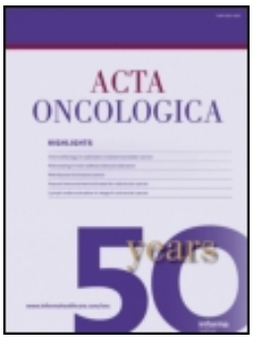

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Marianne Ewertz, Lars Holmberg, Steinar Tretli, Bo V. Pedersen, Allan Kristensen (2001) Risk Factors for Male Breast Cancer?*A Case-Control Study from Scandinavia*, Acta Oncologica, 40:4, 467-471, DOI: 10.1080/02841860117406

To link to this article: https://doi.org/10.1080/02841860117406

Published online: 08 Jul 2009.

Risk Factors for Male Breast Cancer

A Case-Control Study from Scandinavia

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Acta Oncologica Vol. 40, No. 4, pp. 467–471, 2001

We report a population-based case-control study on risk factors for male breast cancer. Data on a broad range of previously suggested risk factors were collected in a set of Scandinavian breast cancer cases and matched controls. Incident cases (n = 282) with histologically verified carcinomas of the breast were identified from notification to the cancer registries of Denmark, Norway and Sweden over a 4-year period 1987–1991 and of these cases, 156 men could be approached and responded. Controls were identified through national central population registers and were matched individually for country, sex and year of birth. Controls with a diagnosis of breast cancer were excluded; 468 of 780 controls responded. Data on risk factors were collected by self-administered questionnaires mailed to the cases between 1and 2 years after diagnosis and to controls during the same period. The findings were compatible with an increased risk associated with family history of breast cancer (odds ratio (OR) = 3.3, 95% confidence interval (CI) 2.0–5.6), obesity 10 years before diagnosis (OR = 2.1, 95% CI 1.0–4.5) for BMI > 30, diabetes (OR = 2.6, 95% CI 1.3–5.3) and the use of digoxin and methyldopa (OR = 2.0 and 2.1, respectively). The association with family history of breast cancer has been repeated in several studies, while the relation to anthropometric measures has been equivocal. We could not substantiate some associations seen in other studies; namely those with high education, fertility, marital status, testicular injury, liver disease and religion. The detailed questions about gynaecomastia indicated that many cases reported signs of breast cancer as a gynaecomastia. This type of misunderstanding may explain the strong association with gynaecomastia seen in other studies. Several patients died before contact. Thus, risk factors related to a more aggressive male breast cancer or related to high risk of dying (e.g. liver cirrhosis, heavy smoking) may have been missed.

Received 9 May 2000
Accepted 29 November 2000

Breast cancer is rare in males, accounting for approximately 1% of malignant breast neoplasm in most countries. Knowledge about risk factors for developing the disease derives mainly from case-control studies, seven of which were reviewed by Sasco et al. (1). They found an increased risk of male breast cancer associated with never being married, being Jewish, having a history of benign breast disease, gynaecomastia, testicular pathology, liver diseases and a positive family history of breast cancer. No association was detected with smoking, reproductive history, education, anthropometric variables and exposure to various other diseases and drugs. Other studies (or new analyses of the previously reviewed studies) have linked male breast cancer with exposure to electromagnetic fields (2–4), ionizing radiation (1, 5), increasing socioeconomic status index, employment in motor vehicle manufacturing, blast furnaces, steel works and rolling mills, obesity (6, 7) and with liver cirrhosis (8). The association with electromagnetic fields has, however, been questioned (5, 9). We report a population-based case control study of 156 cases and 468 matched controls. Data on a broad range of the previously suggested risk factors were collected in a questionnaire.

MATERIAL AND METHODS

Incidences of male breast cancer were identified from notification to the cancer registries of Denmark, Norway and Sweden, which have an almost 100% coverage of all cancer occurring in Scandinavia. Details of the cancer registration have been described elsewhere (10). The study population included men diagnosed with histologically verified carcinomas of the breast over a 4-year period, 1 August 1987 to 30 July 1991. Cases were continuously reported to the study secretariat as soon as they were notified to the cancer registries. Cases with a breast cancer predating the study period were excluded. A total of 282 eligible cases were identified, of whom 29% died before the data collection and 21% did not respond, leaving a total of 156 cases available for analysis. The contribution from each country is recorded in Table 1.

 ISSN 0284-186X

Table 1

Description of the study population in the Scandinavian case-control study of male breast cancer, 1987–1991

	Denmark No. (%)	Norway No. (%)	Sweden No. (%)
Cases			
Total eligible	87 (100)	48 (100)	147 (100)
Deceased	22 (25)	10 (21)	45 (31)
Non-respondents	11 (13)	9 (19)	29 (20)
Included	54 (62)	29 (60)	73 (49)
Median age (range)	65.5 (30–84)	66.0 (42–80)	65.0 (42–90)
Controls			
Total selected	270 (100)	145 (100)	365 (100)
Included	157 (57)	81 (56)	230 (63)
Median age (range)	64.0 (30–84)	66.0 (42–80)	65.0 (41–91)

For each case, five control subjects (four in Norway) were matched individually for country, sex and year of birth (± 2 years). They were identified through the national central population registries, which keep track of all members of the Scandinavian population by means of their unique personal ID-number. Controls diagnosed with breast cancer were excluded. Of the 780 controls selected, 468 (60%) responded and were included in the study, yielding an average case:control ratio of 1:3 (Table 1).

Data on risk factors were collected by self-administered questionnaires mailed to the cases between 1 and 2 years after diagnosis and to controls during the same period. The questionnaire was designed to be closely comparable among the three countries to avoid problems with coding and interpretation. Areas covered by the questionnaire included: basic demographic information; a detailed description of employment in 36 different groups of occupation; fertility; antropometric variables; physical activity during the past 10 years; information about gynaecomastia and testicular disorders; diabetes; liver diseases and a probing question about other chronic diseases; exposure to radiation, assessed as number of chest x-rays or fluoroscopies; any drug use for hypertension, heart disease, duodenal or gastric ulcer, psychoactive drugs. The choice of drugs was based on findings related to gynaecomastia and male breast cancer in previous studies. Furthermore, there were detailed questions on smoking and a food frequency questionnaire on diet. Dietary habits are not analysed in this report.

In the analysis, controls were assigned a date of diagnosis equivalent to that of the matched case, in order to calculate ages and other time-related exposures.

Statistical methods

Odds ratios with a 95% confidence interval were estimated using conditional logistic regression models. When variables were categorized, dummy variables were used in the models to relax the assumption of a linear relationship. Tests for trend were made by using the variables in their continuous form. SAS software® was used in all calculations.

RESULTS

The age distribution of cases and controls was similar in all three countries, with a median age around 65 years (Table 1). Neither marital status nor level of education, or religion was significantly associated with breast cancer.

No clear or significant associations with type of employment emerged. Of particular interest from previous studies was occupation in the armed forces (odds ratio (OR) 1.4, 95% confidence interval (CI) 0.7–2.7), founderies(OR = 1.3, 95% CI 0.2–7.3), electronics (OR = 1.5, 95% CI 0.3–2.1), carpeting (OR = 1.5, 95% CI 0.8–2.8) and the rubber and plastic industry (OR = 4.5, 95% CI 0.7–28).

No significant associations were found for parity, age at first childbirth, infertility, mumps, testicular diseases and traumas (data not shown).

Among the anthropometric variables (Table 2), there were indications of increasing risk with increasing height, body weight 10 years before diagnosis, and body mass index (BMI = weight (kg) divided by height $(m)^2$) 10 years before diagnosis, of which the last two reached statistical significance with ORs of 2.3 (95% CI 1.2–4.4) and 2.1 (95% CI 1.0-4.5) for the respective top categories.

Physical activity, evaluated by exercise at work and in leisure time, was not related to breast cancer risk (Table 2).

Concerning the disease-related risk factors, we found that cases reported breast swelling as a symptom of their breast cancer and it was thus not possible to assess the role of gynaecomastia. Diabetes mellitus was associated with a significantly increased risk (OR = 2.6, 95% CI 1.3–5.3), whereas liver diseases were rare, present only in one case and 11 controls. Other chronic conditions were no more common in cases than they were in controls (OR = 1.3, 95% CI 0.8–2.3). Exposure to more than 10 chest x-ray examinations or fluoroscopies yielded a non-significant risk elevation (OR = 1.4, 95% CI 0.9–2.1).

For medications, elevated risks were observed for five or more years of use of digoxin (OR = 2.0, 95% CI 0.9-4.4) and methyldopa (OR = 2.1 95% CI 0.9-4.7), while no clear associations were detected for spironolactone, cimetidine, chlorpromazine, and clomipramine (Table 3). From the responses to questions about medications, it appeared that many subjects choose to leave the questions blank when they had no medication of the particular type probed for. We therefore categorized blanks as 'never' in these analyses. Analyses omitting blanks essentially showed the same pattern, but with broader confidence intervals.

Diabetes, heart disease and hypertension are associated with obesity, particularly in a study population of elderly men like ours. Furthermore, digoxin and methyldopa are

Table 2

Height, weight and patterns of exercise among male breast cancer cases and controls in Scandinavia, 1987--1991. Association between exposure and breast cancer risk is analysed as odds ratio (OR) with 95% confidence interval (CI)

	Cases (%)	Controls (%)	OR (95% CI) [1]	Linear trend
Height in cm				
<170	22 (14)	81 (17)	1.0 (R) [2]	
170–179	79 (51)	252 (54)	1.1 (0.6–1.9)	
180+	51 (33)	124 (27)	1.6 (0.9–2.8)	p = 0.2
Unknown	4 (2)	11 (2)	–	
Current weight in kg				
<70	32 (20)	85 (18)	1.0 (R)	
70–79	48 (31)	162 (35)	0.8 (0.5–1.3)	
80–89	45 (29)	137 (29)	0.9 (0.5–1.6)	
90+	31 (20)	77 (17)	1.1 (0.6–2.0)	p>0.5
Unknown	–	7 (1)	–	
Weight 10 years before diagnosis (kg)				
<70	28 (18)	92 (20)	1.0 (R)	
70—79	47 (30)	176 (38)	1.7 (1.1–2.6)	
80—89	44 (28)	133 (28)	1.1 (0.6–2.0)	
90+	33 (21)	49 (10)	2.3 (1.2–4.4)	p = 0.02
Unknown	4 (3)	18 (4)	–	
BMI [3] 10 years before diagnosis				
<25	60 (39)	239 (51)	1.0 (R)	
25–30	75 (49)	180 (38)	1.7 (1.1–2.6)	
30+	14 (9)	27 (6)	2.1 (1.0–4.5)	p = 0.07
Unknown	7 (4)	22 (5)	–	
Exercise at work				
Sedentary	32 (21)	95 (20)	1.0 (R)	
Light	46 (29)	123 (26)	1.0 (0.6–1.8)	
Moderate	34 (22)	126 (27)	0.8 (0.4–1.3)	
Heavy	34 (22)	111 (24)	0.8 (0.4–1.4)	p>0.5
Unknown	10 (6)	13 (3)	–	
Leisure time exercise 10 years prior to diagnosis				
Sedentary	17 (11)	38 (8)	1.0 (R)	
Light	70 (45)	230 (49)	0.8 (0.4–1.5)	
Moderate	38 (24)	109 (23)	1.0 (0.5–2.1)	
Heavy	3 (2)	19 (4)	0.4 (0.1–1.6)	p>0.5
Unknown	28 (18)	72 (15)	–	

[1] Odds ratio (95% confidence interval).
[2] R denotes reference category.
[3] Body Mass Index (weight/height squared).

prescribed for heart disease and hypertension. The increased risks observed here for obesity, diabetes, use of digoxin and methyldopa were therefore adjusted for potential confounding. Owing to the matched design of the study and the small number of exposed subjects, we could not include all the variables simultaneously in one multivariate analysis. Instead, each variable was adjusted for the effect of each one at a time. Table 4 shows that the risk estimates changed little after adjustment, statistical significance remained for obesity (BMI of 25 or more) and diabetes, while the p-values were 0.08 for use of digoxin and methyldopa.

Several aspects of smoking (including passive smoking) were examined. An increased risk was seen among subjects who smoked for less than 10 years (OR = 2.7, 95%CI 1.0–7.5) but no clear or consistent patterns of a risk relation to smoking emerged.

Finally, information on family history of cancer (Table 5) revealed a significantly increased risk (OR = 3.3, 95% CI 2.0–5.6) if one or more first-degree female relatives (mother, sister, daughters) had breast cancer. Non-significant risk elevations were seen for fathers with prostate cancer and other male relatives with breast cancer. To check against patients generally overreporting cancer in

Table 3

Medication among male breast cancer cases and controls in Scandinavia, 1987--1991. Association between an exposure and breast cancer risk is analysed as odds ratio (OR) with 95% confidence interval (CI)

Type of drug	Cases (%)	Controls (%)	OR (95% CI) [1]
Digoxin			
Never	136 (87)	436 (93)	1.0 (R) [2]
<5 years	8 (5)	15 (3)	1.8 (0.7–4.4)
5+years	12 (8)	17 (4)	2.0 (0.9–4.4)
Methyldopa			
Never	143 (92)	440 (94)	1.0 (R)
<5 years	2 (1)	11 (2)	0.5 (0.1–2.6)
5+years	11 (7)	17 (4)	2.1 (0.9–4.7)
Spironolactone			
Never	145 (93)	442 (94)	1.0 (R)
< 5 years	7 (4)	13 (3)	1.7 (0.6–4.3)
5+years	4 (3)	13 (3)	0.9 (0.3–2.8)
Cimetidene			
Never	149 (96)	447 (96)	1.0 (R)
Ever	7 (4)	21 (4)	1.0 (0.4–2.4)
Chlorpromazine			
Never	154 (99)	464 (99)	1.0 (R)
Ever	7 (4)	4 (1)	1.6 (0.3–9.2)
Clomipramine			
Never	152 (97)	457 (989)	1.0 (R)
Ever	4 (3)	11 (2)	1.3 (0.4–4.4)

[1] Odds ratio (95% confidence interval).
[2] R denotes reference category.

their family, the wife was included on the list of female relatives. A similar percentage of cases and controls (4%) stated that their wives had breast cancer.

DISCUSSION

Our findings are compatible with an increased risk associated with family history of breast cancer, obesity, diabetes and the use of digoxin and methyldopa. The correlation with family history of breast cancer has been repeated in several studies while the relation to anthropomorphic measures has been questioned (1). In a previous study by Thomas et al. (11) however, weight gain was associated with an increased risk and Hsing et al. (7) found a correlation with obesity. In a cohort of patients with diabetes identified in the Swedish inpatient register, an increased risk of breast cancer was seen following non-insulin-dependent diabetes mellitus (12). Medication with digoxin and methyldopa has been associated with gynaecomastia (13).

Table 4

Risk of male breast cancer (odds ratio (OR)) associated with body mass index (BMI) 10 years before diagnosis, diabetes, and drug use

Exposure	Adjusted for	OR [1]	p-value [2]
BMI 25+	Diabetes	1.9	0.01
Diabetes	BMI	2.3	0.04
BMI 25+	Digoxin	1.7	0.01
Digoxin	BMI	1.8	0.08
BMI 25+	Methyldopa	1.7	0.01
Methyldopa	BMI	2.2	0.08

[1] Odds ratios with reference categories: BMI <25, no diabetes, never use of digoxin, and less than 5 years' use of methyldopa.
[2] Tests for interaction between variables not significant ($p > 0.05$).

Table 5

Family history of cancer in male breast cancer cases and controls in Scandinavia, 1987–1991

	Cases (%)	Controls (%)	OR (95% CI) [1]
Prostate cancer (father)			
No/unknown	149 (96)	454 (97)	1.0 (R) [2]
Yes	7 (4)	14 (3)	1.6 (0.6–4.1)
Breast cancer (female relatives)			
No/unknown	123 (79)	433 (93)	1.0 (R)
Yes	33 (21)	35 (7)	3.3 (2.0–5.6)
Breast cancer (male relatives)			
No/unknown	153 (98)	473 (99)	1.0 (R)
Yes	3 (2)	5 (1)	1.5 (0.3–6.3)
Breast cancer (wife)			
No/unknown	150 (96)	460 (96)	1.0 (R)
Yes	6 (4)	18 (4)	0.9 (4–2.4)

[1] Odds ratio (95% confidence interval).
[2] R denotes reference category.

Several associations were seen in other studies, which were not substantiated in this setting; namely an association with high education, fertility, marital status, testicular injury, liver disease and religion. We found few associations for types of employment, with the exception of a possible association with work in the plastic and rubber industry, which was not observed in a previous study on occupational risk factors for male breast cancer in Sweden (14). This study, based on the Cancer Environment Registry in Sweden, showed the largest standard incidence ratios for soap- and perfume-making, for journalists and editors. There was also a statistical association with working in the newspaper printing industry.

For exposure to test x-rays and fluoroscopies, the result is less certain, but compatible with an increased risk, but we could not distinguish between chest x-rays and fluoroscopies.

The respondents filled out the questionnaires to a high degree and there was little indication that proxy respondens helped them. The questionnaire was detailed enough on many items to allow for thorough analyses (e.g. occupation, smoking and medication). By posing the questions about gynaecomastia so that patients also indicated when they sought for symptoms and at which hospital, we discovered that many patients reported the signs of their breast cancer as a gynaecomastia and we therefore

refrained from further evaluation of that variable. This type of misunderstanding may lie behind some of the strong relations seen in previous studies.

Despite the fact that this study is large compared with most other studies in the field, the number of cases does not permit an extensive evaluation of complex confounding patterns and/or interactions. Thus, theoretically, residual confounding may be present despite our stratified analyses of, for example, BMI, diabetes and medication. On the other hand, we found no plausible biological theory that could motivate a more speculative statistical modelling in this case.

Overall, there was a low response rate, most pronounced in the higher age group. For most of the risk factors studied here, however, there are no strong reasons why a lower response rate should introduce a bias. The exception may be a strong family history, where cases with a family history may be more likely to report symptoms than controls in the same situation.

The main methodological constraint is that many cases died before making contact. Exposures related to more aggressive male breast cancer may be missed. Also, if an important exposure is related to a high risk of dying—e.g. liver cirrhosis, heavy smoking—the effect of such an exposure may be underestimated.

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