

Research Article

**EBF1 Exhibits Crosstalk Regulation with  $ER\alpha$  and  $ER\beta$  in Some Hormone-Based Cancers**Mary J. Lotesto <sup>‡</sup>, Stacey L. Raimondi <sup>\*</sup>

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**Received:** June 26, 2020**Accepted:** September 29, 2020**Published:** October 07, 2020**Abstract**

Estrogen-based cancers affect a substantial portion of the female population in the United States. While multiple studies have examined the effect of estrogen receptor alpha ( $ER\alpha/ESR1$ ) in cancer, the effects of  $ER\beta/ESR2$  are not as well understood in tumor tissues. Furthermore, there are few studies examining the role of specific binding partners of the estrogen receptors, such as early B-cell factor 1 (EBF1). EBF1 has been shown to have a role in B cell development and differentiation and is also known to bind to and crosstalk with both  $ER\alpha$  and  $ER\beta$ . However, to date those studies have only been performed *in vitro* in one breast cancer cell line. Therefore, it is imperative that we determine if there is a clinical role for that interaction. To that end, we utilized a bioinformatics approach to examine *EBF1*, *ESR1*, and *ESR2* gene expression levels in patient tumor tissues from estrogen-based cancers of the breast, cervix, ovary, and uterus. Our results show a correlation between *EBF1* and *ESR1* or *ESR2* expression, as well as some crosstalk regulation between *EBF1* and *ESR2*, but the relationship between *EBF1* and *ESR1* is inconsistent across cancers. Furthermore, contrary to previous reports, we did not find a significant loss of *EBF1* expression across all



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cancer types. Taken together, these results indicate that there is still much we do not understand about this interaction in clinical samples and provide an area for future studies.

### Keywords

EBF1; ER $\alpha$ ; ER $\beta$ ; hormone-based cancer; bioinformatics

## 1. Introduction

According to the American Cancer Society, approximately 380,000 women will be diagnosed with an estrogen-based cancer of the breast, cervix, ovary, or uterine corpus in 2020 [1]. While five-year survival rates have improved for almost all cancers due to improved diagnosis and treatments, including a 90% survival rate for breast cancer, the same is not true for cervical and uterine cancers. Due to a lack of good treatment options, these cancers have shown no increase in survival in the past 50 years. Furthermore, uterine corpus cancers show some of the largest racial disparities in survival with a 22% difference between white and black patients [2]. The combination of breast, ovarian, and uterine corpus cancers represents approximately 24% of all cancer deaths in women indicating the need for continued research to develop novel treatments and improve patient outcomes. Therefore, it is imperative that we understand the role of estrogen and associated proteins that may lead to the development and progression of these hormone-based cancers.

EBF1 is a transcription factor that promotes B cell development and differentiation. Specifically, it is important for the suppression of alternative B cell fates, both in early development and in already committed B cells [3]. Interestingly, EBF1 expression has been shown to be altered in cancer cells. Specifically, decreased EBF1 expression has been shown in cholangiocarcinoma and is associated with a more aggressive phenotype, indicating that EBF1 may act as a tumor suppressor gene [4]. EBF1 protein is also shown to be reduced in acute lymphoblastic leukemia, possibly influencing the translation of B-cell differentiation genes [5].

Recently, EBF1 was shown to interact and crosstalk with estrogen receptors alpha and beta [6]. Le and colleagues demonstrated that estrogen receptors are negatively regulated by EBF1 and also provided evidence for a crosstalk interaction between ER $\beta$  and EBF1 on a post-translational level. In the same study, ER $\alpha$  was also shown to interact with EBF1, although less dramatically. The role of ER $\alpha$ /*ESR1* in cancer is well-documented and previous studies have found that loss of *ESR1* leads to increased proliferation, migration, and progression of breast cancer cells [7]. The role of ER $\beta$ /*ESR2* in cancer is less understood. While a loss of ER $\beta$  has been observed as a sign of colon and breast cancer progression in multiple studies [8-12], an opposing study has shown that loss of ER $\beta$  in a breast cancer cell line leads to decreased proliferation, migration, and invasion [13]. Studies have shown that there are multiple isoforms of ER $\beta$  due to alternative splicing and that isoform 1 acts as a tumor suppressor while isoforms 2-5 may act as oncogenes [14-15]. These differing isoforms may explain the contradictory data described above. Unfortunately, we do not know which isoform was utilized for Le and colleagues' study described above [6]. Therefore, if loss of ER $\beta$ /*ESR2* is a sign of cancer progression, and *EBF1* is a negative regulator of *ESR2*, then we would expect to see high levels of *EBF1* in tumor tissues associated with low *ESR2*. However, if the

opposite is true and increased ER $\beta$ /*ESR2* is associated with decreased proliferation, then we would expect to see low levels of *EBF1* in tumor tissues. Taken together, these data highlight the need for additional studies to fully comprehend this important interaction.

Because of the implications *EBF1* has on the control of estrogen receptor proteins, and the conflicting role of estrogen receptors in disease progression, it is necessary to further investigate how *EBF1* expression may be altered in cancer types and its effects on ER $\alpha$  and ER $\beta$  encoding genes, *ESR1* and *ESR2*. In this study we utilized a bioinformatics approach to analyze *EBF1* gene expression and its relationship to *ESR1* and *ESR2* in patients with breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), ovarian serous cystadenocarcinoma (OV), uterine corpus endometrial carcinoma (UCEC) and uterine carcinosarcoma (UCS). Based on previous studies, it was expected that all cancers would show a decrease in *EBF1* expression in tumor tissue when compared to normal tissue, and that high levels of *EBF1* would correlate with decreased *ESR2* and, possibly, *ESR1* expression. However, our analysis showed inconsistent patterns of expression based on cancer type, indicating that further research is needed to fully delineate the molecular mechanisms of *EBF1* and estrogen receptor interactions in hormone-based cancers.

## **2. Materials and Methods**

### **2.1 Collection of Data from Genomic Data Commons**

RNASeqV2 expression data and clinical data for five hormone-based tumors – BRCA, CESC, OV, UCEC, UCS – were collected from the Genomic Data Commons as previously described [16-18]. *EBF1*, *ESR1*, and *ESR2* (isoform 1) expression levels were obtained from the Genomic Data Commons utilizing a custom C# script and organized using Microsoft Excel.

### **2.2 Statistical Analysis**

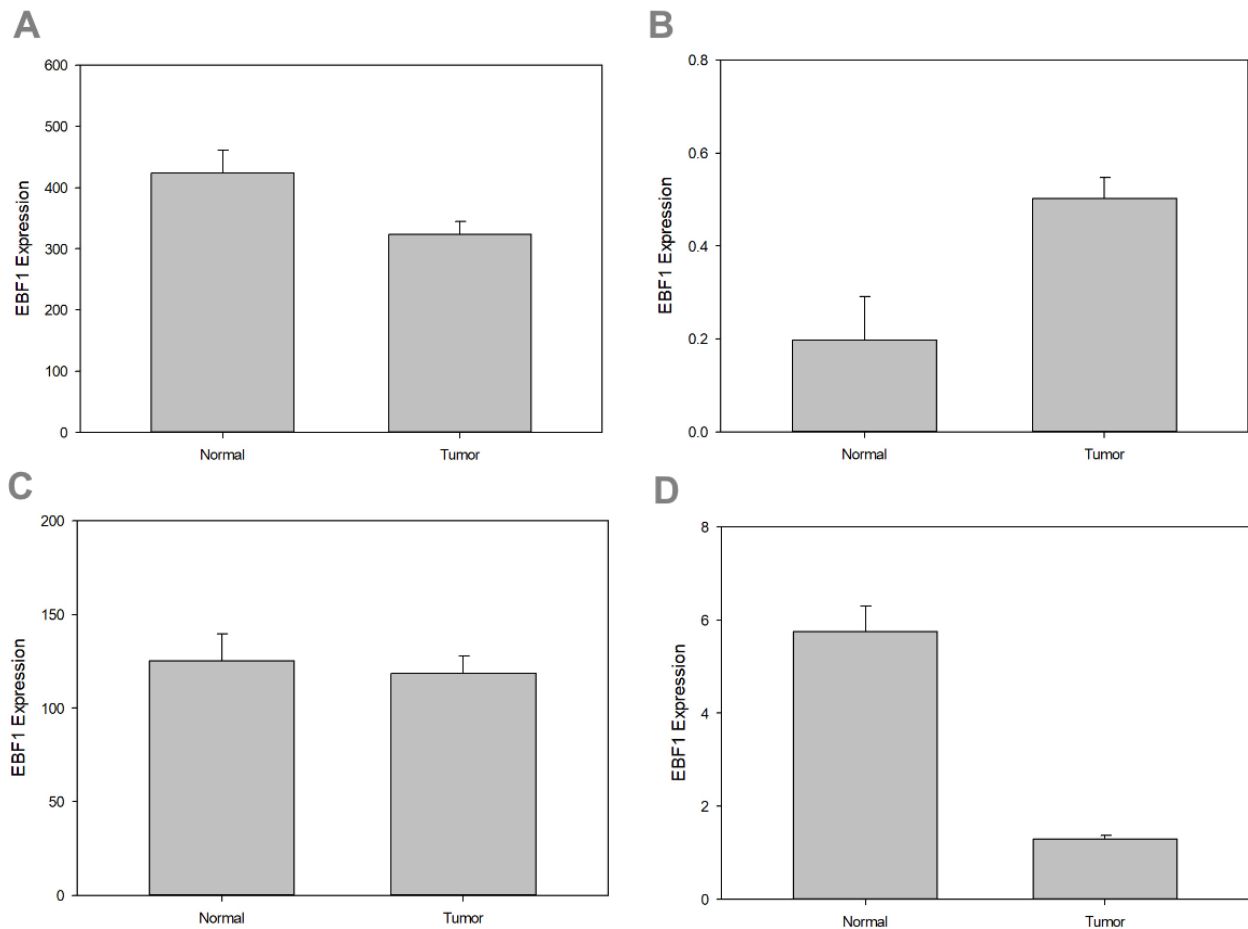
All statistical analysis was performed using SigmaStat software (Systat, Chicago, IL). Mean *EBF1* expression in primary tumors versus normal tissues for each cancer was compared using a T-test or a Mann-Whitney Rank Sum Test in situations where a normal distribution was not observed. Correlation studies were performed using a Spearman Rank Order Correlation to obtain R and P values between *EBF1* and *ESR1* or *ESR2*. In order to examine expression in low or high transcript conditions, the median expression in primary tumor tissues for *EBF1*, *ESR1*, or *ESR2* was determined for each hormone-based cancer. Based on that median number, samples were then divided in half into the low-expression and high-expression groups. The mean expression of the transcript being measured on the y-axis was then determined and a T-test or Mann-Whitney Rank Sum Test was utilized to determine statistical significance.

## **3. Results**

### **3.1 *EBF1* Expression is Decreased in Uterine Carcinoma Tumor Tissues**

Based on previous reports indicating a role for *EBF1* in cancer progression as well as its potential interaction with ER, gene expression was compared between normal and tumor tissues in five hormone-based tumors utilizing data from the Genomic Data Commons. Interestingly, a

significant decrease of expression was only observed in tumor tissues of UCEC ( $p < 0.001$ , Figure 1D). No significant difference in *EBF1* expression was observed when comparing normal and tumor tissues in BRCA, CESC, or OV (Figure 1A-C). Normal tissues were not available for UCS so the analysis could not be completed for this tumor type.



**Figure 1** *EBF1* expression is only inhibited in UCEC tumor tissues. Mean *EBF1* expression data in normal and tumor tissues was calculated in A) BRCA, B) CESC, C) OV, and D) UCEC and no difference was observed in any cancer except UCEC ( $p < 0.001$ ).

### 3.2 *EBF1* Expression is Correlated to *ESR1* and *ESR2* Expression in Estrogen-Based Tumor Tissues

Because Le and colleagues [6] had previously demonstrated an interaction between *EBF1* and  $ER\beta$  (*ESR2*), we performed a Spearman Rank Order Correlation analysis to determine if there was a correlation between *EBF1* and *ESR1* or *ESR2* expression in tumor tissues of all five estrogen-based cancers (Table 1). *EBF1* significantly correlated with *ESR1* in CESC, OV, and UCEC. Interestingly, a positive correlation between *EBF1* and *ESR1* was observed in CESC and UCEC while a negative correlation was observed in OV. Furthermore, our analysis showed that *EBF1* positively correlated with *ESR2* in BRCA, CESC, and UCEC. UCS did not show any level of correlation between *EBF1* and either estrogen receptor gene.

**Table 1** Correlation analysis of *EBF1* with *ESR1* or *ESR2*.

Cancer Type	<i>ESR1</i>		<i>ESR2</i>	
	R	P	R	P
BRCA	-0.0353	0.331	+0.353	0.0000002
CESC	+0.27	0.00000186	+0.172	0.00269
OV	-0.302	0.0000786	-0.147	0.0588
UCEC	+0.233	0.0000000355	+0.268	0.000000000193
UCS	+0.124	0.361	+0.121	0.374

R represents Spearman Rank Order Correlation

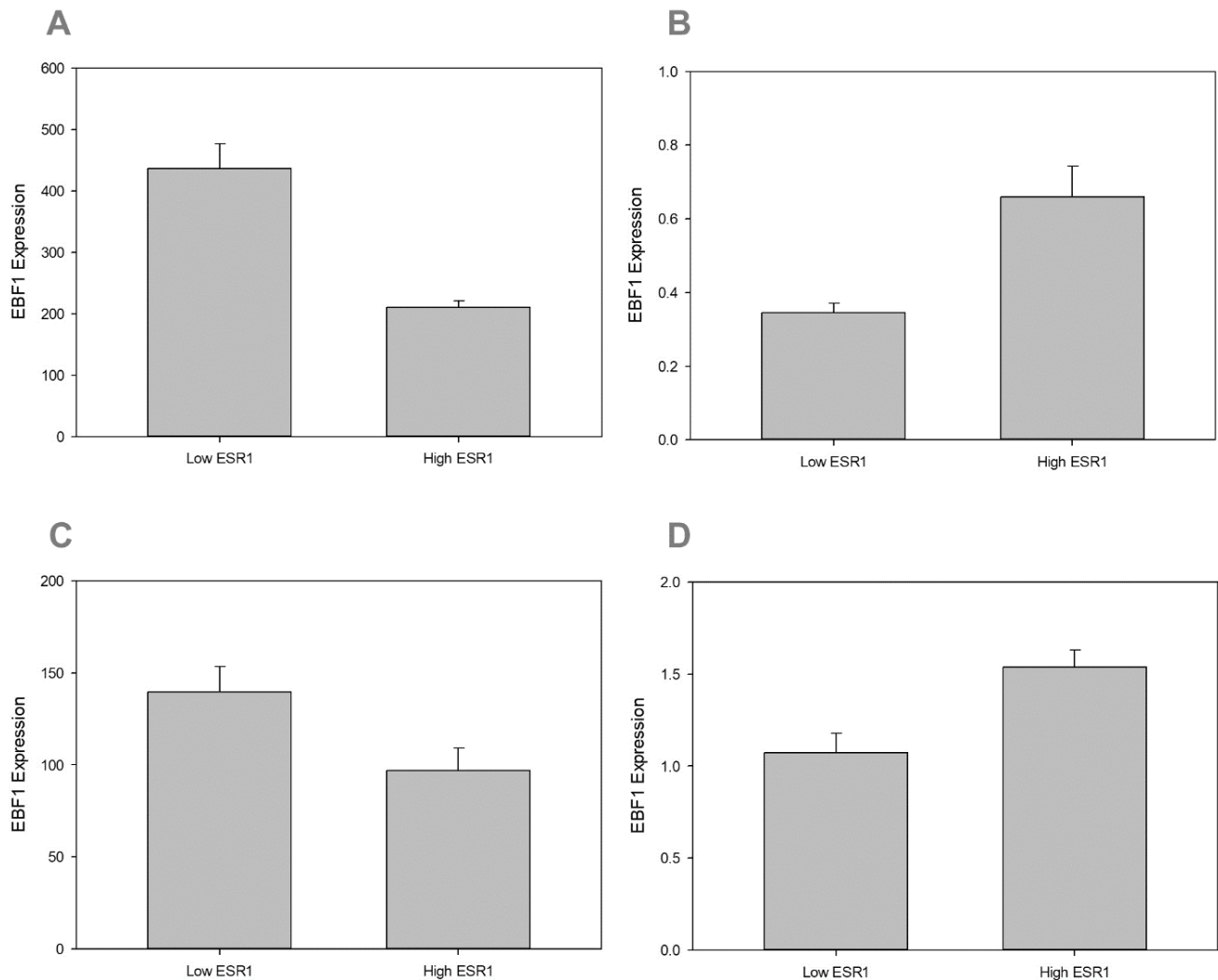
+ indicates a positive correlation between *EBF1* and *ESR1/ESR2*

- indicates a negative correlation between *EBF1* and *ESR1/ESR2*

Yellow shading indicates significant data

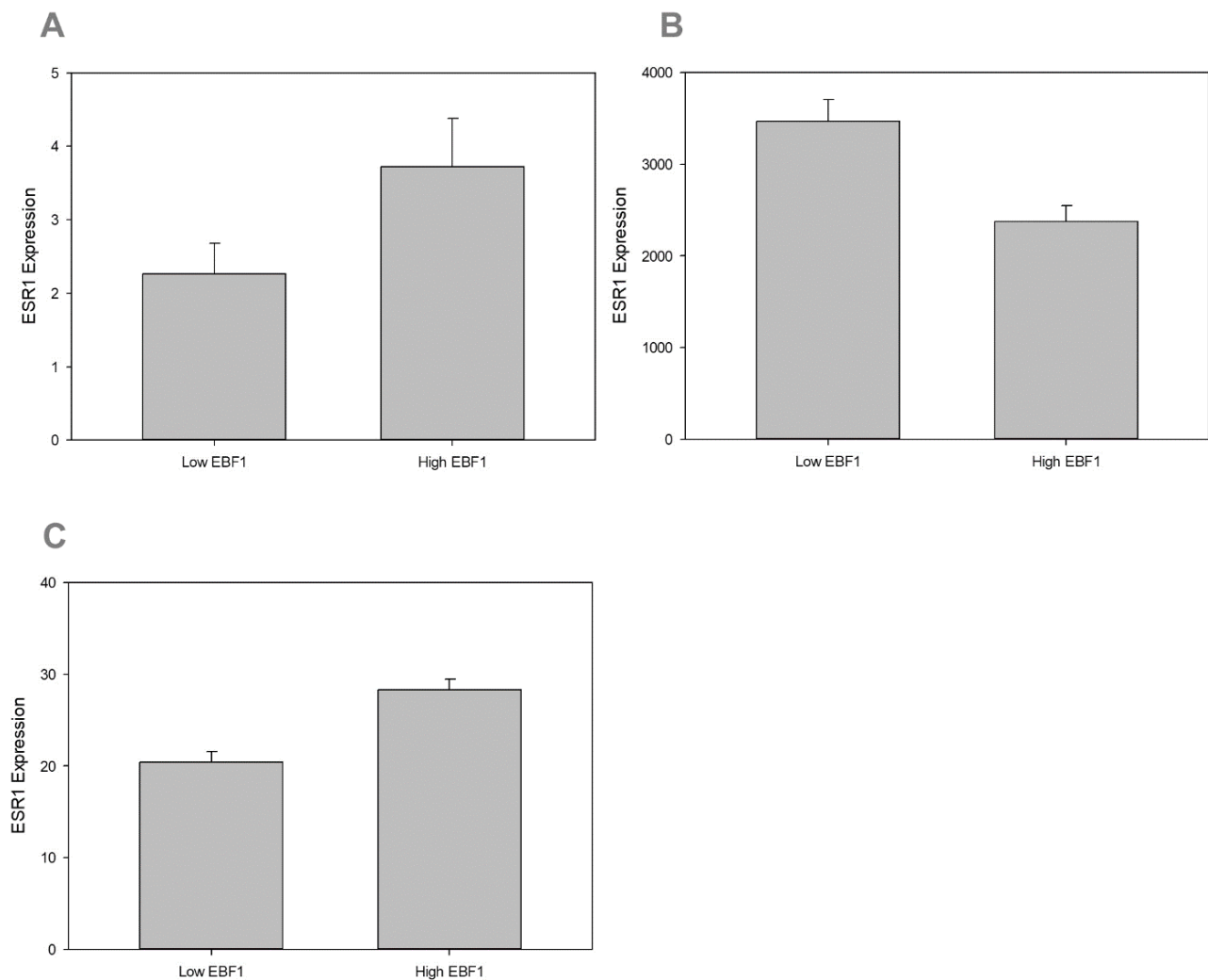
### 3.3 *EBF1* and *ESR1* Expression Show a Crosstalk Pattern in Some Hormone-Based Cancers.

Le and colleagues [6] showed that not only do *EBF1* and *ESR2* interact with each other, but that they also crosstalk leading to altered regulation of both genes. Therefore, we wanted to further characterize this interaction in clinical samples for all five hormone-based cancers. To that end, we examined *EBF1* expression in tumor tissues with high or low *ESR1* expression to determine if there was a significant difference. We then performed the reciprocal analysis, looking at *ESR1* expression in high or low *EBF1* tumor conditions. When examining *EBF1* expression in conditions of high and low *ESR1* expression in tumor tissue, results were inconsistent across the cancers tested (Figure 2). BRCA and OV cancers showed a significant increase in *EBF1* expression in conditions of low *ESR1* expression ( $p=0.003$  and  $p=0.001$ , respectively; Figure 2a and Figure 2c). Interestingly, CESC and UCEC showed the opposite; *EBF1* expression in these tumors was increased in the presence of high *ESR1* expression ( $p<0.001$ ; Figure 2b and Figure 2d).



**Figure 2** *EBF1* expression does not show a consistent regulatory pattern in the presence of *ESR1*. Median *ESR1* expression was determined in tumor samples for all five cancers and then patient samples were divided into “low” and “high” *ESR1* based on the median for each cancer. Mean *EBF1* expression was subsequently determined for the “low” and “high” groups and statistical significance determined using a T-test or Mann Whitney Rank Sum Test. Graphs for A) BRCA ( $p=0.003$ ), B) CESC ( $p<0.001$ ), C) OV ( $p=0.001$ ), and D) UCEC ( $p<0.001$ ) show significant results.

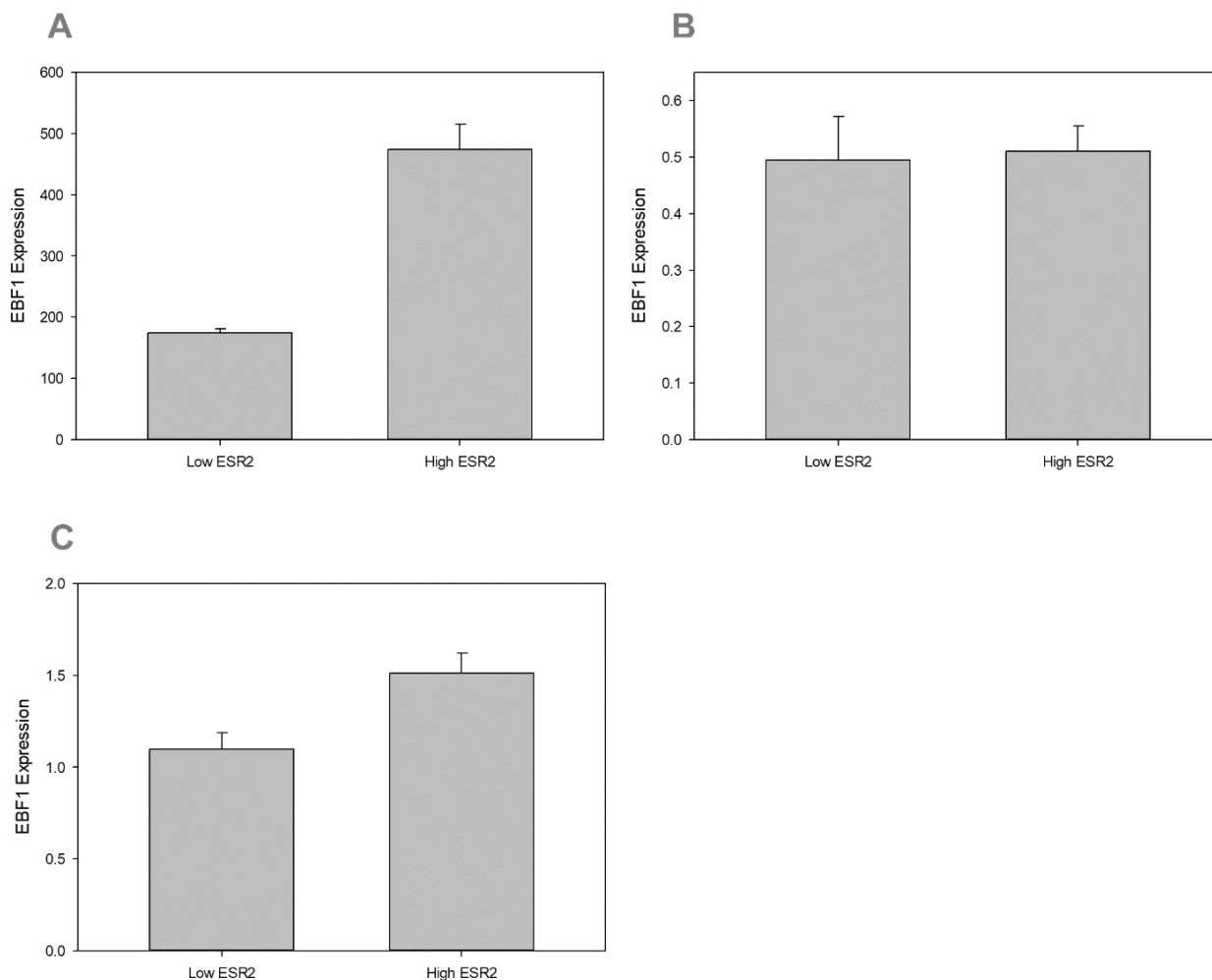
When performing the reciprocal analysis, a similar trend was observed. *ESR1* expression was shown to be increased in CESC and UCEC tumors with high *EBF1* expression compared to those with low *EBF1* expression ( $p<0.001$ ; Figure 3a and 3c). Contradictory to this data, *ESR1* was shown to be increased in tumors with low *EBF1* expression in OV ( $p<0.001$ ; Figure 3b). There was no significant difference in expression in BRCA in the reciprocal analysis. These data indicate *EBF1* may interact with *ESR1*, but not in a uniform way across tumor types.



**Figure 3** *ESR1* expression does not show a consistent regulatory pattern in the presence of *EBF1*. Median *EBF1* expression was determined in tumor samples for all five cancers and then patient samples were divided into “low” and “high” *EBF1* based on the median for each cancer. Mean *ESR1* expression was subsequently determined for the “low” and “high” groups and statistical significance determined using a T-test or Mann Whitney Rank Sum Test. Graphs for A) CESC ( $p < 0.001$ ), B) OV ( $p < 0.001$ ), and C) UCEC ( $p < 0.001$ ) show significant results.

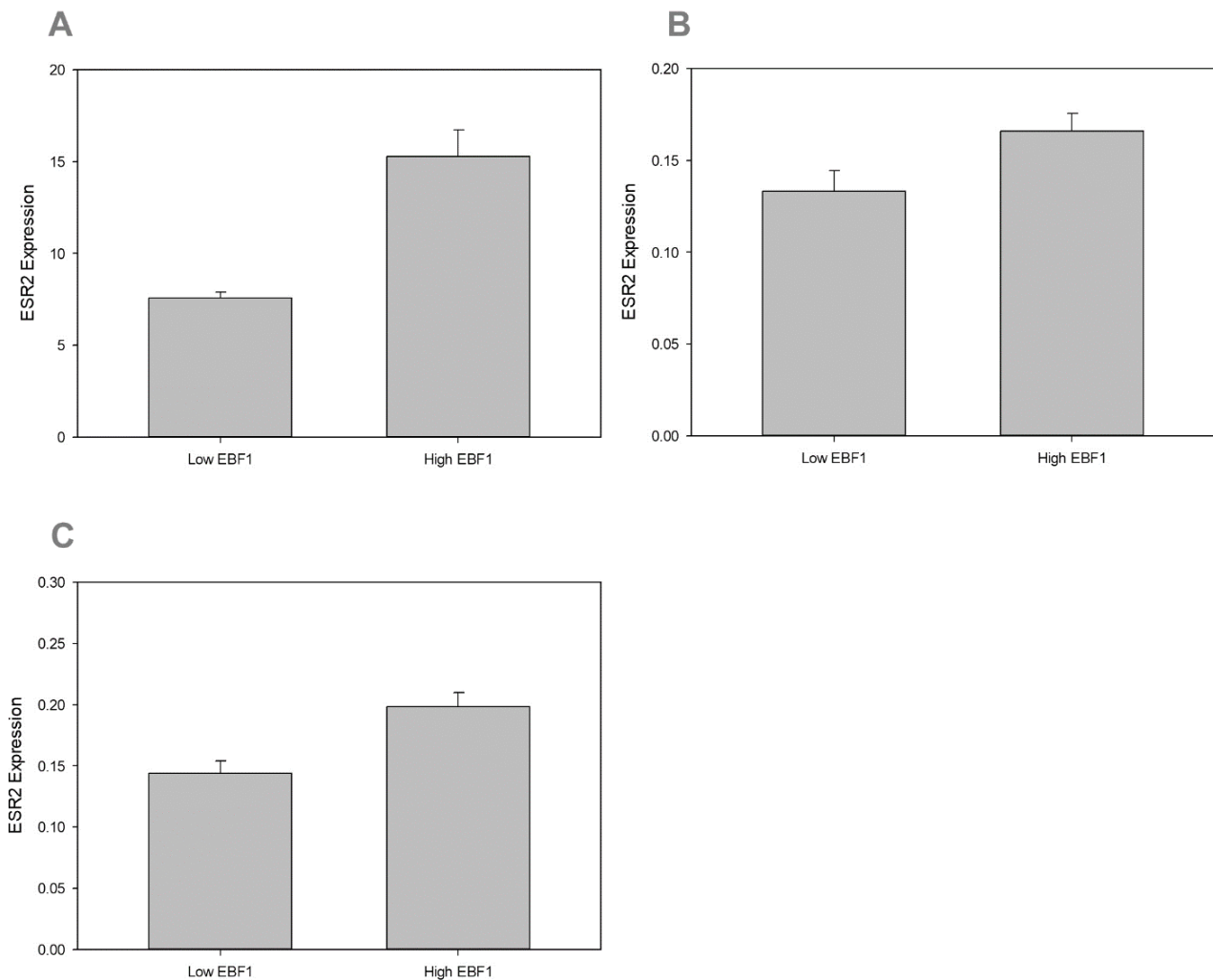
### 3.4 *EBF1* and *ESR2* Show a Crosstalk Pattern in Some Hormone-Based Cancers.

The same analysis performed above was repeated with *EBF1* and *ESR2*. We were especially interested in this analysis based on the previous work by Le and colleagues [6] which indicated that *EBF1* negatively regulates *ESR2* in a breast cancer cell line. Unexpectedly, *EBF1* expression was increased in BRCA, CESC, and UCEC tumors with high *ESR2* expression ( $p < 0.001$ ,  $p = 0.012$ ,  $p < 0.001$ , respectively; Figure 4). The same response was seen when *ESR2* expression was evaluated in the presence of low or high *EBF1* in hormone-based tumors. A significant increase in *ESR2* was observed when *EBF1* expression was also high in BRCA, CESC, and UCEC tumors ( $p < 0.001$ ; Figure 5). There was no significant difference seen in either analysis for OV or UCS tumors.



**Figure 4** *EBF1* expression corresponds to *ESR2* expression in estrogen-based cancers. Median *ESR2* expression was determined in tumor samples for all five cancers and then patient samples were divided into “low” and “high” *ESR2* based on the median for each cancer. Mean *EBF1* expression was subsequently determined for the “low” and “high” groups and statistical significance determined using a T-test or Mann Whitney Rank Sum Test. Graphs for A) BRCA ( $p < 0.001$ ), B) CESC ( $p = 0.012$ ), C) UCEC ( $p < 0.001$ ) show significant results.





**Figure 5** *ESR2* expression corresponds to *EBF1* expression in estrogen-based cancers. Median *EBF1* expression was determined in tumor samples for all five cancers and then patient samples were divided into “low” and “high” *EBF1* based on the median for each cancer. Mean *ESR2* expression was subsequently determined for the “low” and “high” groups and statistical significance determined using a T-test or Mann Whitney Rank Sum Test. Graphs for A) BRCA ( $p < 0.001$ ), B) CESC ( $p < 0.001$ ), and C) UCEC ( $p < 0.001$ ) show significant results.

#### 4. Discussion

While the role of  $ER\alpha/ESR1$  in breast cancer is well-defined and its expression is monitored as part of diagnosis and treatment, the same is not true for all hormone-based cancers. Furthermore, our understanding of the role of  $ER\beta/ESR2$  is far less defined. Indeed, most studies involving *ESR2* have focused on its role in colon cancer rather than the cancers studied here. Therefore, it is clear that there is much that we still do not understand about the role of estrogen and binding partners like *EBF1* in all cancers. This study examining the interactions between *EBF1*, *ESR1*, and *ESR2* is the first, to our knowledge, to be completed utilizing clinical samples from these cancers rather than an *in vitro* cell line model. Therefore, it is hoped that these data will better inform future studies on estrogen receptor binding partners.

Five different estrogen-based cancers were utilized for our study. However, it should be noted that one of the cancers, UCS, showed no significant data for any analysis that was performed. We suspect that may be due to sample size as there are currently only 56 patient samples with relevant RNASeqV2 data available on the Genomic Data Commons. The next smallest sample size of all cancers examined was OV with 167 patient samples. Therefore, we suspect that the lack of significant data in UCS does not indicate that there is no role for *EBF1*, *ESR1*, and/or *ESR2* in UCS but, instead, that the analysis is limited by sample size and no conclusions can be drawn at this time. However, we were able to observe significant data in the other four cancers, indicating that there is some interaction between *EBF1* and the estrogen receptor genes in these cancers.

Previous studies [4-5] have shown that *EBF1* is down-regulated in tumor tissues across cancer types. However, we did not see a similar response in four out of five cancers tested. Instead, only UCEC showed a significant down-regulation of *EBF1* in tumor tissues compared to normal (Figure 1). These data indicate that *EBF1* may not be a good marker for tumor progression in clinical samples at this time, contrary to results seen *in vitro*. Furthermore, our analysis emphasizes the importance of verifying results in clinical samples rather than a complete reliance on cell lines to understand molecular mechanisms of tumor progression.

Previous studies have shown that decreased levels of *ESR1* and *ESR2*, isoform 1, correspond to a more aggressive cancer phenotype [14-15]. Furthermore, because studies had shown that *EBF1* is down-regulated in tumor cells, one could assume that there should be a positive correlation between *EBF1* and *ESR1* or *ESR2*. Indeed, except in the case of OV, we consistently observed a positive correlation between these genes across cancers (Table 1). However, our negative correlation in OV in which a low level of *EBF1* correlated with high *ESR1* may be explained by the fact that a subset of ovarian cancers are known to have increased *ESR1* expression in aggressive tumors, matching what we see here [19-20]. Therefore, our correlation data are consistently matching what would be expected based on previous studies on *EBF1* and *ESR1/ESR2* separately.

Le and colleagues [6] were the first to show an interaction between *EBF1* and ER $\alpha$  and ER $\beta$ . Interestingly, they observed this crosstalk regulation in a breast cancer cell line at the protein, but not transcript level. The data presented here clearly showed changes in expression at the RNA level, indicating that the regulation may happen at an earlier point in clinical samples than originally expected. It is important to note that Le and colleagues utilized a modified MCF-7 cell line for their study, which is a non-aggressive tumor line that normally shows high levels of estrogen receptor and has not undergone an epithelial-to-mesenchymal transition. Based on known clinical data from the tumor samples available in GDC [18], the majority of the tumor samples utilized for this study have progressed beyond the non-aggressive state modeled in MCF-7 cells, which could lead to inconsistencies in results between our two studies. Similar to Le and colleagues, while there is an interaction between *EBF1* and *ESR1*, as seen through both correlation and cross-talk data (Table 1 and Figures 2-3), it is inconsistent across cancers making it difficult to determine what is happening in those patients. Importantly, it should be noted that our correlation data shown in Table 1 matches the cross-talk data observed in Figures 2-5, indicating that our results are consistent throughout our various analytical methods. Similar to Le and colleagues, in two cases - BRCA and OV - we observed negative cross-talk regulation of *EBF1* and *ESR1*. However, we also observed regulation in the opposite direction where high *EBF1* corresponded to high *ESR1* levels in CESC and UCEC (Table 1 and Figures 2-3). These ambiguous results indicate that there is much we do not understand about the *EBF1/ESR1* interaction in

hormone-based cancers. Conversely, the interaction between *EBF1* and *ESR2* was consistent across all cancers tested indicating a potential binding interaction similar to what was observed by Le and colleagues [6]. However, unlike their analysis, we saw that high levels of *EBF1* corresponded to high levels of *ESR2* in BRCA, CESC, OV, and UCEC tumor tissues (Figures 4 and 5). This would imply a positive feedback mechanism in patients that was not previously seen *in vitro*. Perhaps these results are not that surprising based on the previous conflicting data in which some cancers see an up-regulation and some see a down-regulation of *ESR2* corresponding to tumor progression, as well as the previously discussed expectation that *EBF1* and *ESR2* are normally both decreased in aggressive tumors. Finally, it is important to note that the sequencing data obtained from GDC comes from a whole tumor, rather than a specific cell line. Therefore, it is quite possible that the heterogeneous nature of a whole tumor sample can lead to altered gene expression profiling due to interactions with the tumor microenvironment [21]. While we do not have the ability to measure the effect of the microenvironment based on the data obtained in GDC, it is an important factor that can affect our findings and should be noted for future studies.

Taken together, previous studies, along with our work, clearly indicate that there is much we still do not know about the interaction between *EBF1*, *ESR1*, and *ESR2* in estrogen-based cancers as well as any potential role in tumor progression. Future studies could potentially examine this relationship with regard to clinical stage as a sign of tumor progression to determine whether we see changes in *EBF1* and estrogen receptor expression correlated with high or low stage. Unfortunately, given the current sample sizes and uneven distribution of clinical stage data available on the Genomic Data Commons dataset, these analyses are difficult, if not impossible, to compile statistically relevant data at the current time. It is hoped that as the databases grow, analyses such as this will be more effective in future years. In conclusion, the work presented here indicates that there is a likely interaction between *EBF1* and the estrogen receptor genes in clinical patient samples. While the interaction with *ESR1* is less clear, there is an obvious positive feedback interaction between *EBF1* and *ESR2* in the cancers tested. These results provide novel information on this unique interaction and the molecular mechanisms of tumor progression which could lead to innovative diagnostic and treatment options in the future.

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## **Author Contributions**

M.J.L. proposed and conceived of the work. M.J.L. and S.L.R. designed and performed the experiments and analyzed the data. M.J.L. and S.L.R. wrote the manuscript together.

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## **Competing Interests**

The authors have declared that no competing interests exist.

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