant relation between relative age at onset of puberty and risk of male breast cancer (Table 4). However, a history of never having had children (OR = 1.29; 95% CI = 1.01 to 1.66) was a statistically significant risk factor, with some evidence of lower risks for men with multiple children (OR = 0.94, 95% CI = 0.84 to 1.06 for each child born; OR = 0.65, 95% CI = 0.45 to 0.94 for ≥4 children vs 1 child). These associations persisted when we eliminated subjects with conditions known to result in impaired fertility, such as Klinefelter syndrome. In contrast, a history of infertility, examined only in a few case–control studies, was not statistically significantly related to risk.

We assessed whether there were any substantial differences in the risk factor relations according to whether the age at diagnosis of the male breast cancer was greater or less than the median (66 years) (Table 5). The risk estimates were comparable for most factors, although a history of fractures was a statistically significant risk factor only among the older subjects (OR = 1.41, 95% CI = 1.07 to 1.86; vs OR = 0.99, 95% CI = 0.76 to 1.29 for the younger subjects).

Sensitivity analyses, which separately excluded subjects in the National Mortality Follow-back Survey and male breast cancers that developed only as second cancers, showed little differences in odds ratios as compared with those derived from the full study population.

Discussion

This pooling project provided a unique opportunity to assess risk factors for male breast cancer, a rare disease whose etiology is not well understood. By combining data across the majority of case–control studies undertaken for this cancer site and supplementing information from cases that had developed within numerous cohort investigations, we confirmed that male breast cancer is associated with a number of anthropometric and hormonally related factors. With a large number of events, we were able to disentangle effects of correlated risk factors (eg, medical conditions linked with obesity) and examine more conclusively some reproductive factors that may reflect hormonal alterations.

Similar to other investigations (21,39), we found that patients with Klinefelter syndrome were at a very high risk of male breast cancer. Although the extra X chromosome that defines this syndrome has been extensively discussed as a basis for the elevated cancer risk, associated hormonal explanations remain unclear. It is of particular interest that such patients have low levels of testosterone and high levels of estrogens (15), resulting in a high estrogen/androgen ratio. This has been hypothesized to lead to abnormal hormonal stimulation of cell proliferation of the mammary ductal epithelium (40).

The association for obesity observed in men was of interest given a similar recognized pattern for female postmenopausal breast cancer. In fact, the approximate 30% increased risk we observed in men is nearly identical to that for postmenopausal breast cancer risk (13). We observed a stronger relation of BMI (and especially weight) in the case–control studies than the cohort studies. This could reflect selection biases in the case–control studies (eg, thinner control subjects being willing to be interviewed). Alternatively, the difference could result from case–control studies focusing on more recent measures of obesity because anthropometric measures in cohort studies usually derived from the time of cohort establishment. Of note is that a stronger influence of contemporary weight has been observed for female breast cancer (13). In women, the association between obesity and postmenopausal breast cancer risk may be mediated, in part, by the peripheral conversion of androgens to estrogens (41), which are clearly linked with risk elevations (42). In men, obesity is associated with high estrogen levels as well as low testosterone and sex hormone binding globulin (43,44) levels, leading to greater estrogen bioavailability.

Klinefelter patients often have gynecomastia, another recognized risk factor for male breast cancer that was confirmed in this study. Although gynecomastia is associated with the detection of male breast cancer (45,46), its relevance as an etiologic factor has been questioned (47). It has been postulated that it might affect risk through providing increased tissue at risk, but it is also possible that increased surveillance, recall biases, or uncontrolled confounding for other risk predictors could be involved. However, our findings suggested that the association of gynecomastia appeared independent from that of BMI.

We also assessed several other medical conditions that have not been definitively linked with male breast cancer. We found slightly elevated risks associated with a history of diabetes. Although this could reflect residual confounding by obesity, particularly because the relation was strongest among obese individuals and our obesity measure was limited to recent BMI, low testosterone levels have been reported among male diabetics (48)—possibly supporting a biological explanation. Results from other studies have also raised interest in possible relations with liver cirrhosis (17,18), given excessive production of estrogens and a reduction in circulating free testosterone due to elevated sex steroid hormone binding globulin. Furthermore, cholelithiasis has been postulated as a potential risk factor (17) because estrogens increase biliary cholesterol secretion that can result in cholesterol supersaturation of bile ducts and the formation of stones (49). However, we failed to observe risk relations with either liver or thyroid diseases, including hyperthyroidism, which has been related to risk in one previous investigation (17).

Other hormonally related medical conditions include osteoporosis and bone fractures, which have been shown to be inversely related to female breast cancers, presumably because of low estrogen levels (50). Both estrogen and testosterone are important for bone maintenance in men (51); thus, decreasing levels of bioavailable testosterone with age (52) could lead to alterations in the bioavailable ratio of estrogen to testosterone and increases in male breast cancer (40). We found no relation of either osteoporosis or

Table 4. Relationship of reproductive parameters to male breast cancer risk

	Meta-analysis					Case–control studies					Cohort studies				
Factors	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***	**Studies**	**Case patients**	**Control subjects**	**OR* (95% CI)**	***P***
Relative age at onset of puberty†						2				.54‡					
Somewhat earlier							28	281	1.00 (referent)						
Same age							232	1508	0.85 (0.54 to 1.35)	.50					
Somewhat later							41	255	1.07 (0.60 to 1.89)	.83					
P_{trend}									.72						
Ever had children	8					6				.02‡	2				.46‡
Yes		471	4183	1.00 (referent)	.04		427	2364	1.00 (referent)	.05		44	1819	1.00 (referent)	.54
No		113	634	1.29 (1.01 to 1.66)			107	450	1.29 (0.99 to 1.67)			6	184	1.33 (0.54 to 3.26)	
Number of children	6					5				.06‡	1				
Continuous		432	3353	0.94 (0.84 to 1.06)	.30		407	2290	0.98 (0.87 to 1.10)	.71		25	1063	0.65 (0.45 to 0.95)	.02
1		97	635	1.00 (referent)	.79		91	503	1.00 (referent)			6	132	1.00 (referent)	
2		140	1279	0.68 (0.50 to 0.92)	.01		132	992	0.68 (0.50 to 0.94)	.02		8	287	0.62 (0.21 to 1.83)	.39
3		127	717	1.05 (0.77 to 1.45)	.74		120	460	1.11 (0.80 to 1.55)	.54		7	257	0.60 (0.20 to 1.83)	.37
≥4		68	722	0.65 (0.45 to 0.94)	.02		64	335	0.72 (0.49 to 1.05)	.09		4	387	0.22 (0.01 to 0.82)	.02
P_{trend}				.30					.71					.03	
History of infertility						4				.39‡					
No					4.00		403	2451	1.00 (referent)						
Yes							17	53	1.36 (0.74 to 2.51)	.33					

* Odds ratios (ORs) were adjusted for study and age and estimated with unconditional logistic regression. All statistical tests were two-sided. CI = confidence interval.

† In comparison with peers.

‡ *P* values for heterogeneity across individual studies within each category of study (case–control or cohort).

Table 5. Meta-analysis results of selected risk factors by median age at diagnosis* of male breast cancers

	Below median (<66 Years)					Above median (≥ 66 Years)			
Factors	**Studies**	**Case patients**	**Control subjects**	**OR † (95% CI)**	***P***	**Case patients**	**Control subjects**	**OR † (95% CI)**	***P***
Adult body mass index, kg weight/m height^2	19								
Continuous		784	8003	1.04 (1.02 to 1.07)	<.001	685	11 628	1.03 (1.00 to 1.05)	.05
Lowest tertile, ≤24.5		240	2605	1.00 (referent)		256	3933	1.00 (referent)	
Middle tertile, 24.6–27.4		261	2637	1.27 (1.04 to 1.56)	.02	218	3931	1.05 (0.86 to 1.29)	.63
Highest tertile, >27.4		283	2761	1.44 (1.17 to 1.76)	<.001	211	3764	1.17 (0.94 to 1.45)	.15
Diabetes melllitus	17								
No		937	20 761	1.00 (referent)		872	23 278	1.00 (referent)	
Yes		149	3097	1.29 (1.07 to 1.56)	.01	136	3419	1.10 (0.90 to 1.34)	.34
Klinefelter syndrome	3								
No		484	17 739	1.00 (referent)					
Yes		1	7	6.60 (0.80 to 55.69)	.07				
Gynecomastia	8								
No		771	18 205	1.00 (referent)		717	16 302	1.00 (referent)	
Yes		97	158	9.86 (7.07 to 13.76)	<.001	67	110	9.55 (6.18 to 14.77)	<.001
Fractures	5								
No		475	17 995	1.00 (referent)		557	19 303	1.00 (referent)	
Yes		71	2218	0.99 (0.76 to 1.29)	.96	66	1784	1.41 (1.07 to 1.86)	.02
Ever had children	8								
No		68	417	1.00 (referent)		45	217	1.00 (referent)	
Yes		292	2669	0.77 (0.56 to 1.06)	.11	179	1514	0.79 (0.53 to 1.18)	
No. of children	6								
Continuous		332	2455	0.85 (0.77 to 0.93)	<.001	209	1512	0.99 (0.90 to 1.19)	.90

* Pertained to age at death for one study, the National Mortality Follow-back Survey.

† Odds ratios (ORs) were adjusted for study and age and estimated with unconditional logistic regression. All statistical tests were two-sided. CI = confidence interval.

fractures with male breast cancer; however, there was some evidence that fractures might predispose to male breast cancers occurring at older ages. Although possibly reflecting greater surveillance, the relation of fractures at older ages to increased male breast cancer risk would be consistent with an effect of an increasing ratio of estrogens to androgens with age. However, it is possible that other hormones could be involved, including prolactin, given that male breast cancers have been associated with skull fractures and other head trauma, established risk factors for prolactinomas (26).

Although female breast cancer is recognized as being associated with a variety of reproductive factors (eg, parity and age at first birth), little attention has focused on reproductive factors related to male breast cancer. We found no evidence for an association of age at puberty with male breast cancer risk, but men who had never had children were at a significantly elevated risk. Although this was not supported by an association with infertility, relatively few studies had information on this parameter. Moreover, older men may not have been evaluated for infertility, and even when tested, the reasons for infertility in men can be quite varied. It is also possible that socioeconomic and lifestyle factors could have contributed to the relation with parity.

The major strength of this analysis is the large number of male breast cancers studied. However, as with most pooling projects, one of the major limitations is the availability of exposure data across all studies, sometimes leading to small numbers for a specific exposure. The manner in which some of the questions were asked varied across studies, which could have impacted the results. We were also unable to stratify results by BRCA status, a major predictor of male breast cancer, nor did we have information on clinical characteristics of the tumors; however, based upon other studies (53), we can assume that most tumors were estrogen receptor positive.

In this pooled analysis, we identified statistically significant associations of male breast cancer with a number of anthropometric and hormonally related risk factors, including BMI and various medical and reproductive parameters. Many of these risk factors support the need for exploring the role of endogenous hormones, which will be assessed in future analyses using samples from our cohort investigations.

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Notes

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