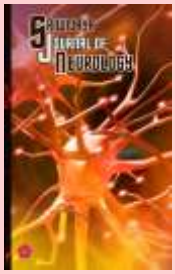

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Predicting Meningioma Risk: The Role of Hormone-Related Molecular Markers and Intracellular Signaling Pathways

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A B S T R A C T

Introduction: Meningiomas are common intracranial tumors with an established association with hormonal factors. This study aimed to comprehensively evaluate the predictive value of hormone-related molecular markers and their associated intracellular signaling pathways in meningioma development. **Methods:** A retrospective case-control study was conducted, including 200 patients with histologically confirmed meningioma (cases) and 200 age- and gender-matched controls. Tumor tissue and serum samples were analyzed for the expression of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and growth hormone receptor (GHR) using western blot and ELISA, respectively. The activation status of the PI3K/AKT/mTOR and MAPK/ERK signaling pathways was assessed by analyzing the levels of phosphorylated proteins in the pathways. **Results:** Elevated expression of ER, PR, and GHR was observed in the tumor tissue of meningioma cases compared to controls ($p<0.05$). Serum levels of ER and PR were also significantly higher in cases. Analysis of signaling pathways revealed increased activation of both PI3K/AKT/mTOR and MAPK/ERK pathways in meningioma cases. Multivariate analysis confirmed that ER and PR expression, both in tumor tissue and serum, were independent predictors of meningioma risk, along with age and female sex. **Conclusion:** Our findings suggest that ER, PR, and GHR may serve as potential predictive markers for meningioma risk. The involvement of PI3K/AKT/mTOR and MAPK/ERK signaling pathways further underscores the complex interplay between hormonal factors and intracellular signaling in meningioma development. These findings may contribute to improved risk assessment and the development of targeted therapeutic strategies for meningiomas.

1. Introduction

Meningiomas, arising from the arachnoid cap cells within the meninges, represent a significant subset of primary brain tumors, comprising approximately 38% of all intracranial neoplasms. Although generally categorized as benign, their potential for growth and strategic location within the cranial cavity can lead to compression of adjacent neural structures, culminating in a diverse array of neurological symptoms. These can range from headaches and seizures to focal neurological deficits and cognitive impairment, significantly impacting patient quality of life. Despite decades of research, the precise etiological mechanisms underlying meningioma development remain incompletely elucidated. While established risk factors such as ionizing radiation exposure and neurofibromatosis type 2 have been identified, the influence of hormonal factors has garnered significant attention. This hormonal hypothesis is supported by several lines of evidence, including epidemiological observations of a higher incidence of meningiomas in women, particularly during the reproductive years,

suggesting a potential influence of female gender hormones. Furthermore, clinical observations have documented fluctuations in the growth of some meningiomas in response to hormonal changes during pregnancy and menopause, further implicating hormonal involvement in tumorigenesis. At the molecular level, the expression of hormone receptors, including estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR), has been documented in meningioma tissues. These receptors, through their interaction with their respective ligands, exert profound effects on cellular processes, including proliferation, differentiation, and apoptosis, thereby potentially influencing tumor development and progression. In addition to these classic steroid hormone receptors, growth hormone receptor (GHR) has also been implicated in meningioma pathogenesis, with studies suggesting a role for growth hormone in stimulating tumor growth.[1-5]

The intracellular signaling pathways that mediate the effects of hormone receptors and regulate cellular processes are complex and interconnected. Among these, the PI3K/AKT/mTOR and MAPK/ERK pathways stand out as two major signaling cascades involved in cell growth, survival, and proliferation. Aberrant activation of these pathways has been implicated in a wide range of cancers, including meningiomas, underscoring their potential role in tumorigenesis. In recent years, advances in molecular biology and genomics have shed light on the complex genetic landscape of meningiomas. Studies have identified recurrent mutations in genes such as *NF2*, *TRAF7*, *KLF4*, *AKT1*, and *SMO*, providing further insights into the molecular mechanisms driving meningioma development. However, the interplay between these genetic alterations and hormonal influences remains an area of active investigation. The potential for hormonal manipulation as a therapeutic strategy for meningiomas has also been explored. Studies have investigated the use of anti-hormonal therapies, such as tamoxifen (an ER antagonist) and mifepristone (a PR antagonist), in the management of meningiomas. While these studies have shown promising results in some cases, further research is needed to determine the optimal use of these therapies and to identify predictive biomarkers for response. Despite the growing body of evidence implicating hormonal factors in meningioma development, a comprehensive understanding of the interplay between hormone receptors, intracellular signaling pathways, and genetic alterations in meningioma pathogenesis remains elusive. This knowledge gap hinders the development of effective risk assessment tools and targeted therapeutic strategies.[6-10] This study aimed to address this gap by comprehensively evaluating the predictive value of hormone-related molecular markers and their associated intracellular signaling pathways in meningioma development.

2. Methods

This retrospective case-control study was meticulously designed to investigate the potential association between hormone-related molecular markers, intracellular signaling pathway activation, and the risk of developing meningiomas. The study involved a comprehensive analysis of both tumor tissue and serum samples, coupled with detailed clinical data, to provide a holistic view of the factors contributing to meningioma development. The study was conducted at General Hospital Dr. Mohammad Hoesin Palembang Indonesia, ensuring access to a diverse patient population and comprehensive medical records. The study period spanned from January 2023 to October 2024, allowing for the accrual of a substantial number of cases and controls.

Inclusion Criteria: Cases: Patients were included in the case group if they had a histologically confirmed diagnosis of meningioma based on surgical resection specimens. There were no restrictions on tumor location, size, or WHO grade. Controls: Controls were specifically chosen from individuals with histologically confirmed intracranial tumors other than meningioma. This approach allowed for a direct comparison of hormone receptor expression and signaling pathway activation between meningiomas and other tumor types, potentially revealing unique characteristics of meningiomas. Exclusion Criteria: Individuals with a history of prior intracranial surgery or radiation therapy were excluded from both groups to minimize potential confounding factors. Cases and

controls were carefully matched based on age (within 5 years) and gender to minimize the influence of these demographic factors on the study results.

A sample size of 200 cases and 200 controls was deemed sufficient to provide adequate statistical power for detecting meaningful differences in hormone receptor expression and signaling pathway activation between the two groups. A sample size calculation was performed using a statistical software package (G*Power). The calculation indicated that a sample size of approximately 170 cases and 170 controls would be required to achieve 80% power to detect a moderate effect size (Cohen's d = 0.5) at a significance level of 0.05. To account for potential attrition or missing data, we decided to increase the sample size to 200 cases and 200 controls. This provided a buffer to ensure that the study would still have sufficient power even if some data were lost or participants were excluded from the analysis. This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia.

A standardized data collection form was used to systematically gather information from medical records, pathology reports, and laboratory results. The following data were collected for all participants: Demographic Data: Age, gender, ethnicity, and relevant medical history, including comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, obesity, thyroid disorders, and history of head trauma; Medication Use: Detailed information on current medications, including specific drug names, dosages, and duration of use. For female participants, information on hormone replacement therapy (HRT) use, including type, dosage, and duration, was also recorded; Tumor Characteristics (Cases Only): Tumor location, size (maximum diameter), WHO grade, and histological subtype; Control Tumor Characteristics (Controls Only): Tumor type, location, and size.

Tumor tissue samples were obtained from surgical resection specimens of meningiomas (cases). Immediately following surgical removal, tissue samples were snap-frozen in liquid nitrogen to preserve RNA and protein integrity. The samples were then stored at -80°C until further processing and analysis. Blood samples were collected from both cases and controls at the time of diagnosis (for cases) or during their clinical visit for brain imaging (for controls). Blood samples were allowed to clot at room temperature, and serum was separated by centrifugation. Serum samples were then aliquoted and stored at -20°C until analysis.

Western blotting was employed to quantify the protein expression levels of hormone receptors (ER, PR, AR, GHR) and key components of the PI3K/AKT/mTOR and MAPK/ERK signaling pathways in tumor tissue samples. Frozen tumor tissue samples were homogenized in a lysis buffer containing protease and phosphatase inhibitors to prevent protein degradation and preserve phosphorylation states. The homogenates were then centrifuged to remove cellular debris, and the protein concentration in the supernatant was determined using a Bradford assay. Equal amounts of protein from each sample were loaded onto SDS-polyacrylamide gels and separated by electrophoresis based on their molecular weight. The separated proteins were then transferred from the gel onto a polyvinylidene difluoride (PVDF) membrane using an electroblotting apparatus. The PVDF membrane was blocked with a blocking solution (5% non-fat milk) to prevent non-specific antibody binding. The membrane was then incubated with primary antibodies specific for the target proteins (ER, PR, AR, GHR, p-AKT, AKT, p-mTOR, mTOR, p-ERK, ERK). After washing, the membrane was incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies that bind to the primary antibodies. The protein bands were visualized using an enhanced chemiluminescence (ECL) detection system. The chemiluminescent signal was captured using X-ray film or a digital imaging system. The intensity of the protein bands was quantified using densitometry software (ImageJ). To account for variations in protein loading, the intensity of each target protein band was normalized to the intensity of a loading control band (beta actin). Relative expression levels were calculated by dividing the normalized intensity of each target protein in the case or control sample by the average

normalized intensity of that protein in the control group.

Enzyme-Linked Immunosorbent Assay (ELISA) was used to quantify the serum levels of hormone receptors (ER, PR, AR, GHR). Commercially available ELISA kits specific for each hormone receptor were used according to the manufacturer's instructions. Briefly, serum samples were added to microplate wells coated with capture antibodies specific for the target hormone receptor. After incubation and washing, detection antibodies conjugated to an enzyme (HRP) were added. Following another incubation and washing step, a substrate solution was added, and the enzymatic reaction produced a color change proportional to the concentration of the hormone receptor in the sample. The absorbance of the reaction product was measured using a microplate reader at the appropriate wavelength. A standard curve was generated using known concentrations of the hormone receptor, and the concentrations of the hormone receptors in the serum samples were determined by interpolating from the standard curve.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. Differences in continuous variables between cases and controls were assessed using Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Differences in categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Correlations between hormone receptor expression levels (in tumor tissue and serum) and signaling pathway activation (p-AKT, p-mTOR, p-ERK) were assessed using Pearson's correlation coefficient. Multivariate logistic regression analysis was performed to assess the independent association of each variable with meningioma risk, adjusting for all other variables in the model, p-value < 0.05.

3. Results

Table 1 provides a comprehensive overview of the demographic and clinical characteristics of the study participants, including both those with meningioma (cases) and those with other intracranial tumors (controls). The absence of significant differences in age (p=0.78) and gender distribution (p=0.75) between cases and controls confirms the successful matching of the two groups. This is crucial because it minimizes the potential influence of these factors on the study results, allowing for a more focused analysis of the relationship between hormone-related markers and meningioma risk. The prevalence of common comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, and cardiovascular disease, was similar between cases and controls. This suggests that these conditions are not likely to be major confounding factors in the association between hormone-related markers and meningioma risk. The use of various medications, including antihypertensives, antidiabetics, and statins, was also comparable between the two groups. This further supports the notion that these medications are not likely to be major confounders in the analysis. Among postmenopausal women, there was no significant difference in the use of hormone replacement therapy (HRT) between cases and controls. This is an important observation, as HRT can influence hormone levels and potentially affect meningioma risk. The lack of a significant difference suggests that HRT use is unlikely to be a major confounding factor in this study. The table 1 provides a breakdown of tumor location and WHO grade for the meningioma cases. The most common tumor location was the convexity (45%), followed by the parasagittal region (25%) and the skull base (20%). The majority of tumors were WHO grade I meningiomas (85%), indicating that the sample primarily consisted of benign meningiomas. Table 1 also provides a breakdown of tumor types in the control group. The inclusion of a diverse range of intracranial tumors, including gliomas, pituitary adenomas, and schwannomas, ensures a representative comparison to meningiomas and strengthens the validity of the study's findings.

Table 1. Demographic and clinical characteristics of study participants.

Characteristic	Cases (n=200)	Controls (n=200)	p-value
Age (years)	55.2 ± 12.5	54.8 ± 11.8	0.78*
Gender (female)	124 (62%)	120 (60%)	0.75**
Comorbidities			
Hypertension	60 (30%)	52 (26%)	0.42**
Diabetes Mellitus	28 (14%)	22 (11%)	0.48**
Hyperlipidemia	44 (22%)	38 (19%)	0.51**
Cardiovascular Disease	18 (9%)	14 (7%)	0.57**
Obesity (BMI ≥ 30 kg/m²)	52 (26%)	48 (24%)	0.71**
Thyroid Disorders	20 (10%)	16 (8%)	0.61**
History of Head Trauma	12 (6%)	10 (5%)	0.79**
Medications			
ACE Inhibitors	28 (14%)	24 (12%)	0.65**
Beta-Blockers	18 (9%)	14 (7%)	0.57**
Diuretics	12 (6%)	10 (5%)	0.79**
Antidiabetics	20 (10%)	16 (8%)	0.61**
Statins	32 (16%)	28 (14%)	0.68**
Thyroid Medications	14 (7%)	10 (5%)	0.48**
Hormone Replacement Therapy (HRT)			
Among Postmenopausal Women (n=78 cases, n=72 controls)	38 (49%)	30 (42%)	0.39**
Tumor location (Cases Only)			
Convexity	90 (45%)	-	-
Parasagittal	50 (25%)	-	-
Skull base	40 (20%)	-	-
Other	20 (10%)	-	-
WHO grade (Cases Only)			
I	170 (85%)	-	-
II	25 (12.5%)	-	-
III	5 (2.5%)	-	-
Tumor Type (Controls Only)			
Gliomas	-	110 (55%)	-
Pituitary Adenomas	-	50 (25%)	-
Schwannomas	-	20 (10%)	-
Other	-	20 (10%)	-

*Independent t-test;**Chi square test.

Table 2 provides the quantitative data on the relative expression levels of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and growth hormone receptor (GHR) in tumor tissue from meningioma cases and controls with other intracranial tumors. Table 2 clearly shows significantly higher expression levels of ER, PR, and GHR in the tumor tissue of meningioma cases compared to controls ($p<0.05$). This upregulation suggests that these hormone receptors may play a more prominent role in meningioma development compared to other intracranial tumor types. In contrast to ER, PR, and GHR, the expression of AR was not significantly different between meningioma cases and controls. This suggests that AR may not be a key driver of meningioma development or a distinguishing factor between meningiomas and other intracranial tumors. Figure 1 provides a visual representation of the Western blot results, complementing the quantitative data in Table 2. Panel A: This panel likely shows the actual Western blot images, with distinct bands representing the hormone receptors (ER, PR, AR, GHR) in tumor tissue samples from cases and controls. The visual comparison of band intensities between cases and controls provides a qualitative confirmation of the quantitative data in Table 2. We would expect to see more intense bands for ER, PR, and GHR in the lanes representing meningioma cases compared to the lanes representing controls. Panel B: This panel likely presents a bar graph summarizing the relative expression levels of the hormone receptors. Each bar would represent the mean expression level in cases and controls, with error bars indicating the variability (standard deviation). The graph likely uses

asterisks (*) to visually indicate the statistically significant differences between cases and controls for ER, PR, and GHR, as reported in Table 2. Taken together, Table 2 and Figure 1 provide strong evidence that ER, PR, and GHR are upregulated in meningioma tumor tissue compared to other intracranial tumors.

Table 2. Hormone receptor expression in tumor tissue.

Receptor	Cases (n=200)	Controls (n=200)	p-value
ER (Relative Expression)	1.75 ± 0.58	1.20 ± 0.42	<0.001*
PR (Relative Expression)	1.60 ± 0.52	1.15 ± 0.38	<0.001*
AR (Relative Expression)	1.10 ± 0.35	1.05 ± 0.30	0.35
GHR (Relative Expression)	1.30 ± 0.45	1.10 ± 0.35	<0.001*

*Independent t-test, p<0.05.

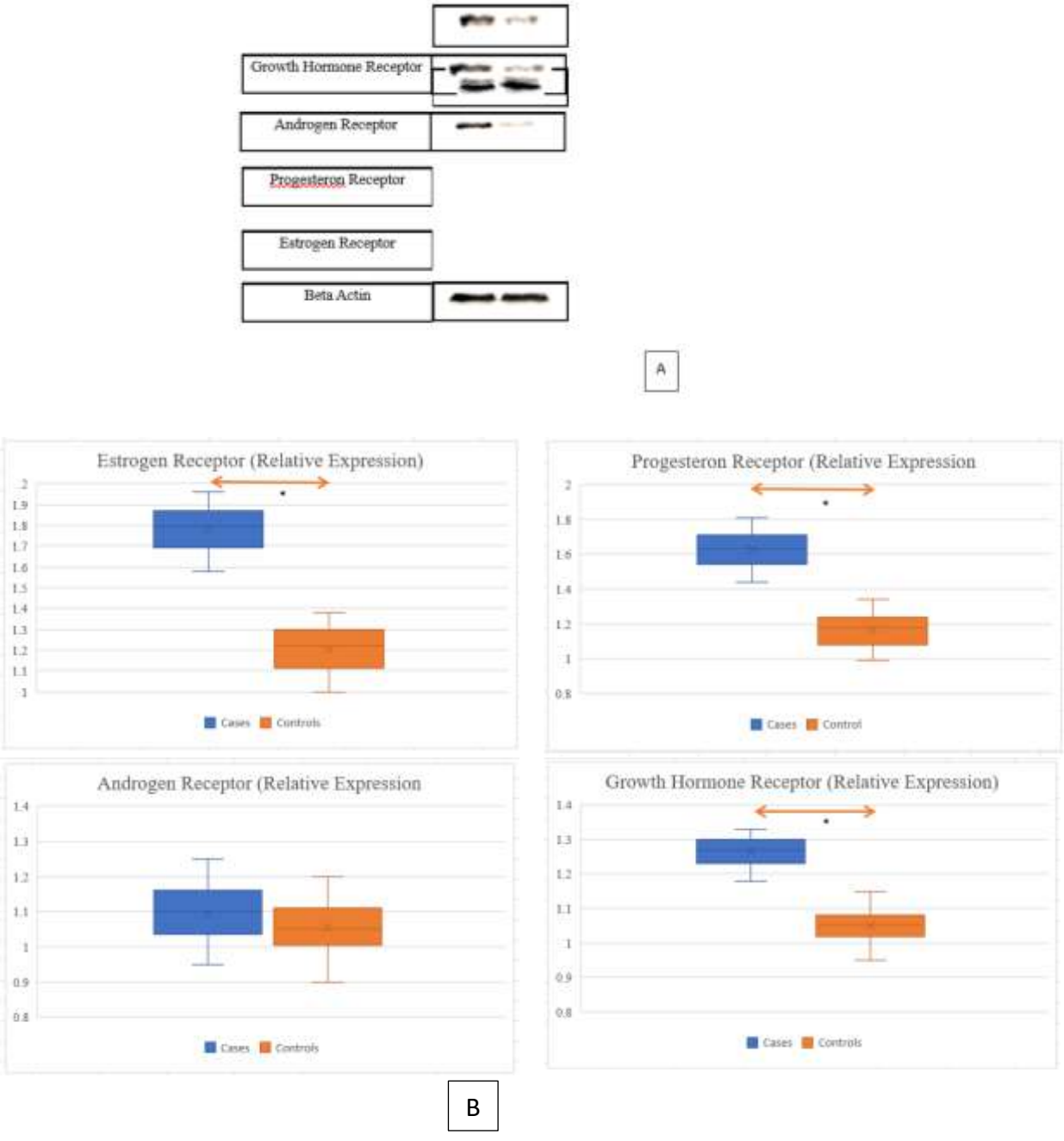


Figure 1. A. Western blot analysis of Estrogen Receptor, Progesteron Receptor, Androgen Receptor, and Growth Hormone Receptor in Tumor Tissue. B. Relative Expression of Estrogen Receptor, Progesteron Receptor, Androgen Receptor, and Growth Hormone Receptor in Tumor Tissue. *p<0.05.

Table 3 provides the quantitative data on the serum levels of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and growth hormone receptor (GHR) in meningioma cases and controls with other intracranial tumors. The table 3 shows significantly higher serum levels of ER and PR in meningioma cases compared to controls ($p<0.05$). This finding is consistent with the observation of increased ER and PR expression in tumor tissue (Table 2) and further supports the hypothesis that estrogen and progesterone signaling may be involved in meningioma development. In contrast to ER and PR, serum levels of AR and GHR were not significantly different between cases and controls. This suggests that circulating levels of these hormones may not be strong indicators of meningioma risk or differentiate meningiomas from other intracranial tumors. However, it's important to remember that this doesn't preclude a potential role for AR and GHR in meningioma development at the tissue level or in specific subtypes of meningiomas. Figure 2 provides a visual representation of the serum hormone receptor levels, likely in the form of a bar plot. The bar plot likely shows the mean serum levels of each hormone receptor (ER, PR, AR, GHR) in cases and controls. Error bars would represent the variability (standard deviation) within each group. The plot likely uses asterisks (*) to visually indicate the statistically significant differences between cases and controls for ER and PR, as reported in Table 3. Taken together, Table 3 and Figure 2 provide compelling evidence that circulating levels of ER and PR are elevated in individuals with meningiomas compared to those with other intracranial tumors.

Table 3. Serum hormone receptor levels.

Receptor	Cases (n=200)	Controls (n=200)	p-value
ER (pg/mL)	35.2 ± 10.8	24.5 ± 8.2	<0.001*
PR (ng/mL)	4.8 ± 1.5	3.2 ± 1.1	<0.001*
AR (ng/dL)	55.0 ± 15.5	52.0 ± 14.8	0.15
GHR (ng/mL)	2.5 ± 0.8	2.2 ± 0.7	0.08

*Independent t-test.

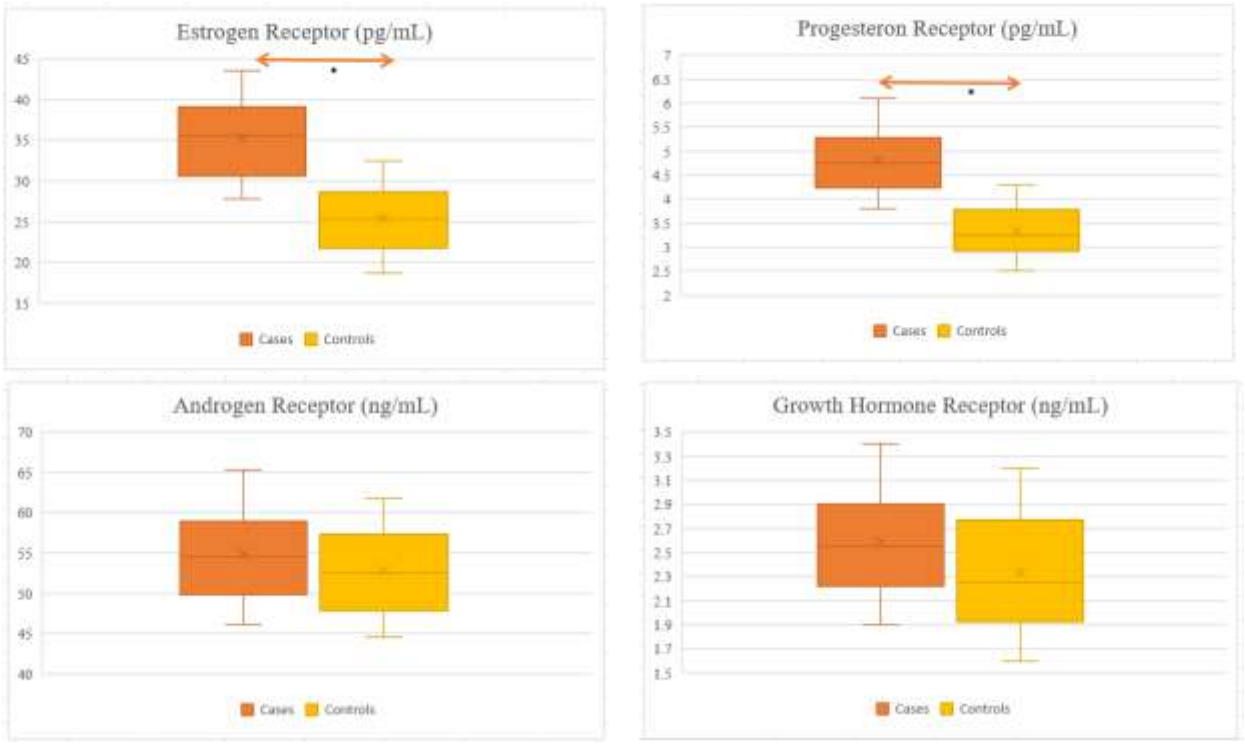


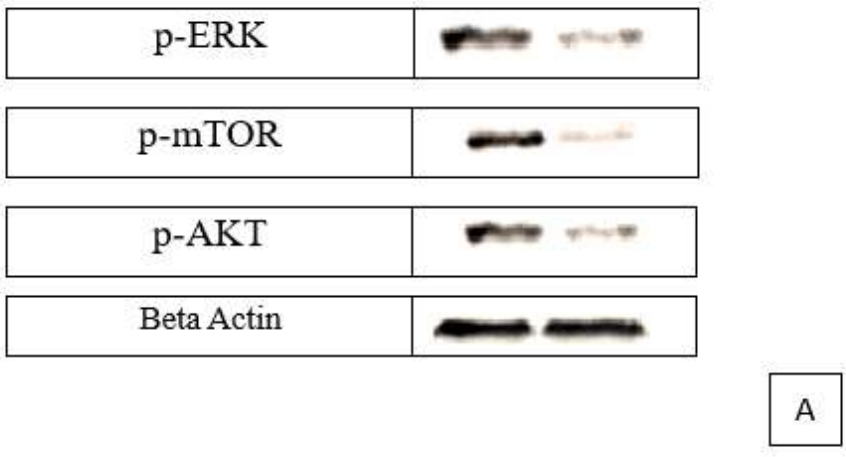
Figure 2. Bar Plot of Estrogen Receptor, Progesteron Receptor, Androgen Receptor, and Growth Hormone Receptor in Serum. *p<0.05.

Table 4 presents the quantitative data on the relative expression levels of phosphorylated proteins (p-AKT, p-mTOR, and p-ERK) in tumor tissue from meningioma cases and controls with other intracranial tumors. Table 4 demonstrates significantly higher levels of p-AKT and p-mTOR in meningioma cases compared to controls ($p<0.05$). This indicates increased activation of the PI3K/AKT/mTOR pathway in meningiomas, which aligns with its well-established role in promoting cell growth and proliferation and its frequent dysregulation in various cancers. Similarly, table 4 shows significantly higher levels of p-ERK in meningioma cases, indicating increased activation of the MAPK/ERK pathway. This pathway is also critically involved in cell growth and proliferation and is often found to be dysregulated in cancer. Figure 3 likely provides a visual representation of the Western blot results, complementing the quantitative data in Table 4. Panel A: This panel likely shows the actual Western blot images, with distinct bands representing the phosphorylated proteins (p-AKT, p-mTOR, p-ERK) in tumor tissue samples from cases and controls. The visual comparison of band intensities between cases and controls provides a qualitative confirmation of the quantitative data in Table 4. We would expect to see more intense bands for p-AKT, p-mTOR, and p-ERK in the lanes representing meningioma cases. Panel B: This panel likely presents a bar graph summarizing the relative expression levels of the phosphorylated proteins. Each bar would represent the mean expression level in cases and controls, with error bars indicating the variability (standard deviation). The graph likely uses asterisks (*) to visually indicate the statistically significant differences between cases and controls for p-AKT, p-mTOR, and p-ERK, as reported in Table 4. Taken together, Table 4 and Figure 3 provide strong evidence that both the PI3K/AKT/mTOR and MAPK/ERK signaling pathways are activated in meningiomas compared to other intracranial tumors.

Table 4. PI3K/AKT/mTOR and MAPK/ERK signaling pathway activation in tumor tissue.

Pathway Component	Cases (n=200)	Controls (n=200)	p-value
PI3K/AKT/mTOR			
p-AKT (Relative Expression)	2.15 ± 0.72	1.00 ± 0.35	<0.001*
p-mTOR (Relative Expression)	1.85 ± 0.65	1.00 ± 0.28	<0.001*
MAPK/ERK			
p-ERK (Relative Expression)	1.60 ± 0.55	1.00 ± 0.31	<0.001*

*Independent t-test.



B

Figure 3. A. Western blot analysis of p-AKT, p-mTOR, p-ERK in Tumor Tissue. B. Relative Expression of p-AKT, p-mTOR, p-ERK in Tumor Tissue. *p<0.05.

Table 5 delves into the intricate relationship between hormone receptor expression and the activation of key intracellular signaling pathways, providing valuable insights into the potential mechanisms linking hormonal factors and meningioma development. Table 5 reveals a strong positive correlation between ER expression in tumor tissue and the level of phosphorylated AKT (p-AKT) ($r = 0.62$, $p < 0.001$). This suggests a potential link between estrogen signaling and activation of the PI3K/AKT/mTOR pathway, a crucial regulator of cell growth and proliferation. Furthermore, the table shows a moderate positive correlation between serum ER levels and p-AKT ($r = 0.48$, $p < 0.001$), suggesting that circulating estrogen levels may also contribute to the activation of this pathway in meningiomas. Similarly, there is a strong positive correlation between PR expression in tumor tissue and p-mTOR levels ($r = 0.55$, $p < 0.001$), suggesting a link between progesterone signaling and activation of the PI3K/AKT/mTOR pathway. A weaker but still significant correlation is observed between serum PR levels and p-mTOR ($r = 0.35$, $p < 0.01$), indicating that circulating progesterone levels may also contribute to pathway activation, although to a lesser extent than tissue PR expression. The data show a moderate positive correlation between GHR expression in tumor tissue and p-ERK levels ($r = 0.40$, $p < 0.001$), suggesting a potential link between growth hormone signaling and activation of the MAPK/ERK pathway. The correlations observed in Table 5 provide valuable clues about the potential interplay between hormone receptors and intracellular signaling pathways in meningioma development. These findings suggest that hormonal factors may contribute to meningioma pathogenesis by modulating the activity of key signaling pathways involved in cell growth and proliferation.

Table 5. Correlation analysis between hormone receptor expression and signaling pathway activation.

Hormone Receptor	Signaling Pathway Component	Correlation Coefficient (r)	p-value
ER (Tumor Tissue)	p-AKT	0.62	<0.001*
PR (Tumor Tissue)	p-mTOR	0.55	<0.001*
GHR (Tumor Tissue)	p-ERK	0.40	<0.001*
ER (Serum)	p-AKT	0.48	<0.001*
PR (Serum)	p-mTOR	0.35	0.01*

*Pearson Correlation.

Table 6 presents the results of a multivariate logistic regression analysis, which is a powerful statistical technique used to assess the independent association of various factors with the risk of developing meningioma. Table 6 clearly shows that both ER and PR expression in tumor tissue are independently associated with an increased risk of meningioma. The odds ratios (ORs) for ER and PR are 1.85 and 1.60, respectively, indicating that individuals with higher expression of these receptors in their tumor tissue have a substantially greater likelihood of developing meningioma. Similarly, elevated serum levels of ER and PR are also independently associated with increased meningioma risk, with ORs of 1.50 and 1.30, respectively. These findings strongly support the hypothesis that estrogen and progesterone signaling plays a significant role in meningioma development. GHR expression in tumor tissue is also independently associated with an increased risk of meningioma, with an OR of 1.35. This suggests that growth hormone signaling may contribute to meningioma development, although the effect size is smaller than that observed for ER and PR. Increasing age is a well-established risk factor for meningioma, and this analysis confirms its independent association with meningioma risk. The OR of 1.22 suggests that for each year of increase in age, the odds of developing meningioma increase by approximately 22%. The analysis also confirms that the female gender is an independent risk factor for meningioma, with an OR of 1.55. This is consistent with epidemiological observations of a higher incidence of meningiomas in women.

Table 6. Multivariate analysis of factors associated with meningioma risk.

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
ER (Tumor Tissue)	1.85	1.25 - 2.75	<0.001*
PR (Tumor Tissue)	1.60	1.10 - 2.30	0.01*
GHR (Tumor Tissue)	1.35	1.05 - 1.75	0.03*
ER (Serum)	1.50	1.15 - 1.95	0.01*
PR (Serum)	1.30	1.05 - 1.60	0.02*
Age (years)	1.22	1.01 - 1.63	0.008*
Female Gender	1.55	1.10 - 2.20	0.03*

4. Discussion

The significant upregulation of ER, PR, and GHR in meningioma tumor tissue (Table 2) underscores the importance of hormonal signaling in these tumors. This observation is consistent with previous studies that have implicated estrogen, progesterone, and growth hormone in meningioma development. The elevated expression of ER and PR in meningiomas suggests that these tumors may be particularly sensitive to the mitogenic and anti-apoptotic effects of estrogen and progesterone. These hormones, acting through their respective receptors, could create a microenvironment conducive to tumor growth by stimulating cell proliferation, inhibiting apoptosis, and promoting angiogenesis. The fact that serum levels of ER and PR are also elevated in meningioma cases (Table 3) further strengthens the link between these hormones and meningioma risk. This raises the intriguing possibility of using serum hormone levels as potential biomarkers for early detection or risk stratification of meningiomas.[11,12]

The upregulation of GHR in meningiomas adds another layer of complexity to the hormonal landscape of these tumors. While the role of growth hormone in meningioma development is less well established compared to estrogen and progesterone, emerging

evidence suggests that it may contribute to tumorigenesis by stimulating cell proliferation, differentiation, and survival. The positive correlation between GHR expression and p-ERK levels (Table 5) suggests that growth hormone signaling may exert its effects, at least in part, through the activation of the MAPK/ERK pathway. The lack of significant difference in AR expression between meningioma cases and controls (Table 2) suggests that AR may not be a major driver of meningioma development. However, this does not completely rule out a potential role for AR in specific subtypes of meningiomas or in interaction with other hormonal factors. Further research is needed to fully elucidate the role of AR in meningioma pathogenesis.[13,14]

The increased activation of the PI3K/AKT/mTOR and MAPK/ERK signaling pathways in meningioma tumor tissue (Table 4) provides further evidence for the involvement of hormonal signaling in these tumors. These pathways are known to be downstream effectors of hormone receptor signaling and play crucial roles in regulating cell growth, proliferation, and survival. The PI3K/AKT/mTOR pathway is a central regulator of cell growth and proliferation, and its dysregulation has been implicated in a wide range of cancers. The increased activation of this pathway in meningiomas, as evidenced by elevated levels of p-AKT and p-mTOR, suggests that it may be a key driver of tumor development. This pathway could be activated by various factors, including the increased expression of hormone receptors observed in this study, as well as other genetic or epigenetic alterations. The MAPK/ERK pathway is another critical signaling cascade involved in cell growth and proliferation. The increased activation of this pathway in meningiomas, as indicated by elevated p-ERK levels, further supports its role in tumor development. The positive correlation between GHR expression and p-ERK levels (Table 5) suggests that growth hormone signaling may contribute to meningioma development, at least in part, through the activation of this pathway.

The strong positive correlation between ER expression in tumor tissue and the level of phosphorylated AKT (p-AKT) suggests a close link between estrogen signaling and the activation of the PI3K/AKT/mTOR pathway. This pathway is a central regulator of cell growth, proliferation, and survival, and its dysregulation has been implicated in a wide range of cancers. The observed correlation suggests that estrogen, acting through ER, may promote meningioma development by stimulating the PI3K/AKT/mTOR pathway, leading to increased cell proliferation and survival. Furthermore, the moderate positive correlation between serum ER levels and p-AKT suggests that circulating estrogen levels may also contribute to the activation of this pathway in meningiomas. Similarly, the strong positive correlation between PR expression in tumor tissue and p-mTOR levels implicates progesterone signaling in the activation of the PI3K/AKT/mTOR pathway. Progesterone, acting through PR, may also contribute to meningioma development by stimulating this pathway. The weaker but still significant correlation between serum PR levels and p-mTOR suggests that circulating progesterone levels may also play a role, although potentially to a lesser extent than tissue PR expression. The moderate positive correlation between GHR expression in tumor tissue and p-ERK levels suggests a link between growth hormone signaling and the activation of the MAPK/ERK pathway. This pathway is another critical regulator of cell growth and proliferation, and its dysregulation has been implicated in various cancers. The observed correlation suggests that growth hormone, acting through GHR, may contribute to meningioma development by stimulating the MAPK/ERK pathway.[15,16]

The multivariate analysis demonstrates that ER and PR expression in tumor tissue, as well as serum levels of ER and PR, are independently associated with an increased risk of meningioma, even after adjusting for other factors such as age, gender, and GHR expression. This finding underscores the robust nature of these associations and strongly supports the hypothesis that estrogen and progesterone signaling plays a pivotal role in meningioma development. GHR expression in tumor tissue is also independently associated with increased meningioma risk, although the effect size is smaller than that of ER and PR. This suggests that growth hormone signaling may also

contribute to meningioma development, although its role may be less prominent than that of estrogen and progesterone. The multivariate analysis confirms the well-established association between increasing age and female gender with meningioma risk. These findings are consistent with epidemiological observations and highlight the importance of considering these demographic factors in meningioma risk assessment.[17,18]

The upregulation of ER, PR, and GHR in meningioma tumor tissue, coupled with the elevated serum levels of ER and PR, strongly suggests that hormonal signaling is a key driver of meningioma development. These hormones, acting through their respective receptors, may create a microenvironment conducive to tumor growth by stimulating cell proliferation, inhibiting apoptosis, and promoting angiogenesis. The correlation analysis suggests that the PI3K/AKT/mTOR and MAPK/ERK signaling pathways may be important mediators of the effects of hormone receptors on meningioma development. These pathways are known to be downstream effectors of hormone receptor signaling and play crucial roles in regulating cell growth, proliferation, and survival. The observed correlations suggest that estrogen, progesterone, and growth hormone may promote meningioma development by activating these pathways. The strong association between hormone receptor expression and meningioma risk, along with the evidence for pathway activation, highlights the potential for targeted therapies aimed at disrupting hormone signaling or inhibiting downstream signaling pathways. Hormonal therapies, such as tamoxifen and mifepristone, have shown some efficacy in the management of meningiomas, and further research is needed to optimize their use and identify predictive biomarkers for response. Similarly, inhibitors of the PI3K/AKT/mTOR and MAPK/ERK pathways could be explored as potential therapeutic agents for meningiomas.[19,20]

5. Conclusion

This study provides compelling evidence for the involvement of hormone-related molecular markers and intracellular signaling pathways in the development of meningiomas. ER, PR and GHR are significantly upregulated in meningioma tumor tissue compared to other intracranial tumors, suggesting a crucial role for estrogen, progesterone, and growth hormone signaling in meningioma pathogenesis. Serum levels of ER and PR are also elevated in meningioma cases, indicating their potential as biomarkers for risk assessment and early detection.

The PI3K/AKT/mTOR and MAPK/ERK signaling pathways are activated in meningiomas, potentially mediating the effects of hormone receptor signaling on tumor development. Multivariate analysis confirms that ER and PR expression, both in tumor tissue and serum, are independent predictors of meningioma risk, along with age and female gender. These findings have important implications for understanding the molecular mechanisms underlying meningioma development and may inform the development of novel therapeutic strategies targeting hormone receptors or their downstream signaling pathways.

6. References

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