Endocrinología, Diabetes y Nutrición 70 (2023) 415–420

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Prevalence of men's health history in male breast cancer patients

Maria Florencia Scagliotti[a,*], **Bruno Rafael Boietti**[b], **Pablo Knoblovits**[a]

[a] *Servicio de Endocrinología y Metabolismo, Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina*
[b] *Área de Investigación Medicina Interna, Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina*

Received 28 October 2021; accepted 8 February 2022
Available online 9 December 2022

KEYWORDS
Gynaecomastia;
Klinefelter syndrome;
Hypergonadotropic hypogonadism;
Testosterone deficiency;
Infertility;
Sexual dysfunction

Abstract
Introduction: Male breast carcinoma (MBC) is an uncommon disease, accounting for less than 0.5% of cancer diagnoses in men. Data on the prevalence thereof in Argentina are unknown.
Primary objective: To estimate the prevalence of a men's health history associated with MBC as well as the anthropometric and clinical characteristics of the study population.
Methods: This cross-sectional study included all men according to original biological sex over 18 years of age with a history of breast cancer who sought care at the Hospital Italiano de Buenos Aires [Italian Hospital of Buenos Aires] between January 2010 and December 2018.
Results: We included 57 men with breast cancer. Their median age was 71 years. Of them, 53.06% had obesity and 24.53% had diabetes. With respect to men's health history, 5.56% (2/36) had infertility, 29.17% (14/48) had gynaecomastia and 60.71% (17/28) had sexual dysfunction. *Some* 63% *(7/11) had androgen deficiency based on laboratory diagnosis; of them,* 45.45% *(5/11) had high gonadotropins.*
Conclusion: We identified similarities with the literature as to the prevalence of obesity, diabetes and infertility in patients with MBC. The prevalence of testosterone deficiency was higher than reported for men of the same age. Many of these factors support the need to examine the role of endogenous hormones. Further research is required to help physicians care for and counsel men at higher risk of this disease.

Abbreviations: AIs, aromatase inhibitors; GnRH, gonadotropin-releasing hormone; IHQ, immunohistochemistry; KS, Klinefelter's syndrome; MBC, male breast cancer; OR, oestrogen receptor; PR, progesterone receptor.

* Corresponding author.
E-mail address: florscagliotti@gmail.com (M.F. Scagliotti).

PALABRAS CLAVE
Ginecomastia;
Síndrome Klinefelter;
Hipogonadismo hipergonadotrófico;
Déficit de testosterona;
Infertilidad;
Disfunción sexual

Prevalencia de antecedentes andrológicos en pacientes con cáncer de mama masculino

Resumen
Introducción: El carcinoma de mama masculino (CMM) es una enfermedad poco frecuente, representa menos del 0.5% de los diagnósticos de cáncer en el hombre. Se desconocen datos de prevalencia en Argentina.
Objetivo primario: Estimar la prevalencia de antecedentes andrológicos asociados a CMM, así como las características antropométricas y clínicas de la población estudiada.
Métodos: Estudio de Corte Transversal, que incluyó a todos los hombres según sexo biológico original, mayores de 18 años, con antecedente de cáncer de mama, que consultaron en el Hospital Italiano entre enero de 2010 y diciembre de 2018.
Resultados: Incluimos a 57 hombres con cáncer de mama. Mediana de edad de 71 años. El 53,06% presentó obesidad y 24,53% diabetes. Respecto a los antecedentes andrológicos, el 5,56% (2/36) tenía infertilidad, 29,17% (14/48) ginecomastia, 60,71% (17/28) disfunción sexual. *El 63% (7/11) presentó deficiencia de andrógenos por laboratorio, de los cuales el 45,45% (5/11) tenía gonadotrofinas elevadas.*
Conclusión: Identificamos similitudes con la literatura acerca de la prevalencia de obesidad, diabetes e infertilidad en pacientes con CMM. La prevalencia de déficit de testosterona fue mayor a la reportada para hombres de la misma edad. Muchos de estos factores respaldan la necesidad de explorar el papel de las hormonas endógenas. Se requiere más investigación para ayudar a los médicos a atender y aconsejar a los hombres con mayor riesgo de esta enfermedad.

Introduction

Male breast cancer (MBC) is an uncommon disease, accounting for <0.5% of cancer diagnoses in men and 1% of all breast carcinoma diagnoses in the United States.[1,2] Data on MBC prevalence in Argentina are unknown.[3]

MBC is a disease with certain unique biological characteristics, unlike those of female breast cancer; it usually presents at a more advanced age, in a more advanced stage and with a higher likelihood of hormone receptor positivity.[4] The five-year survival rate is lower and it is of particular significance given that the mortality rate is 1.43 times higher than in women.[5]

Ferzoco et al. proposed that an imbalanced androgen/oestrogen ratio may lead to ductal breast cancer cell proliferation, resulting in invasive breast cancer.[6] Other working teams have evaluated the role of endogenous hormones in the aetiology of male breast cancer and found a strong relationship to oestradiol levels.[7]

The risk factors postulated for male breast cancer suggest the importance of anthropometric and hormonal factors such as Klinefelter's syndrome (KS) and gynaecomastia.[8] Reproductive history may also be associated with risk; several studies have demonstrated a relationship between male breast cancer and a personal history of late puberty, infertility, cryptorchidism, testicular trauma and infections causing orchitis or epididymitis — conditions often associated with gynaecomastia[9] and primary hypogonadism.

The main objective of this study was to estimate the prevalence of a history of men's health issues in male breast cancer patients seen at the Hospital Italiano de Buenos Aires between 1 January 2010 and 1 December 2018.

Material and methods

This was a cross-sectional, retrospective, observational study that evaluated the clinical, anthropometric and men's health history of male breast cancer patients, as well as the clinical and pathological characteristics of the tumour.

All cisgender men over 18 years of age with a history of breast cancer recorded at Hospital Italiano de Buenos Aires between 1 January 2010 and 1 December 2018 were included. Transgender men and women on gender-affirming hormone therapy were excluded from the study.

The Hospital Italiano de Buenos Aires belongs to the private healthcare subsystem. It also has accreditation as an Academic Hospital granted by Joint Commission International and is a leader in specialisations such as endocrinology and breast disease.

A database was prepared incorporating the data of all cisgender male patients over 18 years of age with a record of the following terms in their electronic medical record: breast cancer, breast ultrasound, mammography, mastectomy, breast radiotherapy, tamoxifen, aromatase inhibitors, gonadotropin-releasing hormone analogues (triptorelin acetate or leuprolide acetate), cytology or pathology consistent with breast carcinoma. A total of 2,932 patients' electronic medical records were reviewed; of these, 57 men diagnosed with breast cancer were included. In a second step, the patients included in the study were contacted by telephone to fill in their missing men's health history through a structured survey once they had granted their informed consent.

Continuous variables were described using mean and standard deviation or as median and interquartile range

Table 1 Characteristics of patients with MBC by different gonadal axis hormone conditions based on laboratory diagnosis.

Hypogonadism	YES (5)				NO (6)					NR (46)				Total
hypergonadotropic	Med.	IQR	AF	%	Med.	IQR	AF	%	p	Med.	IQR	AF	%	(57)
Demographic char.														
Age	72	58–75			73	57–84			0.85	70.5	60–78			
BMI	27	26–30			30	27–31			0.64	30	26–31			
Obesity			2/5	40			4/6	66.7	0.57			20/38	52.6	26
Comorbidities			2/5	40			3/6	50				15/46	32.6	20
Men's health hist.														
Infertility			1/5	20			0		–			1/27	3.7	2
Gynaecomastia			1/5	20			4/6	66.7	0.24			9/37	24.3	14
Sexual dysfunction			4/5	80			2/5	40	0.52			11/18	61.1	17
Delayed puberty			0				0					1/13	7.69	1
Low testicular volume			2/4	50			0					0		2
Orchitis			2/5	40			0					0		2
Testicular trauma			3/5	60			0					2/15	13.3	5
Androgens			2/5	40			1/6	16.7	0.55			0		3
Anti-oestrogens			0				0					1/41	2.44	1
Anti-androgens			0				0					2/41	4.88	2
Family hist.														
Family history			3/4	75			2/5	40	0.52			11/20	55	16
BRCA2+			0				0					2/2	100	2
TNM staging														
Stage I			5/5	100			6/6	100				34/45	75.5	45
Stage II			0				0					5/45	11.1	5
Stage III			0				0					0		0
Stage IV			0				0					6/45	13.3	6
Treatment														
Mastectomy			4/5	80			4/6	66.7	1.00			41/45	89.1	49
Radiotherapy			1/5	20			0					11/44	23.9	12
Chemotherapy			0				0					9/44	19.6	9
Tamoxifen			4/5	80			4/6	66.7	1.00			31/43	67.4	39
Aromatase inhibitor			2/5	40			2/6	33.3	1.00			10/43	21.7	14
GnRH analogue			0				0					2/43	4.3	2
Total			5				6					46		57

Depending on hormone profile, three categories of patients were identified: with hypergonadotropic hypogonadism, without hypergonadotropic hypogonadism and having no laboratory results for hormone levels documented in their electronic medical records. The following variables were compared: demographic data; men's health history; family history; disease stage according to TNM, 8th edition; and treatment received.

AF, Absolute frequency (highlighted in bold); BMI, Body mass index; Demographic char., Demographic characteristics; Family hist., Family history; IQR, Interquartile range; Med., Median; Men's health hist., men's health history; NR, No record.

according to the observed distribution, and categorical variables as absolute and relative frequencies (percentages). Descriptive data were compared using the chi-squared test or Fisher's exact test, according to assumptions, for categorical variables, or Student's t test or the Mann–Whitney U test for continuous variables, depending on distribution. Data were stored in an Access database and processed using the STATA 14 software program.

The study was conducted in accordance with the standards of the Declaration of Helsinki, with informed consent, and was approved by the Hospital Italiano de Buenos Aires independent ethics committee.

Results

Regarding men's health history documented in the electronic medical records, 2/36 patients (5.56%) reported infertility, 14/48 (29.17%) gynaecomastia, 17/28 (60.71%) sexual dysfunction, 1/21 (4.76%) delayed puberty, 2/23 (8.70%) low testicular volume, 2/22 (9.09%) orchitis/epididymitis, 5/24 (20.83%) testicular trauma, 3/52 (5.77%) prior androgen therapy, 1/52 (1.92%) prior anti-oestrogen therapy and 2/52 (3.85%) anti-androgen treatment. None of the patients had a history of cryptorchidism.

Table 2 Baseline clinical and pathology-related characteristics in 56 patients with MBC.

Characteristics	N (56)	%
Histology		
Ductal	45	80.36
Papillary	7	12.50
Tubular/cribriform	2	3.57
Lobular	2	3.57
Bilaterality	1	1.79
Tumour size in cm (x/SD)	1.38 + 0.73	
Lymphadenopathy	21	37.50
Metastasis	6	10.71
TNM 8th edition		
Stage I	45	80.36
Stage II	5	8.93
Stage III	0	–
Stage IV	6	10.71
IHQ (OR,PR+)	54	96.43

IHQ, immunohistochemistry; OR, oestrogen receptor; PR, progesterone receptor.

Eleven of 57 patients had laboratory results for hormone levels prior to breast cancer diagnosis; laboratory values were expressed in terms of mean and standard deviation (x− ± SD): total testosterone 2.7 ± 1.12 ng/mL, bioavailable testosterone 0.78 ± 0.63 ng/mL, free testosterone 9.6 ± 14.44 pmol/l, oestradiol 27.43 ± 8.63 pg/mL, follicle-stimulating hormone (FSH) 7.08 ± 19.37 mU/mL and luteinising hormone (LH) 4.3 ± 10.4 mU/mL. *Some* 63% *(7/11) had androgen deficiency based on laboratory diagnosis; of them,* 45.45% *(5/11) had elevated gonadotropins.* No significant differences were found in relation to prevalence of men's health, family or pathology history between the group with hypergonadotropic hypogonadism and all other patients with androgen deficiency (Table 1). *No patients with a diagnosis of Klinefelter's syndrome were found, although one patient had undergone karyotype testing.*

Median age at diagnosis was 71 years (interquartile range [IQR] 59–78). Regarding the anthropometric and clinical characteristics of the study population, 53.06% of patients had obesity at the time of diagnosis and 13/53 (24.53%) had diabetes.

Sixteen of 29 patients (55.17%) had a family history of breast cancer. Five had been tested for the BRCA2 mutation and 2/5 (40%) of them were BRCA2-positive.

One of 56 patients (1.79%) had bilateral breast cancer. According to the TNM Classification of Malignant Tumours, 8th Edition, 80.36% of patients (45/56) were classified as stage I, 5/56 (8.93%) were classified as stage II, none were classified as stage III and 6/56 (10.71%) were classified as stage IV. Regarding cancer histopathology, 54/56 patients (96.4%) had ductal carcinoma and 2/56 (3.6%) had lobular carcinoma. Immunohistochemistry revealed 96.43% to have positive hormone receptors (Table 2).

The treatment instituted was surgical in 49/56 of the patients (87.5%), radiotherapy in 12/55 (21.82%), chemotherapy in 9/55 (16.36%) and hormonal in 47/54 (87.04%), of whom tamoxifen was prescribed in 39/54 patients (72.22%), aromatase inhibitors in 14/54 (25.93%) and gonadotropin-releasing hormone analogues in 2/54 (3.7%) (Table 3).

Table 3 Adjuvant treatments in patients with MBC.

Treatment	N	%
Surgery	49	87.50
Radiotherapy	12	21.82
Chemotherapy	9	16.36
Hormone therapy	47	87.04
Tamoxifen	39	72.22
AIs	14	25.93
GnRH analogues	2	3.70

AIs, aromatase inhibitors; GnRH, gonadotropin-releasing hormone.

Discussion

As regards gonadal profile, 63% were found to have hypogonadism; of them, 18% (2/11) had hypogonadotropic hypogonadism and 45.45% (5/11) had *hypergonadotropic* hypogonadism. While serum testosterone levels have been reported in the literature to gradually decrease as of age 40 by 0.4%–2.6% per year, the prevalence of androgen deficiency peaks in a man's fifties: 16.7% between 60 and 64 years of age for a population from Hong Kong,[10] 18.4% in men over 70 in the Massachusetts Male Aging Study[11] and 17% between 40 and 79 years of age in the European Male Aging Study.[12] In our group, the prevalence of testosterone deficiency (63%) was higher than reported in the general population, probably influenced by the median age of 71 years. To date, no data on the prevalence of hypergonadotropic hypogonadism in the general population or in patients with MBC have been found so that they may be compared with the results of our study. The Proyecto de Agrupación de Cáncer de Mama Masculino [Male Breast Cancer Clustering Project] measured oestrogen and androgen levels, but not gonadotropin levels.[7]

Regarding men's health history, higher numbers of patients were found with *infertility, sexual dysfunction, orchitis, testicular trauma and prior androgen therapy* in men with hypergonadotropic hypogonadism (Table 1). Hormone imbalances and increased oestrogen levels are known to potentially carry a higher risk of developing MBC.[7] Studies have shown that testicular dysfunction and abnormalities increase the risk of MBC. Specifically, a history of cryptorchidism, orchitis, congenital inguinal hernia or orchiectomy may be associated with a higher risk of breast cancer.[6,9] All of these are causes of hypergonadotropic hypogonadism, raising suspicion that increased gonadotropin levels are associated with an increased oestradiol/testosterone ratio due to stimulation of aromatase expression by Leydig and Sertoli cells. For decades it has been thought that an imbalanced oestrogen/androgen ratio may lead to ductal cell proliferation, resulting in invasive breast cancer.[6] Recent publications have found a strong association with higher levels of oestradiol, but no such association with decreased levels of androgens, as previously speculated.[7]

Although the prevalence of primary hypogonadism is unknown, classic *Klinefelter's syndrome* (KS) (karyotype 47, XXY) is the most common cause of congenital hypogonadism

and affects one out of every 660 men. Mosaicisms (46, XY/47, XXY) may present in 15%–20% of cases of KS; they are associated with a milder phenotype, and therefore their actual prevalence tends to be underestimated as they go undiagnosed.[13] It is estimated that men with KS have a 20- to 50-fold higher risk of developing MBC than the general male population, and some studies have estimated that up to 7% of men with MBC have a diagnosis of Klinefelter's syndrome.[6,14,15] Our study did not feature any patients with a diagnosis of KS, but karyotype testing had been performed in just one man with hypergonadotropic hypogonadism, representing potential bias due to clinical under-recording.

Within the subgroup of patients with hypergonadotropic hypogonadism, two men with a pre-MBC history of prostate cancer were identified; both received treatment with surgery and radiotherapy. Thellenberg et al. reported that prostate cancer doubles the likelihood of suffering from MBC, and that the risk is fivefold when prostate cancer is diagnosed before age 60.[16]

Gynaecomastia was found in 29.17% of men in our population with breast cancer. Both gynaecomastia and obesity are associated with MBC risk, probably independently. Gynaecomastia linked to excess oestrogens could increase the risk of developing MBC; however, it is unclear whether gynaecomastia is an independent risk factor for developing MBC or if the two diseases have similar risk factors.[8]

This would support the hypothesis that elevated oestrogen levels may be a risk biomarker even in the absence of diagnosed gynaecomastia.[7] Other authors have reported that gynaecomastia doubles the risk of MBC; however, this risk factor has not demonstrated statistical significance and could represent just a small percentage of all cases.[17]

In our study group, the median age at the time of diagnosis of MBC was 71 years, consistent with the published literature, and male breast carcinoma presented at an older age (5–10 years older) than its female counterpart. Reports from different cohorts have recorded average ages at diagnosis of 65.5,[14] 67[2] and 68 years.[18]

Some 53.06% of the patients included in the study had obesity. This figure was higher compared to the data published in the fourth Encuesta Nacional de Factores de Riesgo [National Risk Factors Survey], conducted in 2019, according to which the prevalence of obesity in the region was 33.9%.[19]

A *family history of breast cancer* carries a two- to threefold higher risk of developing MBC. Overall, 20% of men with MBC have at least one first-degree female relative with breast cancer; the more relatives who are affected, the higher the risk.[6] *BRCA2 mutation* is a clear causal factor for MBC. Between 4% and 15% of cases of MBC have deleterious BRCA2 mutations, and between 5% and 10% of BRCA2 carriers develop MBC. The mutation is associated with earlier, more aggressive disease.[6] It has also been linked to increased incidence of other types of cancer, such as pancreatic cancer, prostate cancer, melanoma and colorectal cancer.[20]

In our study, 55.17% of patients had a family history of breast cancer. Data from genetic testing for BRCA2 were collected from five of the patients in our sample; just two of them were carriers of the BRCA2 mutation (40% of those tested for it). Coincidentally, they reported a family history. However, at the time of their diagnosis, they were of advanced age and had early-stage disease, which conflicted with that reported in the literature.

With regard to other associated comorbidities in our population, the leading such comorbidity was diabetes, identified in 24.53% of patients with MBC. This was not consistent with the data published in the above-mentioned fourth Encuesta Nacional de Factores de Riesgo,[19] which found a prevalence of high blood glucose/diabetes in the adult Argentine population of 12.7%. While the prevalence of diabetes was not estimated in the latest Análisis de Situación de Salud por Cáncer [Cancer Health Situation Analysis],[3] a direct relationship has been established between cancer and risk factors for developing diabetes (overweight, obesity, sedentary lifestyle, tobacco use, alcohol consumption and low fruit and vegetable intake), consistent with what we found in patients with MBC.

In addition, rates of osteoporosis, liver disease and hyperthyroidism are lower (20%, 2.7% and 4%, respectively). In relation to the published literature, Brinton et al. found no relationship to a risk of liver disease or thyroid disease, which had been reported in prior publications that found an elevated though not significant risk of hyperthyroidism and liver cirrhosis.[8,21]

Although earlier data have suggested that MBC tends to present in a more advanced stage,[22,23] a recent study reported that 73% of patients with MBC (excluding carcinoma in situ) had stage I or stage II disease (according to the TNM Classification of Malignant Tumours, 8th edition[24]), and a small number of cases had extensive lymph node involvement at diagnosis.[25] This was in line with our results, in which the majority of patients had early-stage disease (Table 2).

Regarding tumour histopathology, ductal and papillary carcinomas are the most common histotypes. We also found a high prevalence of hormone receptor positivity in MBC, which was consistent with the published data.[21]

While we found no significant differences in terms of men's health history, family history, MBC stage or treatment pursued between the group of patients with hypergonadotropic hypogonadism and the group of patients with hypogonadotropic/normogonadotropic hypogonadism, the possibility that the results were influenced by the study's low ñčannot be ruled out.

The main limitation of the study was its retrospective design, with data missing from electronic medical records. Efforts were made to compensate for this limitation by means of the structured survey conducted by telephone by the principal investigator. While the study was conducted at a single site, this site is a leading referral hospital that may be representative of the population of Argentina to a certain extent.

The greatest strength of this study was its number of patients with MBC studied in the region, since data in Argentina are unknown. Furthermore, it is the only study that has evaluated hypergonadotropic hypogonadism in patients with MBC.

Conclusion

Hormone imbalance and higher oestrogen levels are known to potentially carry an increased risk of developing MBC. We identified similarities with the published literature as to the prevalence of certain anthropometric and hormonal

risk factors (such as obesity, diabetes and infertility) in the development of MBC. Moreover, in our group, the prevalence of testosterone deficiency was higher than reported in the general population. Many of these risk factors support the need to examine the role of endogenous hormones.

Epidemiological studies of MBC are rare, and to date most have been small-scale case–control studies, increasing the possibility of risk factors reflecting the influences of chance, selection bias and memory bias.

Due to the low incidence and limited research on the disease, delineating causal factors of MBC remains a challenge. Further studies that provide information on the epidemiology of MBC to help physicians care for and counsel men at higher risk of this disease are needed.

Conflict of interest

None.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30, http://dx.doi.org/10.3322/caac.21387.
2. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men. Cancer. 2004;101:51–7, http://dx.doi.org/10.1002/cncr.20312.
3. Boletín de vigilancia epidemiológica - Ministerio de salud. Análisis de Situación de Salud por Cáncer, Argentina, 2018. [cited 2020 Jul 29]. https://bancos.salud.gob.ar/recurso/analisis-de-situacion-de-salud-por-cancer-argentina-2018.
4. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med. 2002;137:678, http://dx.doi.org/10.7326/0003-4819-137-8-200210150-00013.
5. Liu N, Johnson KJ, Ma CX. Male breast cancer: an updated surveillance, epidemiology, and end results data analysis. Clin Breast Cancer. 2018;18(5):e997–1002, http://dx.doi.org/10.1016/j.clbc.2018.06.013.
6. Ferzoco RM, Ruddy KJ. The epidemiology of male breast cancer. Curr Oncol Rep. 2016;18(1):1, http://dx.doi.org/10.1007/s11912-015-0487-4.
7. Brinton LA, Key TJ, Kolonel LN, Michels KB, Sesso HD, Ursin G, et al. Prediagnostic sex steroid hormones in relation to male breast cancer risk. J Clin Oncol. 2015;33:2041–50, http://dx.doi.org/10.1200/jco.2014.59.1602.
8. Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, et al. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. JNCI J Natl Cancer Inst. 2014;106, http://dx.doi.org/10.1093/jnci/djt465.
9. Thomas DB, Margarita Jimenez L, McTieman A, Rosenblatt K, Stalsberg H, Stemhagen A, et al. Breast cancer in men: risk factors with hormonal implications. Am J Epidemiol. 1992;135:734–48, http://dx.doi.org/10.1093/oxfordjournals.aje.a116360.
10. Wong SYS, Chan DCC, Hong A, Woo J. Prevalence of and risk factors for androgen deficiency in middle-aged men in Hong Kong. Metabolism. 2006;55:1488–94, http://dx.doi.org/10.1016/j.metabol.2006.06.019.
11. Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007;92(11):4241–7, http://dx.doi.org/10.1210/jc.2007-1245.
12. Wu FCW, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35, http://dx.doi.org/10.1056/NEJMoa0911101.
13. Ross A, Bhasin S. Hypogonadism. Urol Clin North Am. 2016;43:163–76, http://dx.doi.org/10.1016/j.ucl.2016.01.002.
14. Scheike O. Male breast cancer. Br J Cancer. 1973;28:552–61, http://dx.doi.org/10.1038/bjc.1973.185.
15. Hultborn R, Hanson C, Köpf I, Verbiené I, Warnhammar E, Weimarck A. Prevalence of Klinefelter's syndrome in male breast cancer patients. Anticancer Res. 1997;17(6D):4293–7 https://www.ncbi.nlm.nih.gov/pubmed/9494523
16. Thellenberg C, Malmer B, Tavelin B, Grönberg H. Second primary cancers in men with prostate cancer: an increased risk of male breast cancer. J Urol. 2003;169(4):1345–8, http://dx.doi.org/10.1097/01.ju.0000056706.88960.7c.
17. Casagrande JT, Hanisch R, Pike MC, Ross RK, Brown JB, Henderson BE. A case-control study of male breast cancer. Cancer Res. 1988;48(5):1326–30 https://www.ncbi.nlm.nih.gov/pubmed/3342411
18. Camejo N, Castillo C, Shiavone A, Alfonso AL, Amarillo D, Xavier F, et al. Características del cáncer de mama masculino en una población uruguaya. AnFaMed. 2018;5:26–37, http://dx.doi.org/10.25184/anfamed2018v5n1a7.
19. 4ª Encuesta nacional de Factores de Riesgo - Ministerio de Salud, 2019. [cited 2021 Oct 25] https://www.indec.gob.ar/ftp/cuadros/publicaciones/enfr_2018_resultados_definitivos.pdf.
20. Losurdo A, Rota S, Gullo G, Masci G, Torrisi R, Bottai G, et al. Controversies in clinicopathological characteristics and treatment strategies of male breast cancer: a review of the literature. Crit Rev Oncol Hematol. 2017;113:283–91, http://dx.doi.org/10.1016/j.critrevonc.2017.03.013.
21. Lenfant-Pejovic MH, Mlika-Cabanne N, Bouchardy C, Auquier A. Risk factors for male breast cancer: a Franco-Swiss case-control study. Int J Cancer. 1990;45(4):661–5, http://dx.doi.org/10.1002/ijc.2910450415.
22. Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol. 2013;24(6):1434–43, http://dx.doi.org/10.1093/annonc/mdt025.
23. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006;367(9510):595–604, http://dx.doi.org/10.1016/S0140-6736(06)68226-3.
24. Harold J Burstein et al. Tumor, Node, Metastasis (TNM) staging classification for breast cancer. [cited 2021 Oct 25] https://www.uptodate.com/contents/tumor-node-metastasis-tnm-staging-classification-for-breast-cancer.
25. Masci G, Caruso M, Caruso F, Salvini P, Carnaghi C, Giordano L, et al. Clinicopathological and immunohistochemical characteristics in male breast cancer: a retrospective case series. Oncologist. 2015;20(6):586–92, http://dx.doi.org/10.1634/theoncologist.2014-0243.