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Male gynecomastia and risk for malignant tumours – a cohort study

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Abstract

Background: Men with gynecomastia may suffer from absolute or relative estrogen excess and their risk of different malignancies may be increased. We tested whether men with gynecomastia were at greater risk of developing cancer.

Methods: A cohort was formed of all the men having a histopathological diagnosis of gynecomastia at the Department of Pathology, University of Lund, following an operation for either uni- or bilateral breast enlargement between 1970–1979. All possible causes of gynecomastia were accepted, such as endogenous or exogenous hormonal exposure as well as cases of unknown etiology. Prior to diagnosis of gynecomastia eight men had a diagnosis of prostate carcinoma, two men a diagnosis of unilateral breast cancer and one had Hodgkin's disease. These patients were included in the analyses. The final cohort of 446 men was matched to the Swedish Cancer Registry, Death Registry and General Population Registry.

Results: At the end of the follow up in December 1999, the cohort constituted 8375.2 person years of follow-up time. A total of 68 malignancies versus 66.07 expected were observed; SIR = 1.03 (95% CI 0.80–1.30). A significantly increased risk for testicular cancer; SIR = 5.82 (95% CI 1.20–17.00) and squamous cell carcinoma of the skin; SIR = 3.21 (95% CI 1.71–5.48) were noted. The increased risk appeared after 2 years of follow-up. A non-significantly increased risk for esophageal cancer was also seen while no new cases of male breast cancer were observed. However, in the prospective cohort, diagnostic operations for gynecomastia may substantially have reduced this risk

Conclusions: There is a significant increased risk of testicular cancer and squamous cell carcinoma of the skin in men who have been operated on for gynecomastia.

Background

Gynecomastia is a benign condition appearing both uni- and bilaterally. It is more common during some time periods in life, such as early puberty and late adulthood [1]. Beside an endogenous hormonal imbalance in estrogen/

androgen ratio, drugs having estrogenic effects or diseases associated with injuries to gonads or liver affecting the estrogen/androgen ratio may predispose to gynecomastia [2–4]. Also, many anti-psychotic drugs may induce hyperprolactinemia and thus gynecomastia. It has been claimed

Table 1: Number of individuals are shown in relation to age at inclusion in the cohort and age at last follow up or death.

| | Number of men at inclusion | Number of men at last follow up or death |
|-------|----------------------------|--|
| 10-14 | 18 | 0 |
| 15-19 | 57 | 0 |
| 20-24 | 54 | 0 |
| 25-29 | 36 | 1 |
| 30-34 | 23 | 2 |
| 35-39 | 23 | 22 |
| 40-44 | 15 | 49 |
| 45-49 | 21 | 48 |
| 50-54 | 23 | 48 |
| 55-59 | 25 | 36 |
| 60-64 | 29 | 27 |
| 65-69 | 35 | 29 |
| 70-74 | 43 | 39 |
| 75-79 | 31 | 45 |
| =80 | 12 | 99 |

that gynecomastia is more common among men who later develop testicular cancer and breast cancer [5-12]. Sometimes the treatment of malignancies may be the cause for gynecomastia, such as oestrogen treatment in prostate carcinoma and cytostatic treatment in various malignancies [13-16].

The increased risk for malignant tumours with gynecomastia has previously been described in some case-control studies. However, no earlier prospective study has been published. In order to elucidate the possible adverse or protective effect on malignancy risk of gynecomastia we formed a prospective cohort of men of whom a histopathological diagnosis had been obtained through an operative biopsy.

Methods

Four hundred forty five men who had been operated for diagnostic purpose due to unilateral or bilateral gynecomastia in 1970-79 and of whom the pathology specimens had been sent for diagnosis to the Department of Pathology, University Hospital, Lund, Sweden, were included in the cohort. During this time period diagnostic (open) biopsies were very common in men with breast enlargement to exclude malignant processes. Later the operative biopsy has been replaced with fine needle biopsies. The Pathology Department has an exclusive population based accrual of specimen in the South-West of the South Swedish Health Care Region. In this cohort 198 (44.5 %) men were older than 50 years and 73 (16.4 %) were younger than 20 years of age at time of diagnostic operation for gynecomastia (Table 1).

With the help of the unique personal identification number the vital status and the cancer incidence up to age 99 years of these referents were then identified from the population based Census Registry, the Cause of Death Registry and the Swedish Cancer Registry (South Swedish Regional and the National Swedish Tumour Registry). Any individual could have had more than one tumour registered. The vital status was determined up to Jan 1st, 2000. The median follow up time was 266 months, i.e. 22.2 years. No subject was lost to follow up. During the follow up time, 208 men had died and none emigrated. The observed versus expected numbers of various malignant tumours were then calculated using reference data from the southern health care region. Cause specific standardised incidence ratios (SIRs) and 95 % confidence intervals (CIs) were calculated. The observed number of cancer cases was assumed to follow a Poisson-distribution. Hence, both 95% confidence intervals for the SIR's and the test hypothesis $SIR = 1$ (i.e. the cancer incidence is the same in both populations) were based on the Poisson distribution. The term "significant" refers to a p value of 0.05. All tests were two tailed.

Results

In table 2 the observed and expected numbers of malignant tumours, the SIRs and the 95 % CIs for all malignant tumours and different tumour types are shown. Men with gynecomastia had an overall risk for malignant tumours similar to that in the reference population; i.e. 68 observed versus 66.07 expected cases, $SIR = 1.03$ (95% CI 0.80-1.30). The risk for testicular cancer in the gynecomastia patients was significantly increased; 3 observed versus 0.52 expected, $SIR = 5.82$, (95% CI 1.20-17.00). Also, there were 13 observed cases of squamous cell carci-

Table 2: Risk of malignant tumours in men up to age 99 after a histopathological verified diagnosis of gynecomastia 1970–79. Follow up time includes 1970–1999 (8375.2 years). The cohort consists of 446 men.

| Diagnosis | | OBS | EXP | SIR | 95% Confidence interval |
|----------------|------------------------------|-----|-------|------|-------------------------|
| 140–209 | All malignant tumours | 68 | 66.07 | 1.03 | 0.80 1.30 |
| 140 | Lip | 1 | 0.70 | 1.43 | 0.04 7.97 |
| 141_3_4 | Oral cavity | 0 | 0.51 | 0.00 | 0.00 7.18 |
| 142 | Parotid glands | 0 | 0.19 | 0.00 | 0.00 19.71 |
| 145–148 | Pharynx, hypopharynx | 0 | 0.42 | 0.00 | 0.00 8.69 |
| 150 | Esophagus | 3 | 0.78 | 3.82 | 0.79 11.17 |
| 151 | Stomach | 3 | 4.09 | 0.73 | 0.15 2.15 |
| 153 | Colon | 7 | 5.43 | 1.29 | 0.52 2.66 |
| 154 | Rectum | 0 | 3.57 | 0.00 | 0.00 1.03 |
| 1550 | Liver and intrahepatic ducts | 1 | 0.94 | 1.06 | 0.03 5.90 |
| 1551–1559 | Gallblader & bile ducts | 1 | 0.67 | 1.50 | 0.04 8.34 |
| 157 | Pancreas | 1 | 1.95 | 0.51 | 0.01 2.86 |
| 160 | Nasal cavities & sinus | 0 | 0.13 | 0.00 | 0.00 27.71 |
| 161 | Larynx | 0 | 0.65 | 0.00 | 0.00 5.67 |
| 1620–1621 | Trachea & lung | 6 | 6.31 | 0.95 | 0.35 2.07 |
| 1622 | Mesothelioma | 0 | 0.31 | 0.00 | 0.00 12.04 |
| 170 | Male breast cancer | 0 | 0.09 | 0.00 | 0.00 42.96 |
| 177 | Prostate | 16 | 16.21 | 0.99 | 0.56 1.60 |
| 178 | Testicle | 3 | 0.52 | 5.82 | 1.20 17.00 |
| 180 | Kidney | 1 | 2.18 | 0.46 | 0.01 2.55 |
| 181 | Urinary bl.,urinary tc. | 1 | 4.85 | 0.21 | 0.01 1.15 |
| 190 | Melanoma | 0 | 1.73 | 0.00 | 0.00 2.1 |
| 191 | Skin excl melanoma | 13 | 4.06 | 3.21 | 1.71 5.48 |
| 193 | Brain & nervous system | 1 | 1.71 | 0.59 | 0.01 3.26 |
| 194 | Thyroid | 0 | 0.30 | 0.00 | 0.00 12.43 |
| 196–197 | Bone & soft tissue | 0 | 0.49 | 0.00 | 0.00 7.59 |
| 200+202 | Non-Hodgkin's lymphoma | 1 | 1.96 | 0.51 | 0.01 2.84 |
| 201 | Hodgkin's disease | 0 | 0.28 | 0.00 | 0.00 12.97 |
| 203 | Multiple myeloma | 0 | 0.90 | 0.00 | 0.00 4.11 |
| Acute leukemia | | 1 | 0.54 | 1.86 | 0.05 10.38 |
| 204.1 | Chr. lymph. leukemia | 0 | 0.74 | 0.00 | 0.00 4.98 |
| 205.1 | Chr myeloid leukemia | 0 | 0.18 | 0.00 | 0.00 20.83 |
| 208 | Polycythemia vera | 0 | 0.17 | 0.00 | 0.00 21.67 |

noma of the skin versus 4.06 expected, SIR = 3.21, (95%CI 1.71–5.48). Three men developed esophageal cancer versus 0.78 expected, giving a SIR of 3.82, (95% CI 0.79–11.17), which does not reach the defined significance level. The risk for prostate carcinoma was unaltered and nobody developed breast cancer during the follow-up. A decreased risk was observed for rectal carcinoma 0 cases versus 3.57 expected, SIR = 0.00 (95%CI 0.00–1.03).

In table 3 the SIRs for all malignancies and separately for testicular, esophageal and squamous skin cancer are presented in relation to the time interval since diagnosis of gynecomastia. No increased risk for any malignancy was seen within the first two years following gynecomastia diagnosis. An increased risk was seen for testicular cancer, esophageal cancer and skin cancer after two years of follow up. Whilst the risk of skin and esophageal cancer in-

creased with longer follow up, the risk for testicular cancer remained the same.

In table 4 the SIRs for testicular, esophageal and squamous skin cancer are shown associated with the age at diagnosis and age during follow. The risk for testicular cancer was significantly increased only in men with gynecomastia diagnosed before the age of 50 years and with follow up to the age of 50 years; SIR = 6.71(95%CI 1.38–19.60). The risk for esophageal cancer was significantly increased in men with gynecomastia diagnosed above 50 years of age, SIR = 4.75 (95%CI 1.00–13.90). The risk for skin cancer was increased in men with diagnosis of gynecomastia at any age but with a follow up extending after 50 years of age. Increased risk of squamous skin cancer occurred both in unilateral and bilateral cases while testicu-

Table 3: SIR values(95% CI) in relation to tumour type and different time intervals of follow up since diagnosis of gynecomastia. Also number of individuals and personyears for each interval are shown. The lead time between gynecomastia and tumour diagnosis was for esophageal cancer 8 years (6–10 years), skin cancer 6 years (3–25 years) and testicular carcinoma 10 years (3–18) years.

| Tumour type | Time interval since diagnosis of gynecomastia | | | |
|-------------------------------|---|------------------|-------------------|-------------------|
| | 0–2 years | >2–10 years | =10 years | overall |
| all sites | 0.15(0.00–0.85) | 1.19(0.81–1.68) | 1.07(0.75–1.49) | 1.03 (0.80–1.30) |
| testicle | 0.00(0.00–116.2) | 6.60(0.17–36.76) | 6.02(0.73–21.73) | 5.82 (1.20–17.00) |
| esophagus ca 0.00(0.00–46.43) | 2.57(0.07–14.35) | 6.31(0.76–22.79) | 3.82 (0.79–11.17) | |
| skin cancer (melanoma excl.) | 0.00(0.00–12.33) | 2.23(0.72–5.20) | 5.30(2.29–10.43) | 3.21(1.71–5.48) |
| number | 443 | 426 | 337 | 445 |
| personyears | 870 | 3076 | 4428 | 8375 |

Table 4: Age at gynecomastia diagnosis and risk of tumours in relation to follow up time. SIR values(95% CI).

| Tumour type | Age at diagnosis | | |
|------------------------------|-------------------|-------------------|-------------------|
| | <50 years | =50–99 years | >50 years |
| follow up | 0–49 years | =50–99 years | =50–99 years |
| testicle | 6.71(1.38–19.60) | 0.00(0.00–119.54) | 0.00(0.00–107.07) |
| esophagus cancer | 0.00(0.00–337.54) | 0.00(0.00–27.61) | 4.75(1.00–13.90) |
| skin cancer (melanoma excl.) | 0.00(0.00–36.76) | 7.87(1.62–22.99) | 2.84(1.36–5.23) |
| number | 246 | 124 | 197 |
| personyears | 4869 | 1135 | 2292 |

lar cancer was predominantly seen in unilateral cases (table 5).

Discussion

The present study, being the so far only published prospective investigation in the literature with a maximum follow up time of 30 years, demonstrates a significantly increased risk for testicular and squamous skin cancer in men with a prior histopathological diagnosis of gynecomastia. Also a non-significantly increased risk for esophageal cancer was noted while no cases of male breast cancer was seen. Overall the male patients with gynecomastia did not show an incidence of malignancy different to that in the general population.

Gynecomastia develops in a setting of imbalance between androgens and estrogens where there is a relative estrogen excess [2–4]. Gynecomastia is more common at pubertal ages and in older men [1]. This was also evident in our material (table 1). It has previously been shown in case series that testicular cancer may sometimes prior to diagnosis induce gynecomastia due to pathologic HCG secretion [5–7]. In this prospective series two patients developed testicular seminomas and one patient a testicular teratoma fol-

lowing the diagnosis of gynecomastia years earlier. Chemotherapy may injure gonadal and hormonal functions and are associated with development of gynecomastia [14–16]. Some drugs, mimicking or having estrogenic or antiandrogenic effects, may also be associated with development of gynecomastia [2–4]. This explains the rather large group of cases with gynecomastia with a prior diagnosis of prostate carcinoma where estrogens have been used as a treatment. Interestingly in our study there was no sign of a protective effect for prostate carcinoma due to the relative estrogen excess.

A rare malignancy, male breast cancer, has in epidemiological studies been associated with prior history of gynecomastia [8–12]. In our investigation no prospective cases of male breast cancer was seen, while two men after they had developed male breast cancer later developed gynecomastia that was not drug induced in the contralateral breast. Also one of the cases had gynecomastia surrounding the breast tumour at diagnosis. In 44 of the 445 cases bilateral extirpation of the breast tissue was done and in the remaining cases a unilateral excision was done. This surgical removal of breast tissue in men potentially prone to develop breast carcinomas due to the gynecomastia,

Table 5: SIR values(95%CI) in relation to overall cancer incidence and some selected tumour types and laterality and bilaterality at diagnosis of gynecomastia. Included are only prospective cases.

| Tumour type | Gynecomastia | | |
|------------------------------|---------------------|------------------|-------------------|
| | Unilateral right | left | Bilateral |
| all sites | 1.22(0.89–1.71) | 0.90(0.60–1.31) | 0.87(0.35–1.79) |
| testicle | 4.03(0.10–22.97) | 9.26(1.12–33.47) | 0.00(0.00–71.05) |
| esophagus | 6.11(0.74–22.08) | 0.00(0.00–10.22) | 10.33(0.26–57.55) |
| skin cancer (melanoma excl.) | 2.44(0.67–6.29) | 4.18(1.80–8.24) | 1.99(0.05–11.06) |
| number | 196 | 194 | 55 |
| personyears | 3588 | 3910 | 878 |

may have substantially reduced the risk for carcinoma as prophylactic operations or reduction mammoplasty surgery previously has been shown to reduce the risk of breast cancer in women [17,18]. Liver injury may be associated with gynecomastia [2] and in our series chronic alcoholism was present in 7 cases of which two had known cirrhosis. The increased risk of esophagus cancer may be another indicator of alcoholism and secondary liver injury in a subset of the patients [19]. All cases of esophageal cancer occurred in individuals with a gynecomastia diagnosis after the age of 50 years. We have no explanation for the higher risk of squamous cell carcinoma of the skin. No study has previously associated development of squamous cell carcinoma with gynecomastia and the finding needs to be confirmed in future studies, although the risk relationship in our study was strong. The reason for the relationship is unclear as the development of skin tumours in general has not been associated with hormonal risk factors. That some skin tumours are due to papilloma virus infections could lend support to a theory of increased virus activity/effects in individuals exposed to estrogens as is the case in cervical carcinoma and its virus related carcinogenesis due to papilloma virus [20]. Also synergistic action between chronic estrogen exposure and the oncogenes of HPV16 that coordinates squamous carcinogenesis in the female reproductive tract of K14-HPV16 transgenic mice has been found [21]. HPV16 is however confined to mucous membranes and it is not known if other HPV types in a similar matter would interact in the skin with estrogen. A decreased risk of rectal carcinoma was noted, and we have no biological explanation for this finding although it has long been known that females have a lower death rate and risk of the tumour [22].

It is notable that among the 13 skin tumours 5 occurred in individuals with multiple squamous cell carcinomas of the skin. Including tumours occurring prior to gyneco-

mastia 8 individuals of 9 had multiple tumours of the skin. The age at diagnosis of skin cancer was above 50 years of age in all cases, and the risk increased with longer follow up and was evident both for cases with a gynecomastia diagnosis before as well as after 50 years of age. From a clinical point of view it is questionable whether screening of tumours would be worth while in patients with gynecomastia. On the other hand, the two tumours most clearly displaying an increased risk, ie. testicular carcinoma and squamous skin cancer rather easily can be screened by general examination. If also male breast cancer is included as a risk a possible clinical work up in a man presenting with gynecomastia should evaluate the following points; is there a endogenous or exogenous hormonal cause?; has the patient been taking drugs that may cause gynecomastia?; is there a known accompanying disease causing a liver or gonadal injury?; can tumour disease in testis, skin and breast be excluded on clinical grounds?. For men with a gynecomastia diagnosis after 50 years of age the risk of testicular cancer is negligible whilst a gynecomastia diagnosis before and after 50 years of age may both indicate an increased the risk for skin cancer.

Conclusions

In conclusion the prospective investigation confirms an increased risk for testicular cancer in men with a prior history of gynecomastia. Also skin cancer and esophageal cancer were more common among men with gynecomastia. No prospective case of male breast carcinoma was seen, although two male breast cancer cases occurred prior to gynecomastia diagnosis.

Competing interests

None declared.

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