Marked Increase in Incident Gynecomastia: A 20-year National Registry Study 1998-2017

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Abstract

Context: Gynecomastia, the proliferation of mammary glandular tissue in the male, is a frequent but little studied condition. Available prevalence data are based on selected patient populations or autopsy cases with their inherent bias.

Objective: To evaluate the age-related incidence and secular trends in gynecomastia in the general population.

Design: Observational, 20-year national registry study.

Setting: Population-based study using nationwide registry data.

Participants: All Danish males (0-80 years) with a first-time diagnosis of gynecomastia.

Intervention(s): NA

Main outcome measures: All Danish males (0-80 years) were followed-up for incident diagnosis of gynecomastia in the Danish National Patient Registry from 1998-2017 using International Codes of Diseases, ICD-10 and the Danish Health Care Classification System. Age specific incidence rates were estimated. The hypothesis tested in this study was formulated prior to data collection.

Results: Overall a total 17,601 males (0-80 years) were registered with an incident diagnosis of gynecomastia within the 20-year study period, corresponding to 880 new cases per year and an average 20-year incidence of 3.4 per 10,000 men (0-80 years). The average annual incidence was 6.5/10,000 in post-pubertal males age 16-20 years and 4.6/10,000 in males age 61-80 years, with a respective 5 and 11-fold overall increase in these two age-groups over the 20-year period.

Conclusions: The incidence of gynecomastia has dramatically increased over the last 20 years implying that the endogenous or exogenous sex steroid environment has changed, which is associated with other adverse health consequences in men such as an increased risk of prostate cancer, metabolic syndrome, diabetes type 2 or cardiovascular disorders.

Introduction

Gynecomastia is defined as the benign proliferation of mammary glandular tissue in the male. It is a frequent condition affecting between 32-65%, depending on age and diagnostic criteria used (1). Gynecomastia is clinically diagnosed by breast palpation for glandular tissue by comparing the consistency of the subareolar tissue with the surrounding tissues (2). Further, true gynecomastia (the presence of glandular breast tissue) is distinguished from pseudo-gynecomastia (or lipomastia), which is the result of accumulation of breast adipose tissue in absence of palpable glandular tissue, commonly associated with overweight and obesity (2).

Male breast tissue expresses both estrogen and androgen receptors. Estrogens (or estrogenic compounds) stimulate proliferation of breast tissue and androgens inhibit proliferation (1). Gynecomastia reflects an increased ratio of estrogens to androgens, by either reduced androgen exposure, increased estrogen exposure, or a combination of both (3-5).

Physiological gynecomastia has three major peaks across the male life-course; in infancy, in puberty and in older age. Approximately 70% of infant boys transiently exhibit gynecomastia due to placental transfer of maternal estrogens from the mother to child, while postnatal gynecomastia may be caused by high estrogen secretion during the early postnatal activation of the Hypothalamic-Pituitary-Testis (HPT) hormone axis at around 3 months of age (6). This physiological gynecomastia disappears spontaneously, usually by 12 months of age. Gynecomastia beyond 12 months is rare and may indicate underlying pathology, such as Sertoli cell tumors in boys with Carney complex (7) or Peutz-Jeghers syndrome (8). Also, accidental exposure to estrogen-containing gel can result in infant gynecomastia(1).

In mid-puberty (Tanner genital stages 3-4) around 50-70% of boys exhibit gynecomastia which also usually resolves spontaneously after 6-24 months (9-11). The mechanism is due to decreased testosterone production at the time, resulting in an increased estrogen to testosterone ratio (12). The

most common cause of post pubertal gynecomastia in young adults is often due to persistent normal gynecomastia without an underlying disorder (13), however persistent pubertal gynecomastia is also observed in patients with low circulating androgens due to Klinefelter syndrome or defective androgen receptor signaling due to partial androgen insensitivity syndrome (PAIS) (14).

In adult and elderly men, gynecomastia relates to a reduction in androgen production, especially with concomitant weight gain (15). Around half of adult men have an underlying identified potential cause associated with gynecomastia (13). Most commonly, systemic disorders (chronic kidney or liver disease or obesity), medication including anti-androgens and endocrinopathies (androgen resistance syndrome, hyperprolactinemia, hyperthyroidism, hypogonadism, Klinefelter's syndrome). The likely underlying pathology varies with age. In younger adult men, hCG-producing testicular tumors (non-seminomas), Klinefelter syndrome, marijuana use, and abuse of anabolic steroids are possible causes (1). In older men, obesity, hypogonadism, medications (e.g. spironolactone) are more common (1). Gynecomastia in prepubertal boys and young adults may indicate serious pathology and requires investigation. The condition may also cause cosmetic concerns about body image, local pain, tenderness or a fear of breast cancer (1;2;4).

The prevalence of adult-onset gynecomastia in the general population is unknown. Published data are derived from selected patient populations (16;17) or autopsy cases (18) with their inherent biases. The aim of this study was to evaluate the age-related incidence and secular trends of gynecomastia in the general adult male population using a nationwide, register based study.

Methods

Denmark has a genetically homogenous population of 5.8 million inhabitants in 2019 (of which 2.89 million are men). All are registered with the Danish Civil Registration system with a unique 10-digit personal identification number for national health and administrative purposes. The Danish National Patient Registry (DNPR) established in 1977 is one of the world's oldest nationwide

hospital registries and contains records of all individual level patient-discharges from private and public hospitals. Since 1995 this registry has included all treatments in hospital-based outpatient clinics. Reporting is compulsory and linked to the allocation of resources. At least one diagnostic code according to World Health Organizations International Classification of Diseases, 10th edition (ICD-10, from 1994 onward) is recorded for each patient hospital contact. Although the DNPR follows the current international standards for disease classification, the ICD-10 version used in Denmark sometimes has ABC extensions added to specific diagnostic codes. These extensions make the Danish version of the ICD-10 more detailed than the international ICD-10 (19). The classifications used in the DNPR are provided in the Danish Health Care Classification System (Danish, *Sundhedsvæsenets Klassifikations System* [SKS]) (20), which is a collection of international, Nordic, and Danish classifications. In the present study we identified all hospital patient records of first-time diagnoses of gynecomastia. The identification of gynecomastia was based on the specific gynecomastia SKS code N62.9A and excludes other forms of breast enlargements such as hypertrophy of breast (not otherwise specified, NOS), and massive pubertal hypertrophy of breast included in the ICD-10 N62. Because healthcare is free in Denmark, complete case ascertainment is expected in these high-quality, validated registries (21).

Acknowledging the trimodal age dependence of gynecomastia diagnoses, results are presented according to pre-defined age groups (cf. statistical analyses).

Statistical analyses

First, the crude distribution of incident cases according to predefined age groups: 0-9, 10-15, 16-20, 21-40, 41-60, 61-80 years were recorded and the average incidences were estimated by computing an annual mean of the total number of males in the reported age group in Denmark during the 20-year study period, and in 5-year sub-periods for age groups (0-20, 21-40, 41-60, 61-80 years), within the entire study period from 1998 – 2017. Second, the yearly incidences were estimated for

each age group separately and visualized graphically as a function of calendar year. Finally, age-specific average incidences per 10,000 were calculated. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to calculate incidences by standard methods.

Ethics

Research was conducted in accordance with principles of the Declaration of Helsinki. The present register based study was approved by the Danish Data Protection Agency (J.nr: 2012-58-0004) and according to Danish law, ethical approval is not required for registry based epidemiological studies. The study is reported according to the STROBE (Strengthening the Reporting of Observational Studies) guidelines and checklist (22).

Results

Overall a total of 17,601 males (0-80 years) were registered with a first-time diagnosis of gynecomastia within the 20-year study period, corresponding to an average of 880 new cases per year in Denmark and an average 20-year incidence of 3.4 per 10,000 men per year (0-80 years). The 20-year average incidence of gynecomastia for specified age groups 0-9, 10-15, 16-20, 21-40, 41-60, 61-80 years per 10,000 men was <1, 2.4, 6.5, 4.2, 2.7 and 4.6 respectively (Table 1).

Figure 1 shows the trends incidence of gynecomastia subdivided by calendar year (year of first diagnosis) and according to the age groups specified above. For post-pubertal men (age 16-20 years) we observed the highest overall incidences, with an overall 5-fold increase in the yearly incidence during the 20-year period from 1998 to 2017. An over 10-fold overall increase in incidence was detected in age groups (10-15, 21-40, 41-60, 61-80 years) and no change in incidence was detected for pre-pubertal (age 0-9 years) boys, in which the condition was rare. The increase in incidences within the 20-year period were driven within the first 15-years (1998-2012), and in more recent years (2011-2017) incidence rates levelled off for all age groups (Figure 1).

The trend in age-specific incidence of gynecomastia is shown in Figure 2. Two broad peaks were observed, the first amongst adolescents to young adults (14-30 years) and the second amongst elderly men (age 70-80 years) (Figure 2).

When assessing the time-trends in average 5-year incidences of gynecomastia, a steady increase was observed for all age-groups within the period 1998-2012, with levelling of within the most recent years (2013-2017) (Table 2).

Discussion

This is the first population-based report of gynecomastia across the life-course. Within the 20-year observation period we detected an upward trend in the yearly incidence in gynecomastia apparent in all age groups except the pre-pubertal (0-9 years) boys. The average annual incidence was 6.5/10,000 in post-pubertal males age 16-20 years and 4.6/10,000 in males age 61-80 years, with respective overall 5 and 11-fold increase in these two age-groups over the 20-year period. The highest incidence of gynecomastia was detected in post-pubertal (16-20 years) men.

Although gynecomastia is not a serious condition, this growing trend in incidence suggests that the endogenous or exogenous sex steroid environment has changed, potentially due to lifestyle and environmental factors. This is concerning because changes in sex steroid exposures may have other adverse health consequences in men such as an increased risk of prostate cancer (23), metabolic syndrome (24;25), diabetes type 2 (26) or cardiovascular disorders (coronary heart disease, heart failure, or stroke) (27;28).

Increasing obesity incidence (all ages) within the past 20-years in Denmark could be a large contributory factor to the increase in incident of gynecomastia (29;30), probably through fatty tissue aromatization of testosterone to estradiol, increasing the estrogen/androgen ratio, which may manifest as gynecomastia or because fat resembles breasts (lipomastia).

The high incidence of gynecomastia in elderly men (61-80 years) in this study is consistent with previously published evidence that androgen production decreases with age (16;31), the increase in rate may be due to increased obesity as it is established that rates are high in men with concomitant weight gain in later life (15). Furthermore, elderly men nowadays have lower testosterone than similarly aged men decades ago as shown in a US population (32) and confirmed Europe in Danish (33) and Finish (34) populations. In the present study, a high and increasing incidence of gynecomastia was also observed in post-pubertal men age 16-20 years, even greater than in pubertal males age 10-15 years where pubertal gynecomastia is physiological. The mechanisms underlying these age-related and secular time trends in incidence are unknown but are likely to reflect environmental/lifestyle rather than genetic factors.

Increasing obesity incidence (all ages) within the past 20-years in Denmark (29;30) is probably the main contributary factor to the observed trends. Obese men have an increased estrogen/androgen ratio as testosterone is aromatized to estradiol in fatty tissue which may manifest as gynecomastia. Secondly, growing abuse of non-medical anabolic-androgenic steroids (non-medical AAS), mainly driven by a desire to boost physical strength and improve appearance are considered a serious public health problem worldwide. In Nordic countries the estimated prevalence of use is around 2.3% and increasing (35) and this may have contributed to the high and increasing incidence of gynecomastia. This effect is most likely to manifest in younger men and may explain the trend observed in men aged 16-20 years (1).

Thirdly, increased exposure to environmental endocrine disrupting chemicals (EDCs) may have contributed to our findings. These ubiquitous chemicals such as phthalates and biphenol A are present in plastics and cosmetics and may have estrogenic effects (36). Endocrine disrupting chemical exposures have increased in Demark over the last 20 years and could increase the incidence of gynecomastia due to hormone disrupting mechanisms (37). Relatively few studies have

addressed the association between EDCs and gynecomastia and findings have been conflicting. A small case control study in pubertal boys reported higher circulating concentrations of two forms of phthalates (a ubiquitous EDC) in pubertal boys with gynecomastia (n=44) compared to controls (n=21) without the condition (38). Although a large cross-sectional study in 2012 failed to show an association between urinary phthalate concentrations and gynecomastia in otherwise healthy pubertal boys (39), one small case report from 3 prepubertal boys reported an association between lavender and tea tree oil application (believed to have EDC activity) and gynecomastia (40).

Fourth, medications such as anti-androgens (e.g. flutamide, finasteride, spironolactone etc), hormones (e.g. estrogens, clomiphene citrate, hCG) anti-ulcer drugs (e.g. cimetidine, ranitidine, proton pump inhibitors) psychoactive drugs (e.g. haloperidol, phenothiazines) and alcohol abuse may all potentially cause gynecomastia (1). Thus, any potential time-trend changes in use of these medications or exposures within the same period may partially explain our findings, albeit to our knowledge we do not expect that the use of these drugs has changed significantly.

Finally, there are several established non-drug related causes of gynecomastia including endocrine abnormalities (androgen resistance syndrome, hyperprolactinemia, hyperthyroidism, hypogonadism, Klinefelter's syndrome), systemic disorders (chronic kidney or liver disease or obesity) and cancer (adrenal, testicular, breast, liver, lung) (1). However, apart from obesity, the incidence of these conditions is not increasing at rates high enough to account for the secular trend observed in our study and are unlikely to account for the changes we observed. For example, testicular non-seminomas (132 new cases in Denmark in 2016 (41)) commonly produce hCG which result in gynecomastia. Although the incidence of non-seminomas testicular cancer has increased several fold in all industrialized countries during the 20th century (42-44), the proportion of gynecomastia cases ascribed to the reported upwards trend is expected to be low.

Strengths and limitations.

In Denmark individual level information on disease has been collected in nationwide registries for several decades. Because healthcare is free, these high-quality registries, known for validity and completeness have complete gynecomastia disease ascertainment from public Danish hospitals (including outpatients) with minimal bias in data collection due to socio-economic status. However, there are some limitations: The diagnosis is of gynecomastia is limited to few specialized hospital outpatient clinics by trained clinicians in Denmark and determined according to European Academy of Andrology (EAA) clinical practice guidelines-gynecomastia evaluation and management (breast tissue by palpation) (1). These specialists are supposed to follow these guidelines; however, we have no information on the quality of control in Denmark of the gynecomastia diagnosis in Denmark and the disease codes for gynecomastia were not validated by concurrent investigation of hospital outpatient records. Some of the included men may have had lipomastia misclassified as gynecomastia and this may have affected the number of cases included. Secondly, although the evaluation of gynecomastia is centralized to few specialized hospital outpatient departments, we cannot exclude that some men underwent cosmetic treatment for gynecomastia in a private clinic without registration of the appropriate ICD10 code, or that some with the disease did not seek hospital contact, which may have underestimated incidence rates. Finally, we did not have data on underlying pathologies or other potential underlying causes of gynecomastia such as obesity, medication use, non-medical AAS use, EDC exposure or non-drug related causes and we could not determine the impact of these factors on the trends we detect.

Perspectives.

This is the first population-based report of gynecomastia across the life-course. We have demonstrated a high and growing incidence of gynecomastia in Danish men over the past 20 years. The mechanisms underlying these trends are unknown.

Conclusion

The incidence of gynecomastia has dramatically increased in Denmark over the past 20 years. The mechanisms underlying this trend are uncertain, but growing exposure to environmental factors such as EDC as well as changes in endogenous testosterone levels and lifestyle factors such as obesity may be driving this concerning phenomenon.

Affiliations

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Author contribution Statement

EVB and TK prepared data for analyses, performed statistical analyses and drafted the manuscript. AJ and EVB contributed to the concept and designed the study. All authors contributed to critical interpretation of data, and the final draft of the manuscript.

Data Availability

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Tables

Table 1. Total number of incident cases and average annual 20-year incidence of gynecomastia by age-group, 1998 – 2017.

Age-group (years)	Total incident cases (N)	Average yearly number of cases (N)[b]	Average annual population (N)[a]	Incidence per 10,000 per year
0 – 9	51	<5	335,881	<1
10-15	995	50	203,618	2.4
16-20	2,175	161	166,303	6.5
21 - 40	6,156	308	734,987	4.2
41 - 60	4,075	204	761,583	2.7
61 - 80	4,149	207	453,235	4.6
0-80	*17,601*	*880*	*2,578,803*	*3.4*

[a]Estimated by computing the annual mean of the total population of males in the reported age group in Denmark during the 20-year period.
[b]Estimated by computing the annual mean of the number of incident cases of gynecomastia in Denmark during the 20-year period.

Table 2. Average 5-year incidence of gynecomastia according to age, 1998 – 2017.

Age-group (years)*	Period	Total incident cases (N)	Average yearly number of cases (N)	Average annual population (N)[a]	Incidence per 10,000 per year
10-15	1998 - 2002	56	11	184,908	0.61
	2003 - 2007	192	38	211,042	1.82
	2008 - 2012	328	66	212,597	3.09
	2013 - 2017	419	84	205,927	4.07
16-20	1998 - 2002	135	27	147,499	1.83
	2003 - 2007	402	80	154,890	5.19
	2008 - 2012	843	169	178,573	9.44
	2013 - 2017	795	159	184,249	8.63
21 - 40	1998 - 2002	352	70	785,965	0.90
	2003 - 2007	1155	231	734,366	3.15
	2008 - 2012	2170	434	699,935	6.20
	2013 - 2017	2479	496	719,683	6.89
41 - 60	1998 - 2002	170	34	738,685	0.46
	2003 - 2007	784	157	761,576	2.06
	2008 - 2012	1461	292	767,528	3.81
	2013 - 2017	1414	283	778,543	3.63
61 - 80	1998 - 2002	147	29	372,991	0.79
	2003 - 2007	680	136	415,115	3.28
	2008 - 2012	1448	290	486,602	5.95
	2013 - 2017	1630	326	538,231	6.06

[*]The registered cases of pre-pubertal gynecomastia (0-9 years) in the Danish National Patient Registry (DNPR) is low. Un-aggregated data in numbers so low enough to enable person identification in publications is under the strict control of the General Data Protection Regulation (GDPR) in Denmark (patient confidentiality), thus analysis of 5-year trends in the 0-9 year age group was not feasible.
[a]Estimated by computing the annual mean of the total population of males in the reported age group in Denmark during the specified 5-year period.
[b]Estimated by computing the annual mean of the number of incident cases of gynecomastia in Denmark during the specified 5-year period.

FIGURE LEGENDS

Figure 1. Trends in the annual incidence of gynecomastia amongst males, according to specific age groups and by year of first diagnosis from 1998 to 2017.

Figure 2. Age-specific average incidence of gynecomastia within the 20-year period from 1998 to 2017 amongst males.

Figure 1

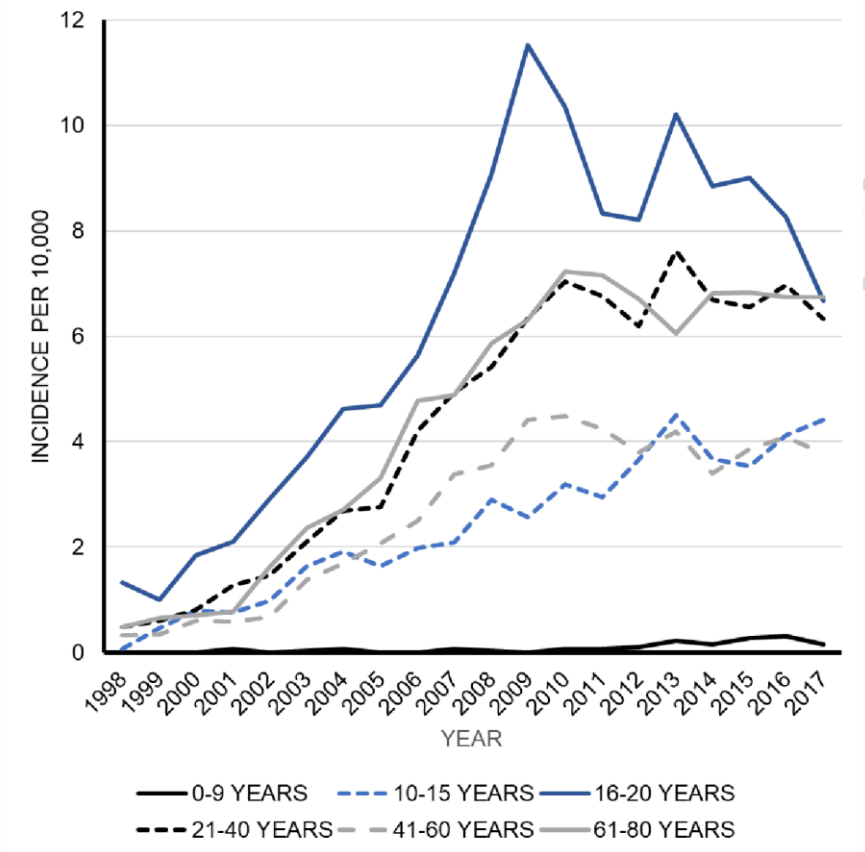

Figure 2