Analysis of the Meningiomas` hormonal profile in patients with Meningioma and Breast Cancer

Guilherme Finger
Instituto Nacional de Cancer

Daniel M Prevedello (dani.prevedello@osumd.edu)
The Ohio State University College of Medicine

Bruno Loyola Godoy
Instituto Nacional de Cancer

Rodolfo Figueiredo Carvalho
Instituto Nacional de Cancer

Luciana Wemersbach Pinto
Instituto Nacional de Cancer

Priscila Valverde
Instituto Nacional de Cancer

Antonio Aversa do Souto
Instituto Nacional de Cancer

Research Article

Keywords: Meningioma, Receptors, Steroid receptors, Progesterone, Estrogen, Breast Neoplasms

Posted Date: August 31st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2005800/v1

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Abstract

Purpose

The objective of this study is to evaluate the meningioma`s hormone receptor expression in patients who presented synchronous or metachronous meningioma and breast cancer and compare its profile to the non-breast cancer associated meningiomas described in the literature.

Methods

The authors conducted a retrospective descriptive study evaluating all cases of synchronous and metachronous meningiomas and breast cancer from January 1st, 1990 to December 31st, 2020. The study was approved by the Ethics Review Board. Variables related to meningioma (age and year of diagnosis, histological grade and subtype, topography, the presence of progesterone and/or estrogen receptors) and to breast cancer (age and year of diagnosis, the histological grade and subtype, the presence of progesterone and/or estrogen receptors) were collected on the hospital`s electronic health records.

Results

A total of 12 cases were included in the study, being 2 (17%) synchronous and 10 (83%) metachronous. The mean age at meningioma diagnosis was 60.58 (± 10.99). The most frequent intracranial topography was convexity and sphenoid wing meningiomas (25% each). Ten patients (83%) had grade 1 meningiomas and 2 patients (16.6%) presented with grade 2 meningiomas. Eleven cases of meningiomas expressed progesterone receptors (91.67%) while 3 cases expressed estrogen receptors (25%). One patient did not express hormonal receptor.

Conclusion

The WHO histological analysis and steroid receptors profile did not seem to be different in the meningiomas included in this sample when compared to the description of no-breast cancer associated meningiomas.

Introduction

Meningioma is the most frequent primary tumor in the central nervous system (CNS), representing 33.8% of all intracranial tumors\(^1,2\). Breast cancer (BC) is the most frequent cancer among women, representing 25.2% of all malignancies in females\(^3\).

Since Schoenberg described in 1975 an increased incidence of meningiomas among patients diagnosed with BC\(^4\), the postulated association between these tumors in women has been increasingly described over the past decades. Even though they are two different tumors, the occurrence of synchronous and metachronous cases is not rare and both tumors intriguingly share epidemiological characteristics and risk factors, such as: higher prevalence in women, the prevalence increases with age, the expression of female steroid receptors in a percentage of tumor cells, hormonal influence and demographic characteristics\(^3,5,6\).

The impact of female steroid receptors is well known in BC, representing one of the most important prognostic factors in these patients, and it is an important target to oncological therapy. On the other hand, there is not much information regarding the impact of these receptors in meningiomas.

Even though there are some articles suggesting an association between meningiomas and breast cancer\(^1,7\), the medical literature lacks an analysis and evaluation of the hormone receptors profile in both tumors among patients who developed both pathologies. The authors conducted a study in order to evaluate the frequency of hormonal receptors and its profile in the breast cancer and in the meningioma, among patients with synchronous or metachronous tumors.

Methods

Study design

The authors conducted a descriptive study evaluating all cases of synchronous and metachronous meningiomas and BC from January 1st, 1990 to December 31st, 2020. The study was approved by the Ethics Review Board (CAAE: 36067320.0.0000.5274) under the number
The study was conducted at the Neurosurgery Department of the Brazilian National Cancer Institute (INCA) with collaboration of the Pathology Department of INCA.

Research in the hospital computed database was performed by the Pathology Department, in order to list all patients diagnosed with meningiomas and breast cancer during the period determined. The lists of patients (meningioma and BC) were crossed, and the patients present in both lists were selected to further analysis.

Variables

The variables analyzed can be classified in meningioma related variables and BC related variables.

Among the meningioma related variables, the authors included the age and year of diagnosis, the meningioma histological grade and subtype, the intracranial tumor topography, the presence of progesterone and/or estrogen receptors, and the percentage of expression in the tumoral sample.

Meningiomas are classified according to its pathological characteristics in grade 1, grade 2 or grade 3. Grade 1 meningiomas are histologically classified in nine different subtypes: meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacytic-rich and metaplastic. Grade 2 meningiomas may be classified in three different subtypes, which are chordoid, clear cells and atypical. Finally, grade 3 meningiomas can be histologically classified in papillary, rhabdoid and anaplastic.

The intracranial topography of meningioma`s origin can be classified in: parasagittal, convexity, falx, olfactory groove, clinoidal, tuberculum sellae, sphenoid wing, cavernous sinus, tentorial, petroclival, jugular foramen, cerebellopontine angle, magnum foramen, intraventricular.

Among the BC related variables, the authors included the age and year at diagnosis, the BC histological grade and subtype, the presence of progesterone and/or estrogen receptors, and the percentage of expression in the tumoral sample.

The authors also evaluated the percentage of metachronous and synchronous cases, and, in the primary group, the authors analyzed which diagnosis was performed first. Synchronous tumor is considered to occur within 2 months after the initial diagnosis of the first tumor, and metachronous tumor is considered tumors diagnosed within a period longer than two months.

Patient eligibility

Inclusion criteria were patients admitted at INCA hospital between January 1st, 1990 and December 31st, 2020, who were diagnosed with Meningioma and BC during this period. The authors included all patients who had both diagnoses, synchronous or metachronous. Among metachronous cases, authors included patients independently which tumor was diagnosed first (BC or meningioma).

Patients who had benign breast lesions (such as fibroadenoma, breast cysts or benign calcification) were not included in the study.

Statistical analysis

Data was collected using Microsoft Excel 2019 software. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Numerical variables were submitted to the Kolmogorov-Smirnov Test in order to evaluate its parametricity, and presented as mean and standard deviation if parametrical or median and interquartile range if non-parametrical. Categorical variables were presented in absolute numbers and proportion.

Results

Demographic data

During the study period a total of 12 patients were diagnosed with Meningioma and BC, of which only two cases were synchronous. Among the ten metachronous cases, six patients were first diagnosed with BC. The mean age at diagnosis of BC was 59.6 (± 10.2) and the mean age at diagnosis of meningiomas was 60.58 (± 10.99). The age variance at diagnosis of BC was from 41 to 80 years-old, while the age variance at diagnosis of meningiomas ranged from 39 to 81 years-old.

The meningioma related characteristics (Table 1) demonstrated that the most frequent tumor topography in this sample was cranial convexity and the sphenoid wing (25% in each topography), followed by falx meningiomas (16.6%). There were no cases of grade 3 meningiomas and only two cases of grade 2 meningiomas. Among the 10 cases of grade 1 meningiomas, the most frequent subtype was meningothelial.
(33.3%), followed by fibrous (25%), psamommatous and atypical (16.6% each). Hormone receptors were present in 11 of the 12 cases analyzed.

<table>
<thead>
<tr>
<th>Meningioma related variables</th>
<th>60.5 (± 10.9)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases with Hormonal Receptor</td>
<td>3 (25%)*</td>
</tr>
<tr>
<td>Estrogen</td>
<td>3 (25%)*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>11 (91.6%)*</td>
</tr>
<tr>
<td>Receptor presence percentage</td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td>20 (20–80) *</td>
</tr>
<tr>
<td>Progesterone</td>
<td>60 (20–80) *</td>
</tr>
<tr>
<td>Meningioma’s Histologic Subtype</td>
<td></td>
</tr>
<tr>
<td>Meningioma Meningothelial</td>
<td>4 (33.3%)*</td>
</tr>
<tr>
<td>Meningioma Fibrous</td>
<td>3 (25%)*</td>
</tr>
<tr>
<td>Meningioma Psammomatous</td>
<td>2 (16.6%)*</td>
</tr>
<tr>
<td>Meningioma Atypical</td>
<td>2 (16.6%)*</td>
</tr>
<tr>
<td>Meningioma Microcystic</td>
<td>1 (8.3%)*</td>
</tr>
<tr>
<td>Meningioma histological grade</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>10 (83.3%)*</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (16.6%)*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0 (0%)*</td>
</tr>
<tr>
<td>Meningioma’s Topography</td>
<td></td>
</tr>
<tr>
<td>Convexity</td>
<td>3 (25%)*</td>
</tr>
<tr>
<td>Sphenoid wing</td>
<td>3 (25%)*</td>
</tr>
<tr>
<td>Falx</td>
<td>2 (16.6%)*</td>
</tr>
<tr>
<td>Pontocerebellar angle</td>
<td>1 (8.3%)*</td>
</tr>
<tr>
<td>Olfactory Groove</td>
<td>1 (8.3%)*</td>
</tr>
<tr>
<td>Parasagittal</td>
<td>1 (8.3%)*</td>
</tr>
<tr>
<td>Petroclival</td>
<td>1 (8.3%)*</td>
</tr>
</tbody>
</table>

*Mean (Standard Deviation); *Number of cases (percentage)

The analysis of the BC characteristics (Table 2), demonstrated that the most frequent histologic subtype was infiltrating ductal carcinoma (66.7%), and all other subtypes occurred each in one patient. The cases of in situ carcinoma and microinvasive carcinoma were not evaluated regarding the histological degree neither the presence of hormone receptors. All other 10 cases were evaluated according to its histologic degree, being 5 patients with grade 2 and 5 patients with grade 3. Hormone receptors were present in 7 of the 10 cases analyzed.
The analysis of the progesterone and estrogen hormone receptor expression in the meningiomas demonstrated that only one case did not express either hormone receptor. Among the 11 cases with the presence of hormone receptor, all of them expressed progesterone receptors (91.67%) and estrogen receptors were present in only 3 cases (25%). The 3 cases of grade 2 meningiomas expressed only progesterone receptors.

Among the 3 cases with the presence of estrogen receptors, in 2 cases the presence was in 20% of the tumor sample and in one case its presence was in 90% of the sample. Regarding the presence of progesterone receptors, the mean percentage of expression in the tumor sample was 58.18% (±18.49), with a variance of 20 to 90%.

The analysis of hormone expression in the BC showed that progesterone receptors were expressed in 5 cases (50%), while estrogen receptors were present in 6 cases (60%). The authors reinforce that the cases of microinvasive carcinoma and in situ carcinoma were not evaluated regarding the presence of hormone receptors. Among the cases with hormone receptors expression, only 1 patient expressed solely estrogen and one patient expressed solely progesterone receptors. Five patients expressed both hormone receptors. Among the 6 cases with the presence of estrogen receptors, the median of expression in the tumor sample was 95%, with a variance ranging from 40 to 100%. On the other hand, among the 5 cases who presented progesterone receptors, the median of expression in the tumor sample was 15%, ranging from 5 to 95%.

The comparison of hormone expression between BC and meningioma demonstrated that among the 6 patients with estrogen receptors in the BC sample, two also presented estrogen receptors in the meningioma sample. Meanwhile, all the patients who presented progesterone receptors in the BC sample also presented progesterone receptors in the meningioma.

**Discussion**

According to medical literature, there are two well-established risk factors for meningiomas, one genetic and one environmental. The genetic risk factor is the mutation of the type 2 Neurofibromatosis gene (NF2). The environmental risk factor is the exposure to ionizing radiation, especially to higher doses of radiation (such as whole brain radiotherapy); but also being described in patients exposed to moderate or low levels of radiation. It is estimated that patients submitted to moderate or high levels radiation have up to 10 times higher risk to develop meningiomas, when compared to regular population\(^{10,11}\).
The relation between female hormone receptors and meningiomas

The higher incidence of meningiomas among women with previous breast cancer seems to be a fact, since recent papers identified a 26% higher meningioma incidence in this population. Due to the reported link between BC and female hormones and also between meningioma and these hormones, it has been hypothesized that meningiomas and BCs may be linked.

The influence of female sex steroids on meningiomas has been suggested based on the following characteristics: a higher incidence in females (two times more frequent than in males), especially during their reproductive period when the ratio increases 3.15 times; the acceleration of tumor growth during the luteal phase of the menstrual cycle and also during pregnancy (two periods when the level of progesterone is elevated), tumor decrease when progesterone levels go back to normal and also the decreasing of meningiomas in size when hormone agonists therapy is suspended.

Despite these characteristics described, there is no robust evidence supporting the influence of estrogen and progesterone in meningioma oncogenesis, development or its growth. The evidence that patients who use hormonal contraceptive have a higher meningioma risk is weak. Also, there is poor evidence in the literature supporting the association of hormone therapy after menopause and meningioma development or growth.

Meningiomas’ expression of hormone receptors

The expression of progesterone receptors in regular arachnoid cells was described in 1994, but normal meningeal tissue does not express ER. The presence of sex hormones receptors in meningiomas have been described since 1980, being PRs present in 48 to 88% and ER in 5 to 33% of the meningiomas.

Meningiomas may express both hormonal receptors, one hormonal receptor, or do not express hormonal receptors. Among these possibilities, most meningiomas present solely PR (68%), followed by the expression of PR and ER (8%) and ER alone in less than 1% of the cases. Approximately 25% of meningiomas do not express PRs nor ERs.

There is no difference in the presence of progesterone receptors when primary meningiomas are compared to recurrent tumors, when meningiomas in males are compared to meningiomas in females, neither when supratentorial meningiomas are compared to skull base meningiomas.

Relation between meningiomas’ hormone receptor profile and tumor aggressiveness

There is an association between the meningioma and its histological degree, biological behavior, genetic profile and prognosis.

It is believed that PR and ER present different meanings in the meningioma. The presence of progesterone receptors is higher in the meningothelial subtype when compared to the other eight WHO Grade 1 subtypes. In the four cases of meningothelial meningiomas in this sample, one case did not express either hormonal receptors, one case expressed both hormonal receptors and two cases expressed only PR. Among the three cases of meningothelial meningiomas who expressed PR, the range of expression was 60–70% of the tumor.

Relation between meningiomas’ hormone receptor profile and tumor prognosis

The presence of PR is a favorable prognostic factor for the clinical and biological behavior in meningiomas, associated with lower proliferative index and lower recurrence rate. Besides, it is believed that the presence of PR alone has a more favorable prognosis than...
tumors that express both receptors\textsuperscript{23}.

According to a multivariate analysis conducted by Hsu et al\textsuperscript{22}, the absence of progesterone receptors is associated with shorter progression free survival and is associated with a worse prognosis. Moreover, meningiomas with aggressive histopathological and genetic characteristics (accumulations of abnormal karyotypes mainly in chromosomes 14 and 22) usually do not express either PRs and ERs, or express solely ER\textsuperscript{23,31}.

The World Health Organization histopathological classification and the extent of surgical resection (Simpson grade) are associated with the meningioma recurrence rate; however, they often fail to accurately predict the clinical behavior of all meningiomas\textsuperscript{1,32}. Therefore, it has been suggested that other variables should be added in the evaluation of meningiomas, guiding the treatment and follow-up. Among these variables, the classification by molecular groups was independently associated with recurrence-free survival, even after accounting for known prognostic clinical factors—including WHO grade, extent of surgical resection and adjuvant radiotherapy\textsuperscript{32}. Moreover, some authors state that the receptor status should be included in any grading classification for meningiomas, especially for women\textsuperscript{23}. Possibly, the findings described in this study, reinforced by previous studies, state that the receptor profile also has an important impact on the outcome and follow-up.

**Relation between BC and meningioma**

The association between BC and meningiomas has been studied by some authors in the past decades, and some believe that there is a non-random association between these pathologies\textsuperscript{33}. The occurrence of both tumors in a single patient has a higher incidence among women older than 65 years old\textsuperscript{6}, and the estimated risk to develop a meningioma in a patient with history of BC (regardless its histologic subtype) is 1.40\textsuperscript{6}.

In a series that analyzed 24 patients who presented both tumors between 1992 and 1998, 10 patients were primarily diagnosed with BC, 11 were diagnosed primarily with meningioma and 3 patients presented synchronous diagnosis\textsuperscript{6}. In another series that analyzed metachronous cases of BC and meningiomas, 80.2% of patients were diagnosed first with BC, with mean interval between diagnoses of 4.5 years\textsuperscript{33}. The sample analyzed in this study reinforced that metachronous cases are more frequent than synchronous cases, and that usually the diagnosis of BC is made before the diagnosis of meningioma.

Even though there is a higher rate of meningioma in patients with previous BC, this higher risk is not related to the hormone receptor profile of the BC. Three recent papers analyzed a large sample of women who developed metachronous BC and meningiomas demonstrating that a positive ER/PR status of the BC tumor did not confer additional risk of subsequent meningioma when compared to negative ER/PR BC patients\textsuperscript{7,12,34}.

**The relation of the hormone receptor profile between BC and meningioma**

The same series that analyzed metachronous BC and meningiomas cases, also analyzed the presence of hormone receptors in both tumors. In that sample, 32% of meningiomas expressed PR and 7% ER; while the expression of PR and ER in the BC were, respectively, 43% and 53%\textsuperscript{33}. These findings are in agreement with the results of this sample, once PR was more frequent than ER in meningiomas, while ER was more frequent than PR in BC. The proportion of estrogen and progesterone receptors in the BC samples of this study was similar to the proportion described by Lieu et al\textsuperscript{33}. However, the presence of PR in meningiomas of this sample was higher when compared to the results described by the same author.

**Strength and limitations**

This study has several limitations that must be recognized. The descriptive characteristic of the study prohibits an analytic comparison between meningiomas of patients with synchronous BC and tumors in patients solely with meningiomas. Therefore, the findings of this paper can only suggest that patients with history of breast cancer do not have a higher risk to develop a more aggressive meningioma and that the hormonal profile is similar to other patients with meningioma. Besides, the retrospective design is also a limitation, since, despite all the variables analyzed were successfully retrieved from the hospital digital system, some cases may had been lost during the research, limiting the sample size. Finally, the results came from the experience of a single center, which may represent a selection bias and restricted the sample size for only 12 patients.

**Conclusion**

The WHO histological analysis and steroid receptors profile did not seem to be different in the meningiomas included in this sample when compared to the description of non-breast cancer associated meningiomas.
Declarations

All authors of the study entitled “Comparison of the hormonal receptor profile between Meningioma and Breast Cancer” declare that they contributed during the project and paper writing; they read and approved the final version of the paper.

Authors have no conflicts of interest to declare.

There was no funding or financial support for this study.

Acknowledgments: The authors have no acknowledgements to report.

FINANCIAL SUPPORT: there was no financial or funding support for the project

Conflict of interest: authors have no conflicts to report

Previous Presentations: The authors declare that this paper has not been published in whole or in part elsewhere in any form. We certify that this manuscript is a unique submission and is not being considered for publication with any other source in any medium.

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