



Table S1: PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3-4 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | - |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4,6-7, Table 1 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4-5, 6-7 fig 1 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4-5, 6-7, fig 1 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4-5, 6-7, Table 1 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5-6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5-6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | 5-6 |



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|-------------------------------|----|--|--------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5-6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5-6 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6-7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6-7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 6-7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7-10 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7-10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6,8 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10-12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 12-13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 13 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Table S2. The association of HIF-2 α protein expression with the clinicopathological features of CRC (negative results) (publications)

| Comparison and studies | Case groups | Frequency | Control groups | Frequency | OR with 95% CI | P value | Heterogeneity (p) |
|---|-------------|-----------|----------------|-----------|--------------------|---------|-------------------|
| Stage 3-4 vs. Stage 1-2 | | | | | | | |
| Yoshimura 2004 | 15/37 | 40.5 | 11/50 | 22.0 | 2.42 (0.95, 6.17) | 0.958 | < 0.001 |
| Imamura 2009 | 7/28 | 25.0 | 21/35 | 60.0 | 0.22 (0.07, 0.66) | | |
| Rasheed 2009 | 18/33 | 54.5 | 40/57 | 70.2 | 0.51 (0.21, 1.24) | | |
| Baba 2010 | 121/289 | 41.9 | 183/367 | 49.9 | 0.72 (0.53, 0.99) | | |
| Wu 2015 | 27/30 | 90.0 | 156/254 | 61.4 | 5.65 (1.67, 19.14) | | |
| Total | 188/417 | 45.1 | 411/763 | 53.9 | 0.98 (0.42, 2.29) | | |
| T3-4 vs. T1-2 | | | | | | | |
| Yoshimura 2004 | 24/59 | 40.7 | 2/28 | 7.1 | 8.91 (1.93, 41.13) | 0.409 | 0.014 |
| Rasheed 2009 | 46/72 | 63.9 | 12/18 | 66.7 | 0.88 (0.30, 2.64) | | |
| Total | 70/131 | 53.4 | 14/46 | 30.4 | 2.64 (0.26, 26.45) | | |
| Lymph node positive vs. negative status | | | | | | | |
| Yoshimura 2004 | 14/34 | 41.2 | 12/53 | 22.6 | 2.39 (0.94, 6.11) | 0.423 | 0.007 |
| Koukourakis 2005 | 17/27 | 63.0 | 15/48 | 31.3 | 3.74 (1.39, 10.08) | | |
| Rasheed 2009 | 18/33 | 54.5 | 40/57 | 70.2 | 0.51 (0.21, 1.24) | | |
| Total | 49/94 | 52.1 | 67/158 | 42.4 | 1.63 (0.49, 5.45) | | |
| Vascular invasion (yes vs. no) | | | | | | | |
| Rasheed 2009 | 17/27 | 63.0 | 41/63 | 65.1 | 0.91 (0.36, 2.33) | 0.848 | NA |
| Metastasis (yes vs no) | | | | | | | |
| Koukourakis 2005 | 6/9 | 66.7 | 26/66 | 39.4 | 3.08 (0.71, 13.40) | 0.134 | NA |
| Cancer (60 years vs. <60 years) | | | | | | | |
| Baba 2010 | 266/559 | 47.6 | 56/136 | 41.2 | 1.30 (0.89, 1.90) | 0.18 | NA |
| Colon vs Rectum | | | | | | | |
| Baba 2010 | 259/543 | 47.7 | 56/139 | 40.3 | 1.35 (0.93, 1.97) | 0.119 | NA |
| Microvessel density ((high HIF-2 α vs. low HIF-2 α) | | | | | | | |
| Koukourakis 2005 | 19/32 | 59.4 | 18/43 | 41.9 | 2.03 (0.80, 5.14) | 0.152 | 0.411 |
| Imamura 2009 | 14/28 | 50.0 | 12/35 | 34.3 | 1.92 (0.69, 5.30) | | |
| Rasheed 2009 | 32/57 | 56.1 | 18/31 | 58.1 | 0.92 (0.38, 2.24) | | |
| Total | 65/117 | | 48/109 | | 1.49 (0.86, 2.56) | | |

HIF-2 α : hypoxia-inducible factor-2 α ; CRC: colorectal cancer; OR: odds ratio; 95% CI: 95% confidence interval.

Table S3. Prognostic role of HIF-2α expression from PrognScan database in human cancers (negative results)

| N | DATASET | PROBE ID | HR [95% CI-low CI-upp] | ENDPOINT | CANCER TYPE | SUBTYPE |
|--|-----------------|--------------|------------------------|---------------------------|-------------------|-------------------------------|
| 62 | GSE12945 | 200879_s_at | 0.95 [0.06 - 14.49] | Overall Survival | Colorectal cancer | |
| 177 | GSE17536 | 200878_at | 1.02 [0.58 - 1.78] | Overall Survival | Colorectal cancer | |
| 177 | GSE17536 | 241055_at | 0.32 [0.05 - 2.22] | Overall Survival | Colorectal cancer | |
| 177 | GSE17536 | 200879_s_at | 0.67 [0.34 - 1.32] | Overall Survival | Colorectal cancer | |
| 55 | GSE17537 | 241055_at | 0.12 [0.00 - 3.40] | Overall Survival | Colorectal cancer | |
| 55 | GSE17537 | 200879_s_at | 0.79 [0.43 - 1.43] | Overall Survival | Colorectal cancer | |
| 55 | GSE17537 | 200878_at | 1.39 [0.70 - 2.75] | Overall Survival | Colorectal cancer | |
| Pooled HR with 95% CI: 0.89 (0.66-1.21), P = 0.470 | | | | | | |
| 177 | GSE17536 | 200879_s_at | 0.65 [0.30 - 1.41] | Disease Specific Survival | Colorectal cancer | |
| 177 | GSE17536 | 241055_at | 0.28 [0.03 - 2.64] | Disease Specific Survival | Colorectal cancer | |
| 177 | GSE17536 | 200878_at | 1.10 [0.58 - 2.09] | Disease Specific Survival | Colorectal cancer | |
| 49 | GSE17537 | 200878_at | 0.91 [0.34 - 2.45] | Disease Specific Survival | Colorectal cancer | |
| 49 | GSE17537 | 200879_s_at | 0.49 [0.20 - 1.18] | Disease Specific Survival | Colorectal cancer | |
| Pooled HR with 95% CI: 0.77 (0.52-1.13), P = 0.183 | | | | | | |
| 30 | GSE5287 | 200879_s_at | 1.70 [0.73 - 3.97] | Overall Survival | Bladder cancer | |
| 30 | GSE5287 | 200878_at | 0.95 [0.51 - 1.76] | Overall Survival | Bladder cancer | |
| 165 | GSE13507 | ILMN_1760034 | 1.09 [0.83 - 1.43] | Overall Survival | Bladder cancer | |
| Pooled HR with 95% CI: 1.11 (0.87-1.40), P = 0.407 | | | | | | |
| 165 | GSE13507 | ILMN_1760034 | 0.91 [0.63 - 1.32] | Disease Specific Survival | Bladder cancer | Transitional cell carcinoma |
| | | | | | | |
| 163 | GSE12417-GPL96 | 200878_at | 1.49 [1.06 - 2.08] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 163 | GSE12417-GPL96 | 200879_s_at | 1.14 [0.32 - 4.16] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 163 | GSE12417-GPL97 | 241055_at | 1.01 [0.18 - 5.77] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 79 | GSE12417-GPL570 | 200878_at | 1.10 [0.80 - 1.51] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 79 | GSE12417-GPL570 | 241055_at | 0.50 [0.10 - 2.52] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 79 | GSE12417-GPL570 | 200879_s_at | 0.40 [0.06 - 2.57] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 58 | GSE5122 | 200879_s_at | 0.90 [0.63 - 1.29] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 58 | GSE5122 | 200878_at | 0.81 [0.56 - 1.17] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 34 | GSE8970 | 200878_at | 0.89 [0.65 - 1.20] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| 34 | GSE8970 | 200879_s_at | 1.10 [0.69 - 1.75] | Overall Survival | Blood cancer | Acute myeloid leukemia |
| Pooled HR with 95% CI:1.02 (0.87-1.18), P = 0.840 | | | | | | |
| 53 | E-TABM-346 | 200878_at | 1.23 [0.56 - 2.73] | Overall Survival | Blood cancer | Diffuse large B-cell lymphoma |
| 53 | E-TABM-346 | 200879_s_at | 1.27 [0.47 - 3.45] | Overall Survival | Blood cancer | Diffuse large B-cell lymphoma |
| Pooled HR with 95% CI: 1.25 (0.67-2.32), P = 0.488 | | | | | | |
| 53 | E-TABM-346 | 200878_at | 1.30 [0.62 - 2.74] | Event Free Survival | Blood cancer | Diffuse large B-cell lymphoma |
| 53 | E-TABM-346 | 200879_s_at | 1.53 [0.58 - 4.04] | Event Free Survival | Blood cancer | Diffuse large B-cell lymphoma |
| Pooled HR with 95% CI: 1.38 (0.77-2.49), P = 0.284 | | | | | | |
| 180 | GSE16131-GPL96 | 200879_s_at | 1.06 [0.80 - 1.39] | Overall Survival | Blood cancer | Follicular lymphoma |

| | | | | | | |
|--|----------------|-------------|-----------------------|---------------------------|---------------|---------------------|
| 180 | GSE16131-GPL96 | 200878_at | 1.10 [0.72 - 1.67] | Overall Survival | Blood cancer | Follicular lymphoma |
| 180 | GSE16131-GPL97 | 241055_at | 1.00 [0.83 - 1.22] | Overall Survival | Blood cancer | Follicular lymphoma |
| Pooled HR with 95% CI: 1.03 (0.89-1.19), P = 0.706 | | | | | | |
| 77 | GSE4271-GPL96 | 200878_at | 0.91 [0.59 - 1.40] | Overall Survival | Brain cancer | Astrocytoma |
| 77 | GSE4271-GPL96 | 200879_s_at | 0.82 [0.59 - 1.14] | Overall Survival | Brain cancer | Astrocytoma |
| 77 | GSE4271-GPL97 | 241055_at | 1.14 [0.83 - 1.58] | Overall Survival | Brain cancer | Astrocytoma |
| Pooled HR with 95% CI: 0.96 (0.78-1.17), P = 0.672 | | | | | | |
| 70 | GSE7696 | 200878_at | 1.08 [0.74 - 1.58] | Overall Survival | Brain cancer | Glioblastoma |
| 70 | GSE7696 | 241055_at | 2.18 [0.21 - 22.70] | Overall Survival | Brain cancer | Glioblastoma |
| 70 | GSE7696 | 200879_s_at | 1.26 [0.38 - 4.20] | Overall Survival | Brain cancer | Glioblastoma |
| Pooled HR with 95% CI: 1.11 (0.78-1.59), P = 0.557 | | | | | | |
| 50 | MGH-glioma | 38092_at | 0.54 [0.14 - 2.08] | Overall Survival | Brain cancer | Glioma |
| 50 | MGH-glioma | 38230_at | 1.01 [0.58 - 1.74] | Overall Survival | Brain cancer | Glioma |
| 74 | GSE4412-GPL96 | 200878_at | 1.38 [0.72 - 2.67] | Overall Survival | Brain cancer | Glioma |
| 74 | GSE4412-GPL96 | 200879_s_at | 0.79 [0.56 - 1.10] | Overall Survival | Brain cancer | Glioma |
| 74 | GSE4412-GPL97 | 241055_at | 1.11 [0.69 - 1.77] | Overall Survival | Brain cancer | Glioma |
| Pooled HR with 95% CI: 0.94 (0.75-1.18), P = 0.608 | | | | | | |
| 67 | GSE16581 | 200878_at | 1.01 [0.23 - 4.53] | Overall Survival | Brain cancer | Meningioma |
| 67 | GSE16581 | 200879_s_at | 1.15 [0.36 - 3.66] | Overall Survival | Brain cancer | Meningioma |
| 67 | GSE16581 | 241055_at | 3.78 [0.01 - 2341.98] | Overall Survival | Brain cancer | Meningioma |
| Pooled HR with 95% CI: 1.12 (0.45-2.78), P = 0.799 | | | | | | |
| 76 | GSE7849 | 38092_at | 0.50 [0.28 - 0.89] | Disease Free Survival | Breast cancer | |
| 76 | GSE7849 | 38230_at | 1.09 [0.37 - 3.22] | Disease Free Survival | Breast cancer | |
| 54 | GSE7378 | 200878_at | 0.56 [0.25 - 1.28] | Disease Free Survival | Breast cancer | |
| 54 | GSE7378 | 200879_s_at | 0.89 [0.14 - 5.54] | Disease Free Survival | Breast cancer | |
| 249 | GSE4922-GPL96 | 200879_s_at | 0.55 [0.32 - 0.94] | Disease Free Survival | Breast cancer | |
| 249 | GSE4922-GPL96 | 200878_at | 0.75 [0.48 - 1.18] | Disease Free Survival | Breast cancer | |
| 249 | GSE4922-GPL97 | 241055_at | 1.25 [0.90 - 1.74] | Disease Free Survival | Breast cancer | |
| Pooled HR with 95% CI: 0.75 (0.54-1.06), P = 0.101 | | | | | | |
| 159 | GSE1456-GPL96 | 200879_s_at | 0.73 [0.33 - 1.62] | Disease Specific Survival | Breast cancer | |
| 159 | GSE1456-GPL96 | 200878_at | 0.61 [0.27 - 1.40] | Disease Specific Survival | Breast cancer | |
| 159 | GSE1456-GPL97 | 241055_at | 1.22 [0.72 - 2.09] | Disease Specific Survival | Breast cancer | |
| 117 | E-TABM-158 | 200879_s_at | 1.39 [0.36 - 5.37] | Disease Specific Survival | Breast cancer | |
| 117 | E-TABM-158 | 200878_at | 1.31 [0.69 - 2.47] | Disease Specific Survival | Breast cancer | |
| 236 | GSE3494-GPL96 | 200878_at | 0.83 [0.46 - 1.49] | Disease Specific Survival | Breast cancer | |
| 236 | GSE3494-GPL96 | 200879_s_at | 0.80 [0.40 - 1.61] | Disease Specific Survival | Breast cancer | |
| 236 | GSE3494-GPL97 | 241055_at | 1.32 [0.86 - 2.01] | Disease Specific Survival | Breast cancer | |
| Pooled HR with 95% CI: 1.04 (0.83-1.30), P = 0.707 | | | | | | |
| 158 | GSE3143 | 38092_at | 0.92 [0.65 - 1.30] | Overall Survival | Breast cancer | |
| 158 | GSE3143 | 38230_at | 1.36 [0.76 - 2.45] | Overall Survival | Breast cancer | |
| 155 | GSE9893 | 2688 | 0.96 [0.58 - 1.61] | Overall Survival | Breast cancer | |
| 159 | GSE1456-GPL96 | 200878_at | 0.50 [0.24 - 1.01] | Overall Survival | Breast cancer | |
| 159 | GSE1456-GPL96 | 200879_s_at | 0.70 [0.35 - 1.37] | Overall Survival | Breast cancer | |
| 159 | GSE1456-GPL97 | 241055_at | 1.38 [0.87 - 2.19] | Overall Survival | Breast cancer | |

| | | | | | | |
|--|----------------|----------------------|---------------------|----------------------------------|----------------------|----------------------------|
| 117 | E-TABM-158 | 200878_at | 1.07 [0.63 - 1.82] | Overall Survival | Breast cancer | |
| 117 | E-TABM-158 | 200879_s_at | 0.70 [0.20 - 2.48] | Overall Survival | Breast cancer | |
| 198 | GSE7390 | 200879_s_at | 1.16 [0.85 - 1.59] | Overall Survival | Breast cancer | |
| 198 | GSE7390 | 200878_at | 1.20 [0.86 - 1.67] | Overall Survival | Breast cancer | |
| Pooled HR with 95% CI: 1.05 (0.90-1.23), P = 0.506 | | | | | | |
| 204 | GSE12276 | 200879_s_at | 0.95 [0.82 - 1.10] | Relapse Free Survival | Breast cancer | |
| 204 | GSE12276 | 241055_at | 1.02 [0.89 - 1.17] | Relapse Free Survival | Breast cancer | |
| 204 | GSE12276 | 200878_at | 0.88 [0.66 - 1.18] | Relapse Free Survival | Breast cancer | |
| 87 | GSE6532-GPL570 | 241055_at | 3.55 [0.43 - 29.46] | Relapse Free Survival | Breast cancer | |
| 87 | GSE6532-GPL570 | 200879_s_at | 0.91 [0.18 - 4.51] | Relapse Free Survival | Breast cancer | |
| 87 | GSE6532-GPL570 | 200878_at | 0.81 [0.51 - 1.26] | Relapse Free Survival | Breast cancer | |
| 77 | GSE9195 | 241055_at | 0.05 [0.00 - 2.58] | Relapse Free Survival | Breast cancer | |
| 77 | GSE9195 | 200879_s_at | 0.31 [0.05 - 2.08] | Relapse Free Survival | Breast cancer | |
| 77 | GSE9195 | 200878_at | 0.76 [0.32 - 1.79] | Relapse Free Survival | Breast cancer | |
| 60 | GSE1378 | 9132 | 1.07 [0.80 - 1.43] | Relapse Free Survival | Breast cancer | |
| 60 | GSE1379 | 9132 | 0.96 [0.62 - 1.49] | Relapse Free Survival | Breast cancer | |
| 159 | GSE1456-GPL96 | 200878_at | 0.49 [0.25 - 0.98] | Relapse Free Survival | Breast cancer | |
| 159 | GSE1456-GPL96 | 200879_s_at | 0.66 [0.34 - 1.31] | Relapse Free Survival | Breast cancer | |
| 159 | GSE1456-GPL97 | 241055_at | 1.11 [0.71 - 1.74] | Relapse Free Survival | Breast cancer | |
| 117 | E-TABM-158 | 200879_s_at | 0.70 [0.20 - 2.48] | Relapse Free Survival | Breast cancer | |
| 117 | E-TABM-158 | 200878_at | 1.07 [0.63 - 1.82] | Relapse Free Survival | Breast cancer | |
| 125 | GSE2990 | 200878_at | 0.94 [0.58 - 1.54] | Relapse Free Survival | Breast cancer | |
| 62 | GSE2990 | 200879_s_at | 0.88 [0.55 - 1.41] | Relapse Free Survival | Breast cancer | |
| 125 | GSE2990 | 200879_s_at | 0.64 [0.29 - 1.40] | Relapse Free Survival | Breast cancer | |
| 62 | GSE2990 | 200878_at | 0.77 [0.49 - 1.21] | Relapse Free Survival | Breast cancer | |
| 198 | GSE7390 | 200878_at | 1.31 [1.01 - 1.71] | Relapse Free Survival | Breast cancer | |
| 198 | GSE7390 | 200879_s_at | 1.03 [0.82 - 1.29] | Relapse Free Survival | Breast cancer | |
| Pooled HR with 95% CI: 0.98 (0.91-1.05), P = 0.559 | | | | | | |
| 63 | GSE22138 | 200879_s_at | 0.43 [0.02 - 11.43] | Distant Metastasis Free Survival | Eye cancer | Uveal melanoma |
| 63 | GSE22138 | 200878_at | 1.46 [1.02 - 2.08] | Distant Metastasis Free Survival | Eye cancer | Uveal melanoma |
| 63 | GSE22138 | 241055_at | 0.00 [0.00 - 4.54] | Distant Metastasis Free Survival | Eye cancer | Uveal melanoma |
| Pooled HR with 95% CI: 0.18 (0.01-5.17), P = 0.320 | | | | | | |
| 28 | GSE2837 | g4503576_3p_a_at | 5.53 [0.32 - 95.95] | Relapse Free Survival | Head and neck cancer | Squamous cell carcinoma |
| 28 | GSE2837 | Hs.201537.0.A1_3p_at | 0.55 [0.02 - 13.58] | Relapse Free Survival | Head and neck cancer | Squamous cell carcinoma |
| 28 | GSE2837 | Hs.8136.0.S2_3p_at | 1.19 [0.87 - 1.64] | Relapse Free Survival | Head and neck cancer | Squamous cell carcinoma |
| Pooled HR with 95% CI: 1.20 (0.88-1.65), P = 0.247 | | | | | | |
| 204 | GSE31210 | 200878_at | 0.18 [0.08 - 0.43] | Relapse Free Survival | Lung cancer | Adenocarcinoma |
| 204 | GSE31210 | 200879_s_at | 0.56 [0.34 - 0.93] | Relapse Free Survival | Lung cancer | Adenocarcinoma |
| 204 | GSE31210 | 241055_at | 0.94 [0.72 - 1.24] | Relapse Free Survival | Lung cancer | Adenocarcinoma |
| Pooled HR with 95% CI: 0.50 0.23-1.10), P = 0.086 | | | | | | |
| 41 | GSE11117 | H300009037 | 0.89 [0.63 - 1.25] | Overall Survival | Lung cancer | Non-small cell lung cancer |

| | | | | | | |
|---|----------|-------------------------------------|--------------------|---------------------------|----------------------|----------------------------|
| 111 | GSE3141 | 200879_s_at | 1.12 [0.81 - 1.54] | Overall Survival | Lung cancer | Non-small cell lung cancer |
| 111 | GSE3141 | 200878_at | 1.01 [0.68 - 1.50] | Overall Survival | Lung cancer | Non-small cell lung cancer |
| 111 | GSE3141 | 241055_at | 0.89 [0.64 - 1.24] | Overall Survival | Lung cancer | Non-small cell lung cancer |
| 90 | GSE14814 | 200878_at | 0.92 [0.62 - 1.36] | Overall Survival | Lung cancer | Non-small cell lung cancer |
| 90 | GSE14814 | 200879_s_at | 0.73 [0.39 - 1.38] | Overall Survival | Lung cancer | Non-small cell lung cancer |
| Pooled HR with 95% CI: 0.95 (0.81-1.11), P = 0.505 | | | | | | |
| 90 | GSE14814 | 200878_at | 0.82 [0.53 - 1.29] | Disease Specific Survival | Lung cancer | Non-small cell lung cancer |
| 90 | GSE14814 | 200879_s_at | 0.73 [0.35 - 1.51] | Disease Specific Survival | Lung cancer | Non-small cell lung cancer |
| Pooled HR with 95% CI: 0.79 (0.54-1.16), P = 0.236 | | | | | | |
| 138 | GSE8894 | 241055_at | 0.00 [0.00 - 1.35] | Relapse Free Survival | Lung cancer | Non-small cell lung cancer |
| 138 | GSE8894 | 200879_s_at | 1.10 [0.89 - 1.37] | Relapse Free Survival | Lung cancer | Non-small cell lung cancer |
| 138 | GSE8894 | 200878_at | 0.93 [0.73 - 1.18] | Relapse Free Survival | Lung cancer | Non-small cell lung cancer |
| Pooled HR with 95% CI: 0.89 (0.52-1.52) | | | | | | |
| 129 | GSE4573 | 200879_s_at | 0.80 [0.47 - 1.34] | Overall Survival | Lung cancer | Squamous cell carcinoma |
| 129 | GSE4573 | 200878_at | 0.86 [0.52 - 1.42] | Overall Survival | Lung cancer | Squamous cell carcinoma |
| 56 | GSE17710 | 26208 | 0.91 [0.64 - 1.29] | Overall Survival | Lung cancer | Squamous cell carcinoma |
| 56 | GSE17710 | 19165 | 0.85 [0.56 - 1.30] | Overall Survival | Lung cancer | Squamous cell carcinoma |
| 56 | GSE17710 | 6376 | 0.70 [0.39 - 1.25] | Overall Survival | Lung cancer | Squamous cell carcinoma |
| Pooled HR with 95% CI: 0.84 (0.69-1.03), P = 0.099 | | | | | | |
| 56 | GSE17710 | 19165 | 0.89 [0.58 - 1.36] | Relapse Free Survival | Lung cancer | Squamous cell carcinoma |
| 56 | GSE17710 | 6376 | 0.84 [0.50 - 1.41] | Relapse Free Survival | Lung cancer | Squamous cell carcinoma |
| 56 | GSE17710 | 26208 | 0.96 [0.67 - 1.37] | Relapse Free Survival | Lung cancer | Squamous cell carcinoma |
| Pooled HR with 95% CI: 0.91 (0.71-1.16), P = 0.445 | | | | | | |
| 278 | GSE9891 | 200879_s_at | 0.72 [0.50 - 1.05] | Overall Survival | Ovarian cancer | |
| 278 | GSE9891 | 241055_at | 0.92 [0.30 - 2.88] | Overall Survival | Ovarian cancer | |
| 278 | GSE9891 | 200878_at | 1.06 [0.86 - 1.31] | Overall Survival | Ovarian cancer | |
| 133 | DUKE-OC | 200879_s_at | 0.82 [0.54 - 1.25] | Overall Survival | Ovarian cancer | |
| 133 | DUKE-OC | 200878_at | 0.83 [0.71 - 0.98] | Overall Survival | Ovarian cancer | |
| 81 | GSE8841 | 4415 | 0.44 [0.10 - 2.01] | Overall Survival | Ovarian cancer | |
| 185 | GSE26712 | 200879_s_at | 0.96 [0.57 - 1.63] | Overall Survival | Ovarian cancer | |
| 185 | GSE26712 | 200878_at | 1.12 [0.91 - 1.38] | Overall Survival | Ovarian cancer | |
| 110 | GSE17260 | A_23_P430120 | 0.94 [0.66 - 1.33] | Overall Survival | Ovarian cancer | |
| 110 | GSE17260 | A_23_P210210 | 1.01 [0.72 - 1.41] | Overall Survival | Ovarian cancer | |
| 80 | GSE14764 | 200879_s_at | 1.14 [0.56 - 2.33] | Overall Survival | Ovarian cancer | |
| 80 | GSE14764 | 200878_at | 0.87 [0.52 - 1.46] | Overall Survival | Ovarian cancer | |
| Pooled HR with 95% CI: 0.94 (0.86-1.03), P = 0.159 | | | | | | |
| 185 | GSE26712 | 200878_at | 1.12 [0.92 - 1.37] | Disease Free Survival | Ovarian cancer | |
| 185 | GSE26712 | 200879_s_at | 0.97 [0.61 - 1.56] | Disease Free Survival | Ovarian cancer | |
| Pooled HR with 95% CI: 1.10 (0.91-1.32) , P = 0.328 | | | | | | |
| 110 | GSE17260 | A_23_P430120 | 1.07 [0.82 - 1.40] | Progression Free Survival | Ovarian cancer | |
| 110 | GSE17260 | A_23_P210210 | 1.08 [0.85 - 1.37] | Progression Free Survival | Ovarian cancer | |
| Pooled HR with 95% CI: 1.08 (0.90-1.29), P = 0.423 | | | | | | |
| 281 | GSE16560 | DAP3_0296 | 0.89 [0.70 - 1.12] | Overall Survival | Prostate cancer | |
| 59 | E-DKFZ-1 | rzpd.de:huber1:Reporter:IMAGE:32120 | 1.11 [0.33 - 3.71] | Overall Survival | Renal cell carcinoma | |

| | | | | | | |
|--|----------|-------------|--------------------|------------------|-------------|----------|
| 38 | GSE19234 | 200879_s_at | 1.30 [0.81 - 2.09] | Overall Survival | Skin cancer | Melanoma |
| 38 | GSE19234 | 200878_at | 0.71 [0.32 - 1.54] | Overall Survival | Skin cancer | Melanoma |
| 38 | GSE19234 | 241055_at | 0.74 [0.51 - 1.07] | Overall Survival | Skin cancer | Melanoma |
| Pooled HR with 95% CI: 0.90 (0.60-1.34), P = 0.605 | | | | | | |

HIF-2 α : hypoxia-inducible factor-2 α ; HR: hazard ratio; 95% CI: 95% confidence interval.

Table S4. Prognostic role of both HIF-2 α and VEGF or HIF-2 α alone expression from PROGGeneV2 database in CRC (negative results)

| N | DATASET | HR [95% CI-low CI-upp] | ENDPOINT | Gene | |
|---|-----------|------------------------|--------------------------|-----------------|--|
| 122 | GSE28814 | 2.41 (0.07 - 83.99) | Relapse free survival | HIF2A | |
| 75 | GSE17536 | 0.9 (0.33 - 2.47) | Relapse free survival | | |
| 21 | GSE17537 | 0.4 (0.09 - 1.87) | Relapse free survival | | |
| 187 | GSE14333 | 1.1 (0.44 - 2.74) | Relapse free survival | | |
| 37 | GSE31595 | 0.4 (0.02 - 9.05) | Relapse free survival | | |
| 44 | GSE38832 | 0.84 (0.54 - 1.32) | Relapse free survival | | |
| 269 | GSE39582 | 1.13 (0.88 -1.46) | Relapse free survival | | |
| Pooled HR with 95% CI: 1.03 (0.84 - 1.26), P = 0.802 | | | | | |
| 122 | GSE28814 | 2.83 (0.08 - 105.03) | Metastasis free survival | HIF2A and VEGFA | |
| 125 | GSE28722 | 3.6 (0.12 - 103.89) | Metastasis free survival | | |
| Pooled HR with 95% CI: 3.21 (0.27 - 37.69), P = 0.352 | | | | | |
| 122 | GSE28814 | 0.54 (0.1 - 2.97) | Overall Survival | | |
| 174 | GSE17536 | 1.35 (0.62 - 2.95) | Overall Survival | | |
| 52 | GSE17537 | 0.81 (0.36 - 1.85) | Overall Survival | | |
| 121 | TCGA DATA | 0.9 (0.24 - 3.42) | Overall Survival | | |
| 62 | GSE12945 | 1.12 (0.16 - 7.62) | Overall Survival | | |
| 32 | GSE16125 | 1.72 (0.67 - 4.4) | Overall Survival | HIF2A and VEGFB | |
| 160 | GSE24551 | 1.17 (0.53 - 2.57) | Overall Survival | | |
| 125 | GSE28722 | 0.54 (0.1 - 3.01) | Overall Survival | | |
| 43 | GSE30378 | 0.96 (0.46 - 1.98) | Overall Survival | | |
| 182 | GSE41258 | 1.56 (0.82 - 2.99) | Overall Survival | | |
| 65 | GSE29621 | 1.51 (0.46 - 4.97) | Overall Survival | | |
| 121 | GSE38832 | 1.06 (0.76 - 1.48) | Overall Survival | | |
| 286 | GSE39582 | 1.29 (0.96 - 1.73) | Overall Survival | | |
| Pooled HR with 95% CI: 1.18 (0.99 - 1.40), P = 0.069 | | | | | |
| 122 | GSE28814 | 4.1 0.24 71 | Overall Survival | HIF2A and VEGFB | |
| 174 | GSE17536 | 0.7 0.28 1.72 | Overall Survival | | |
| 52 | GSE17537 | 0.56 0.2 1.58 | Overall Survival | | |
| 121 | TCGA | 0.84 0.26 2.69 | Overall Survival | | |
| 62 | GSE12945 | 0.48 0.06 3.87 | Overall Survival | | |
| 32 | GSE16125 | 1.95 0.89 4.28 | Overall Survival | | |
| 160 | GSE24551 | 0.68 0.31 1.5 | Overall Survival | | |
| 125 | GSE28722 | 4.02 0.23 69.98 | Overall Survival | | |
| 45 | GSE30378 | 0.7 0.33 1.48 | Overall Survival | HIF2A and VEGFB | |
| 182 | GSE41258 | 2.4 1.04 5.55 | Overall Survival | | |
| 65 | GSE29621 | 0.58 0.12 2.83 | Overall Survival | | |
| 121 | GSE38832 | 1.02 0.73 1.43 | Overall Survival | | |
| 284 | GSE39582 | 1.19 0.82 1.72 | Overall Survival | | |
| Pooled HR with 95% CI: 1.04 (0.82 - 1.32), P = 0.729 | | | | | |
| 122 | GSE28814 | 64.09 (2.38 - 1726.65) | Relapse free survival | | |

| | | | |
|-----|----------|----------------|-----------------------|
| 73 | GSE17536 | 1.78 0.54 5.84 | Relapse free survival |
| 20 | GSE17537 | 0.59 0.09 3.73 | Relapse free survival |
| 187 | GSE14333 | 2.83 0.9 8.88 | Relapse free survival |
| 37 | GSE31595 | 0.02 0 1.48 | Relapse free survival |
| 46 | GSE38832 | 0.82 0.48 1.43 | Relapse free survival |
| 264 | GSE39582 | 1.65 1.08 2.51 | Relapse free survival |

Pooled HR with 95% CI: 1.39 (0.70 - 2.77), P = 0.350

| | | | |
|-----|----------|----------------|------------------|
| 122 | GSE28814 | 0.42 0.04 4.09 | Overall Survival |
| 174 | GSE17536 | 1.68 0.78 3.65 | Overall Survival |
| 52 | GSE17537 | 1.08 0.49 2.37 | Overall Survival |
| 121 | TCGA | 0.88 0.35 2.2 | Overall Survival |
| 62 | GSE12945 | 1.09 0.21 5.52 | Overall Survival |
| 32 | GSE16125 | 1.54 0.82 2.9 | Overall Survival |
| 160 | GSE24551 | 0.57 0.29 1.13 | Overall Survival |
| 125 | GSE28722 | 0.4 0.04 3.95 | Overall Survival |
| 44 | GSE30378 | 0.68 0.34 1.37 | Overall Survival |
| 182 | GSE41258 | 1.66 0.66 4.15 | Overall Survival |
| 65 | GSE29621 | 1.37 0.25 7.71 | Overall Survival |
| 121 | GSE38832 | 0.95 0.64 1.41 | Overall Survival |
| 287 | GSE39582 | 1.38 1.05 1.82 | Overall Survival |

HIF2A and VEGFC

Pooled HR with 95% CI: 1.11 (0.91 - 1.35), P = 0.293

| | | | |
|-----|------------|-----------------|-----------------------|
| 122 | GSE28814 - | 9.78 1.17 81.65 | Relapse free survival |
| 74 | GSE17536 - | 4.86 1.84 12.87 | Relapse free survival |
| 18 | GSE17537- | 0.56 0.08 3.8 | Relapse free survival |
| 187 | GSE14333 - | 5.48 2.23 13.51 | Relapse free survival |
| 37 | GSE31595 - | 0.15 0.01 1.88 | Relapse free survival |
| 44 | GSE38832 - | 0.87 0.44 1.72 | Relapse free survival |
| 269 | GSE39582 | 1.44 1.05 1.97 | Relapse free survival |

Pooled HR with 95% CI: 1.90 (0.93 - 3.88), P = 0.080

HIF-2 α : hypoxia-inducible factor-2 α ; HR: hazard ratio; 95% CI: 95% confidence interval; VEGF: vascular endothelial growth factor; CRC: colorectal cancer.

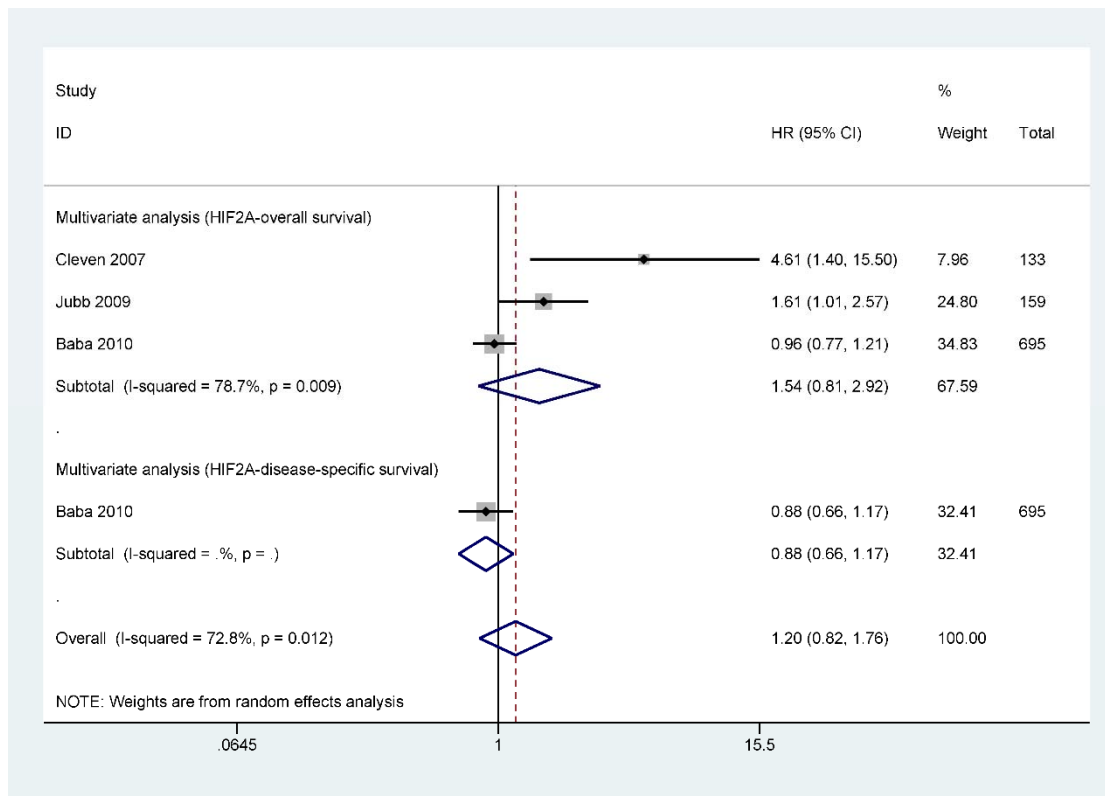


Figure S1. Forest plot of the association between HIF-2 α protein expression and the prognosis of CRC in overall survival (OS) and disease-specific survival (DSS) (publications)

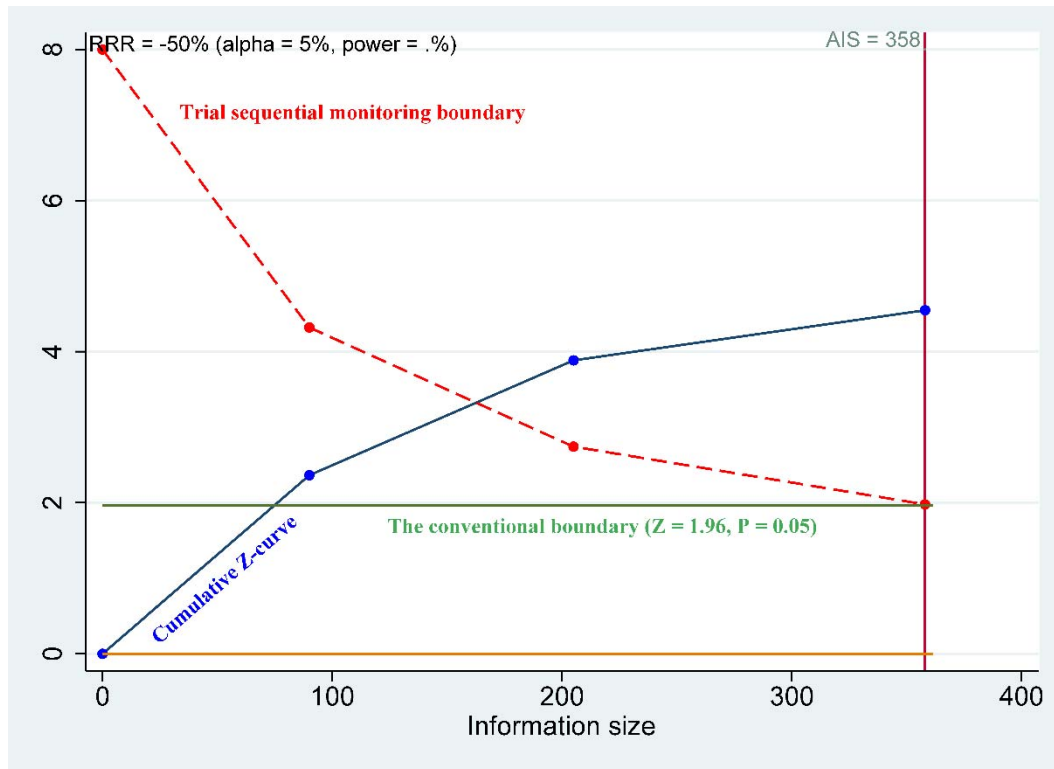


Figure S2. Trial sequential analysis assessing the association between HIF-2 α expression and CRC, CRC vs. normal tissue samples, the accrued information size (AIS) method, a relative risk reduction (RRR) of -50%, cumulative Z-curve crossed trial sequential monitoring boundary, indicating that the cumulative evidence is conclusive

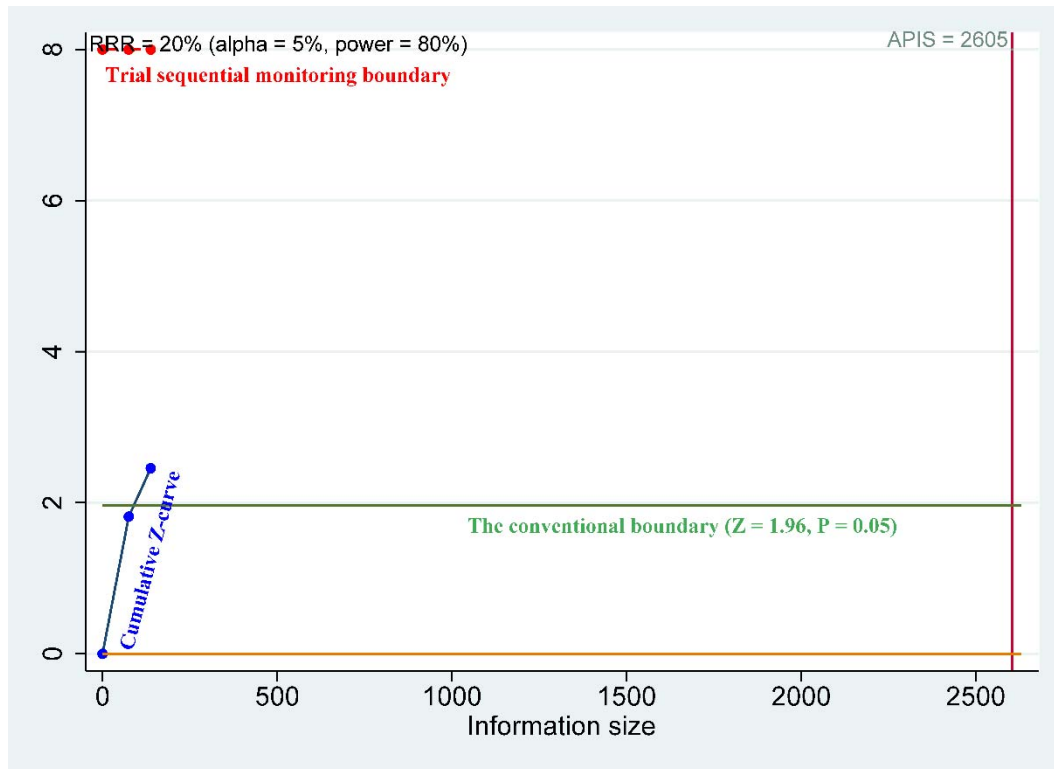


Figure S3. Trial sequential analysis assessing the association between HIF-2 α and VEGF expression, the optimal a priori anticipated information size (APIS) method (RRR = 20%, power = 80%), and the only cumulative Z-curve crossed the conventional boundary ($Z = 1.96$, $P = 0.05$), suggesting that the cumulative evidence is inconclusive

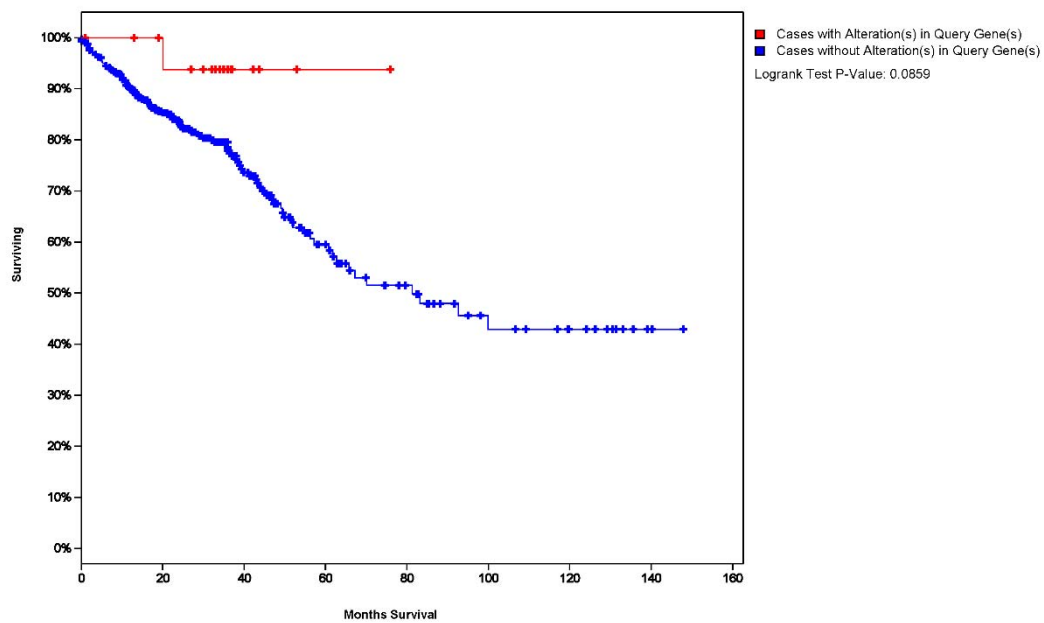


Figure S4. Prognostic role of HIF-2 α alteration in overall survival (OS) in CRC (cBioPortal database)

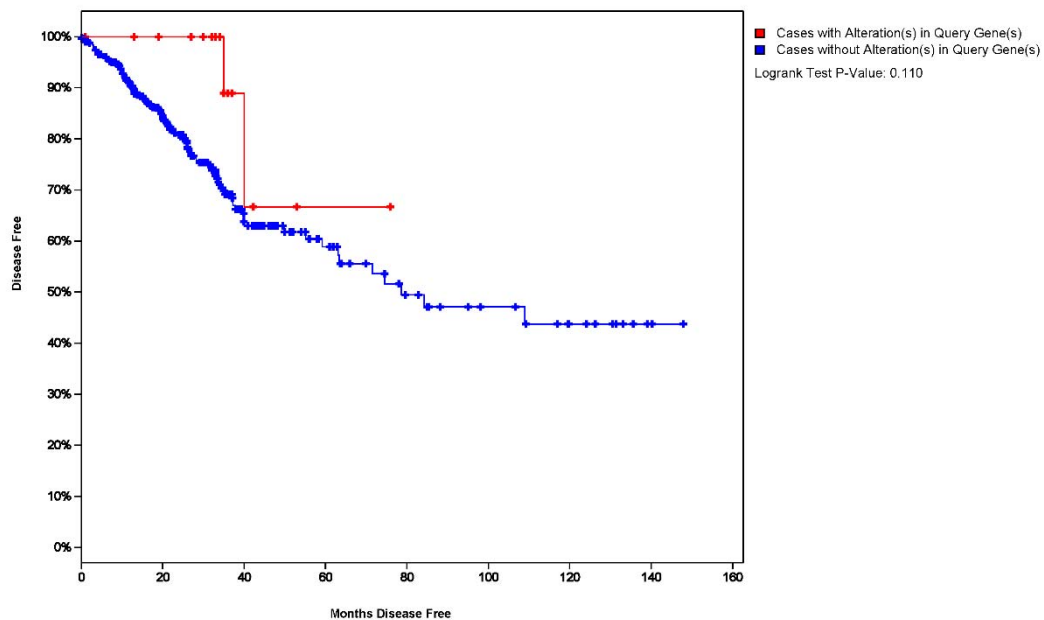


Figure S5. Prognostic role of HIF-2 α alteration in disease-free survival (DFS) in CRC (cBioPortal database)

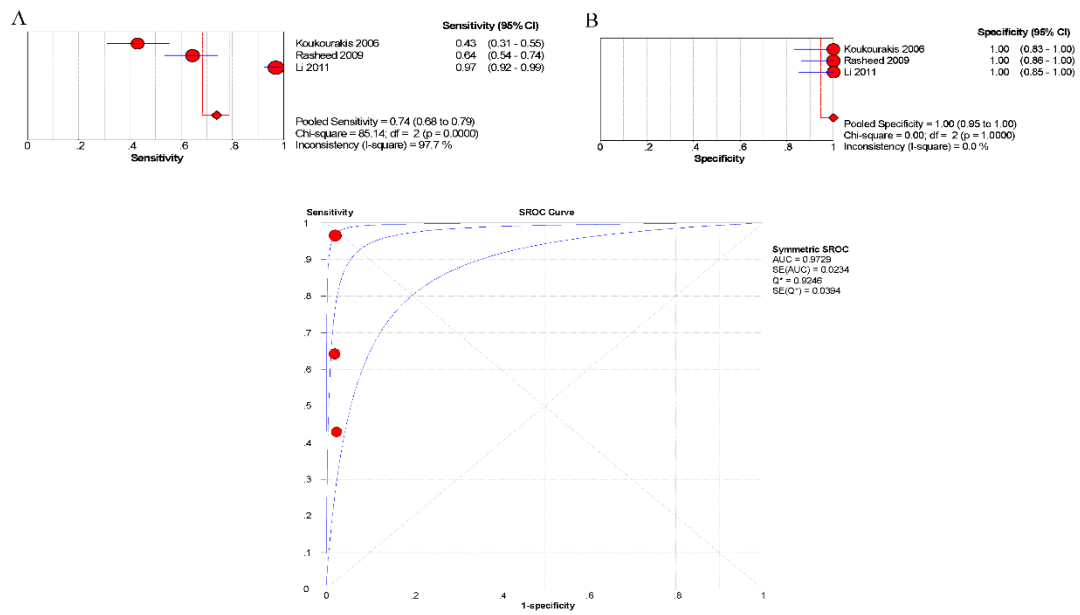


Figure S6. Summary receiver operating characteristics (SROC) estimation of HIF-2 α protein expression in patients with CRC vs. normal controls (publications)