EUROPEAN JOURNAL OF CANCER 43 (2007) 2559–2579

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Almost all articles on cancer prognostic markers report statistically significant results

Panayiotis A. Kyzas[a], *Despina Denaxa-Kyza*[a], *John P.A. Ioannidis*[a,b,c,*]

[a]*Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece*

[b]*Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, Greece*

[c]*Institute for Clinical Research and Health Policy Studies, Department of Medicine, Tufts-New England Medical Center, Boston, USA*

ARTICLE INFO

Article history:
Received 12 July 2007
Received in revised form 28 August 2007
Accepted 29 August 2007

Keywords:
Prognosis
Cancer
Bias
Reporting
Publication bias
Selective reporting bias
Statistical significance

ABSTRACT

We aimed to understand the extent of the pursuit for statistically significant results in the prognostic literature of cancer. We evaluated 340 articles included in prognostic marker meta-analyses (Database 1) and 1575 articles on cancer prognostic markers published in 2005 (Database 2). For each article, we examined whether the abstract reported any statistically significant prognostic effect for any marker and any outcome ('positive' articles). 'Negative' articles were further examined for statements made by the investigators to overcome the absence of prognostic statistical significance. We also examined how the articles of Database 1 had presented the relative risks that were included in the respective meta-analyses. 'Positive' prognostic articles comprised 90.6% and 95.8% in Databases 1 and 2, respectively. Most of the 'negative' prognostic articles claimed significance for other analyses, expanded on non-significant trends or offered apologies that were occasionally remote from the original study aims. Only five articles in Database 1 (1.5%) and 21 in Database 2 (1.3%) were fully 'negative' for all presented results in the abstract and without efforts to expand on non-significant trends or to defend the importance of the marker with other arguments. Of the statistically non-significant relative risks in the meta-analyses, 25% had been presented as statistically significant in the primary papers using different analyses compared with the respective meta-analysis. We conclude that almost all articles on cancer prognostic marker studies highlight some statistically significant results. Under strong reporting bias, statistical significance loses its discriminating ability for the importance of prognostic markers.

1. Introduction

Cancer prognosis has been a field of intensive research for many years. Besides traditional clinical markers, basic and translational research have generated hundreds of candidate markers for prediction of outcomes in cancer patients.[1,2] The expectation is that eventually some of these markers should also be clinically useful to change clinical practice.[3–6] However, progress in 'individualised' medicine based on prognostic information has been slow, in contrast to the vast amount of published data. Several methodological problems have been implicated for prognostic marker studies. They include poor study design and execution and poor and selective reporting of results.[1,7–10]

* *Corresponding author:* Address: Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina 45110, Greece. Tel.: +30 26510 97807; fax: +30 26510 97867.
E-mail address: jioannid@cc.uoi.gr (J.P.A. Ioannidis).

0959-8049/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2007.08.030

Selective reporting is a particular threat to the credibility of this literature. It includes both publication bias[11,12] and selective reporting of specific analyses and outcomes favouring results that pass the threshold of nominal statistical significance.[9] These biases have been well documented even for rigorous study designs, such as randomised trials.[13,14] Selective reporting has been difficult to probe for prognostic investigations. There is no study registration mechanism and study protocols are typically not available.[15] Therefore, here we aimed to probe into these biases using an indirect approach. We evaluated two large samples of articles on cancer prognostic markers and estimated how many of them claim nominally statistically significant findings. Publication and other selective reporting biases all cause an excess of statistically significant results in the literature.[16,17] With publication bias, studies with non-significant results would be left unpublished; thus, the published literature would be relatively enriched in statistically significant findings. With selective reporting of specific analyses or outcomes, the end result is the same: studies that should have been presented as 'negative' (non-statistically significant) based on their primary analyses get published with 'positive' (statistically significant) results based on data dredging and manipulated analyses.

2. Materials and methods

2.1. Search strategy and eligibility criteria for cancer prognostic marker studies

We used two large databases of published articles. The first (Database 1) comprised 340 articles on cancer prognostic markers with data that were included in meta-analyses of cancer prognostic markers published until 2005. The database has been built as part of a previous project.[10] In that project, we have identified 20 meta-analyses of prognostic markers for cancer by searching MEDLINE and EMBASE up to 2005. The primary studies included in these meta-analyses were used to create Database 1 in the current project.

The second database (Database 2) assembled articles on cancer prognostic markers published in 2005. We searched PubMed with the readily available high specificity prognosis search algorithm (Clinical Queries/Prognosis/narrow, specific search).[18] We combined the terms prognostic marker, prognostic factor, molecular marker AND malign* OR neoplasm* OR cancer OR haematological malignancy OR leukaemia AND survival, mortality, recurrence, prediction, outcome. We also added terms for commonly used molecular markers (Appendix).

For both databases, we accepted articles that had an abstract and that addressed with original data at least one potential prognostic marker, as defined by the recently published guidelines for transparent and complete reporting of cancer prognostic marker studies (REMARK consensus[19]), in any malignancy and for any outcome. When screening for Database 2, we have excluded letters, case reports, meta-analyses and reviews.

2.2. Data extraction

Two investigators extracted data from eligible articles independently, and then discussed to resolve controversies. A third investigator settled remaining discrepancies. For each article we examined whether the abstract reported at least one statistically significant prognostic effect for any marker and any eligible outcome, regardless of whether any non-statistically significant results were also reported or not.

Statistical significance could be conveyed either by a p-value < 0.05 or an effect metric with 95% confidence interval (CI) falling entirely on one side of the null; or only a statement by the authors that the prognostic effect was statistically significant. We recorded whether that statement contained the words 'statistical(ly)' and/or 'significant(ly)'. If only other words had been used (e.g. 'associated'/'related'/'correlated'/'larger'/'smaller'/'higher'/'lower'/'better'/'worse'), we screened the full text of the article to confirm the allusion of statistical significance. For articles where the statement contained the words 'statistical(ly)' and/or 'significant(ly)', we examined the full text for one-third of them (85/264) and found no occasion where the full text contradicted the statistical significance of the association presented in the abstract; therefore, we assume that practically all of these statements convey statistically significant results. Articles with claims of statistical significance (based on p-value, CI or confirmed language) are collectively termed 'positive' for convenience.

We further examined the articles that did not make any such clear statements on statistical significance for prognostic effects in their abstract ('negative' articles). Authors may use various ways of reporting their results, to make them more attractive to the editors, peer-reviewers and readers.[9,19] We considered the following possibilities based on what the abstract stated:

Claiming significance for other analyses: when authors presented formally statistically significant results for other analyses that do not reflect directly the assessment of prognostic effects (e.g. correlation analyses between baseline characteristics).

Expanding on non-significant trends: when authors discussed trends for any prognostic effect(s) for any outcome(s) without formal statistical significance. Lack of formal statistical significance could be visible in the abstract itself based on the presented p-value and/or CIs; alternatively no numbers were mentioned in the abstract, but the full text revealed the lack of formal statistical significance.

Apologies: when authors suggested other/larger/different studies might reveal the prognostic effect(s) or mentioned that the examined factor(s) are still important in other regards – still useful to pursue further.

We recorded the exact phrasing for each otherwise 'negative' article that used any of these three mechanisms above alone or in combination. All 'negative' articles were examined by all three investigators. Discrepancies were discussed for consensus.

Results from the two databases are presented separately and the proportions of 'positive' articles and other categories are compared by χ^2 tests. Since Database 1 was created from studies included in meta-analyses, one may wonder whether meta-analyses may be more likely to be performed for associations expected to be statistically significant; however, there is no documentation for such selection bias. Selection bias is also possible in the opposite direction: some meta-analyses may use very comprehensive search strategies to unearth and

include prognostic effect data that appear in fine print in articles where the main focus is different; this fine print information may be more likely to be 'negative'.[9,20–22] Conversely, Database 2 included studies regardless of whether there was interest for meta-analysis; Database 2 was also less likely to include articles where prognostic effect data appeared in fine print and the article was not readily recognised as a prognostic study. To address this issue, we checked in PubMed how many articles of Database 1 would be retrieved using the algorithm of Database 2, without restriction for year.

Furthermore, authors may present the more interesting (and significant) results in the abstract, but the full text may convey more complete, balanced information. Therefore, we also performed the following evaluation in the articles of Database 1. We examined for each of the relative risks included in the respective meta-analyses of prognostic marker studies, whether they were nominally statistically significant or not based on the 95% CI coverage. Then we examined how many of the statistically significant ones and how many of the non-significant ones were presented in the abstract, elsewhere in the full text, or nowhere in the primary articles. We also accommodated for the possibility that statistical significance status for the estimate might have been different in the original article than in the meta-analysis, because meta-analysis further standardise some data.

3. Results

3.1. *Eligible articles*

Database 1 included 340 articles and Database 2 incorporated 1575 articles.The articles had been published in 97 and 343 different journals, respectively (Appendix). With the exception of seven articles in Lancet, five in New England Journal of Medicine, four in JAMA and one in Nature Medicine, these were specialty journals. The 10 most common venues (along with the number of articles per database) were Clinical Cancer Research (24 + 127 = 151), Journal of Clinical Oncology (22 + 75 = 97), Cancer (27 + 62 = 89), British Journal of Cancer (23 + 35 = 58), Anticancer Research (8 + 46 = 53), International Journal of Cancer (17 + 34 = 51), Cancer Research (16 + 20 = 36), Gynecological Oncology (0 + 35 = 35), International Journal of Radiation Oncology Biology and Physics (4 + 31 = 35) and Human Pathology (10 + 22 = 32). The median journal impact factor was 4.1 and 2.7 for Databases 1 and 2, respectively.

3.2. *'Positive' prognostic articles*

'Positive' prognostic articles accounted for 90.6% and 95.8% in the two databases, respectively (Fig. 1). In the vast majority (83.6% and 90.4%, respectively), the prognostic association was indicated either with a *p*-value and/or CI, or by a statement containing the word 'statistical(ly)' and/or 'significant(ly)'. Only two articles (both in Database 2) implied a possible significant prognostic effect in the abstract (using *slightly better* or *worse* language[23,24]) without the effect being confirmed in the full text.

For Database 2, the journal impact factor was significantly higher in 'positive' than 'negative' prognostic articles (Mann–Whitney $p < 0.001$); the difference was not significant in Database 1 ($p = 0.17$). Overall, among journals with impact factor exceeding 4, the proportion of 'positive' prognostic articles was 92.9% (170/183) and 98.1% (565/576) in Databases 1 and 2, respectively. Across the 10 journals that were most common venues for the publication of these prognostic studies (as mentioned in the previous section), the rates of 'positive' articles varied from 81.3% (Hum Pathol) to 100% (Cancer Res, Int J Cancer) for the two databases combined, but these differences were not beyond chance.

The proportion of the 'positive' articles was higher in Database 2 than Database 1 ($p = 0.001$), whereas the proportion of 'positive' articles with a *p*-value and/or CI was similar ($p = 0.39$). A total of 274 (80.6%) articles from Database 1 would be retrieved by the search algorithm of Database 2. Among them, the proportion of 'positive' articles was 252/274 (91.9%). The search algorithm did not miss 'positive' articles far less than 'negative' ones ($p = 0.10$). The 66 non-retrieved articles were nevertheless all indexed in PubMed.

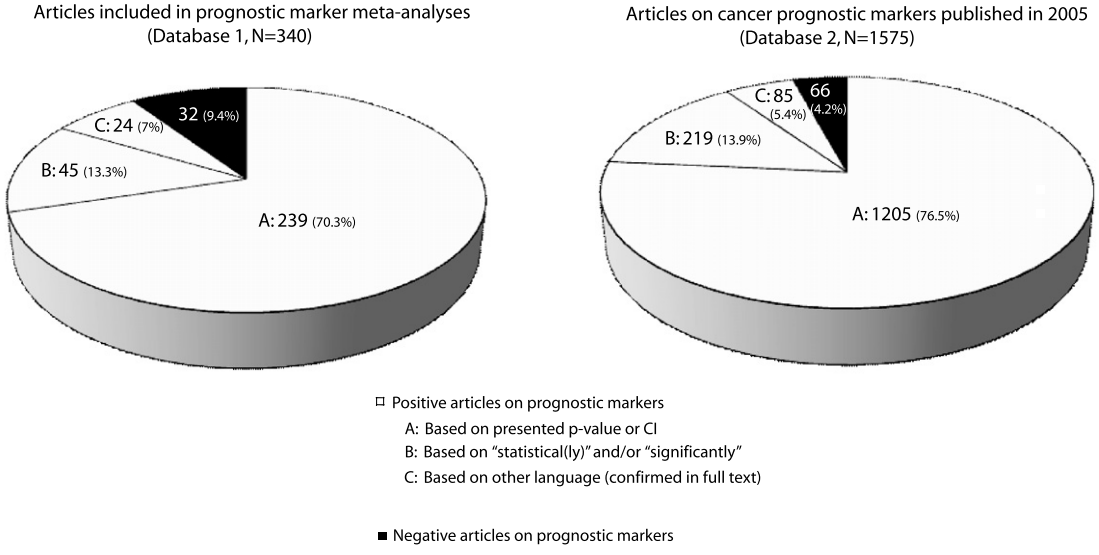

Fig. 1 – Distribution of 'positive' and 'negative' articles on prognostic markers of cancer.

3.3. 'Negative' prognostic articles

Of the 32 'negative' prognostic articles in Database 1, thirteen claimed significance for other analyses, 6 expanded on non-significant trends, and 18 offered some other apologies. Overall, one of the 3 mechanisms was used in 27 articles and 10 of them used more than one of the three mechanisms (Table 1). Of the 66 'negative' prognostic articles in Database 2, 23 claimed significance for other analyses, 14 expanded on non-significant trends, and 26 offered some other apologies. Overall, one of the three mechanisms was used in 45 articles and 16 of them used more than one of the three mechanisms (Table 1). Only one 'negative' article presented some statistically significant prognostic effects in the full text that were not shown in the abstract.[25]

Of the 19 articles that discussed non-significant trends in the two databases, 9 offered *p*-values, and 1 offered CI. Of the 14 *p*-values presented in these articles, 10 were between 0.05 and 0.10, two were between 0.10 and 0.20 and two were greater than 0.20.

Of the 43 articles that offered apologies, 20 suggested that larger and/or different studies should be conducted, e.g. *Further studies, on other uniform populations, with tumour features different from those described here, are necessary in order to reveal the prognostic significance of the molecules discussed*[26] or *The cohort examined was relatively small and with larger patient numbers, MDM2 over-expression may emerge as a more significant covariate.*[27] Twelve other articles suggested that the marker may have an important role in a different setting or stage, e.g. *The absence of statistically significant correlations between p53 gene mutations and progressive disease, however, does not exclude its putative relevance in early phases of tumour development.*[28] There was also a large variety of other considerations raised to defend the prognostic marker. Some articles offered quite stretched apologies, commenting on issues not examined in the study or totally irrelevant with its aims (e.g. *HIF-1 alpha does not appear to predict survival; however, this study suggests that bioreductive drugs should be investigated in clinical trials of MPM*[29]); or referred to previous successes of the team on some other, unrelated marker, e.g. an abstract concluded that *These results vary from our previous study on the expression of the differentiation marker cytokeratin 18, which showed that positive staining of tumour cells was associated with a statistically significant poorer prognosis at stage I regardless of histological types.*[30] Exact statements of all 'negative' articles appear in Appendix.

Eventually, there were only five articles in Database 1 and 21 in Database 2 that were fully 'negative' for all presented results in the abstract and without any effort being made to expand on non-significant trends or to offer any apologies. These represent 1.5% and 1.3% of the two databases, respectively.

3.4. Presentation in primary articles of the relative risks included in meta-analyses

Almost all (139/151, 92.1%) the statistically significant relative risks that were included in meta-analyses (Database 1) had appeared in the abstract of the primary studies and with few exceptions ($n = 6$) they were also shown to be 'positive'

Table 1 – Further analysis of claims in 'negative' prognostic studies

	Database 1, N (%)	Database 2, N (%)
Not admitted to be fully 'negative'	27 (7.9)	45 (2.8)
Significance for other (non-prognostic) analyses	6 (1.7)	11 (0.6)
Discussion of non-significant trends	2 (0.6)	5 (0.3)
Offered apologies	9 (2.8)	13 (0.8)
Significance for other analyses + discussion of non-significant trends	1 (0.3)	3 (0.2)
Significance for other analyses + offered apologies	6 (1.7)	7 (0.5)
Discussion of non-significant trends + offered apologies	3 (0.8)	4 (0.3)
All three mechanisms	–	2 (0.1)
Admitted to be fully 'negative'	5 (1.5)	21 (1.3)

Table 2 – Comparison of prognostic effect included in the meta-analysis with the effect presented by the primary studies (Database 1)

	Significant effects in meta-analysis N = 151 (39.7%)	Non-significant effects in meta-analysis N = 229 (60.3%)
Presented in abstract	139 (36.6)	167 (43.9%)
Significant in the abstract[a]	133 (35%)	49 (12.9%)
Non-significant in the abstract	6 (1.6%)	118 (31%)
Presented in full article (not abstract)	10 (2.6%)	48 (12.7%)
Significant in the full article[b]	7 (1.8%)	6 (1.6%)
Non-significant in the full article	3 (0.6%)	42 (11.1%)
Not presented even in full article	2 (0.5%)	14 (3.7%)

a Based on *p*-value, CI, or implied language confirmed in the full text.
b Based on *p*-value or CI.

in the abstract (Table 2). Conversely, only half (118/229, 51.5%) of the non-statistically significant relative risks that were included in the meta-analyses had been presented as 'negative' in the abstract; in fact, a sizeable proportion of the non-statistically significant risks had been presented as 'positive' in the primary studies (55/229, 24%), even in their abstracts (49/229, 21.4%), but the numbers entered in the meta-analysis showed them as 'negative'. This is because the primary studies had selectively highlighted analyses based on different follow-up, definitions of marker positivity, and/or adjustments (or lack thereof) for other variables compared to what the meta-analyses tried to standardise.

Overall, only 39.7% (151/380) of the relative risks that were included in meta-analyses were statistically significant. However, when we considered the full text of primary papers, 53.6% (195/364) were shown as positive and when we considered the abstracts 59.5% (182/306) were shown as 'positive' (Table 2). Sixteen relative risks that were used by the meta-analyses were not presented at the full primary articles and 14 of them were non-statistically significant.

4. Discussion

This survey shows that articles on cancer prognostic markers almost ubiquitously highlight significant prognostic associations. In the rare articles where no prognostic markers are presented as significant, authors often have other (non-prognostic) statistically significant analyses to show, they expand on the importance of non-significant trends, or defend the importance of the cancer marker with other arguments. Eventually, totally 'negative' articles on prognostic cancer markers represent less than 1.5% of this literature that is served by a wide variety of journals.

The selection for publication of 'positive' studies has been observed in other experimental designs as well, including randomised controlled trials,[13,14] and epidemiological studies.[31] For prognostic studies the situation may be even more extreme. Apparently, a publishable unit should include at least one piece of statistically significant information. Even the few 'negative' articles rarely ever conclude that the tested marker simply has no prognostic effect and is not important to pursue further. While new candidate markers emerge continuously, none seems to be abandoned based on what this literature says.

These empirical observations probably indicate a research culture that is driven by the pursuit of statistical significance. However, the meaning of significant p-values is probably widely misunderstood.[17,32] Currently, nominal significance at the $p = 0.05$ threshold should not necessarily offer high credibility to a proposed prognostic effect.[33] Given the rapid evolution of molecular medicine, an enormous number of potential prognostic markers can be tested promptly in the same, usually limited,[10,19] sample of patients. Taking into account all this extreme multiplicity of analyses is very difficult, if not impossible, as one would have to account not only for the analyses reported in a single paper, but also for unreported analyses, analyses performed on the same sample in other articles and on other samples on the same associations. At stark contrast to a literature that is replete with claims of statistical significance, only a tiny fraction of the initially proposed 'significant' prognostic markers have found a clinical application.[1,4,5,19]

Some caveats should be acknowledged. First, the Abstract is the face of an article and may be selectively highlighting the more interesting (and significant) results, but the full text may convey more complete, balanced information. We did not focus on counting the presence of all 'negative' results in the abstracts of these articles. Approximately, half of the non-statistically significant relative risks included in prognostic marker meta-analyses were not presented as 'negative' in the abstract of the primary articles. Thus, it would make no sense to try to count 'negative' results in these abstracts. Instead, we tried to see whether 'negative' prognostic effects from meta-analyses had appeared in the primary articles and if so, where and how. We found that a quarter of the non-statistically significant relative risks included in prognostic marker meta-analyses were actually presented as 'positive' in the primary studies. The opposite scenario was very rare. The reason is that for prognostic makers there is a wide variety of different exploratory analyses that can be performed, by shifting the definition of outcome, performing analyses at different durations of follow-up, playing with the cut-off definition of marker positivity, and adjusting or not for various combinations of other markers and covariates. Statistical significance may be claimed for some select mode of analysis and this may be reported and highlighted. Then the meta-analysis tries to standardise definitions and analyses. In the absence of selective reporting of analyses and outcomes, standardization should have caused the same number of 'positive' results to become 'negative' versus the opposite transition.

With this perspective, one might claim that definitive evaluation of the prognostic effects should await the conduct of proper meta-analyses. Unfortunately, meta-analyses are not exempt from these biases and they may even magnify them. Performing meta-analyses in an environment of strong selective reporting may simply lead to spurious precision of the summary estimates.[34] Most prognostic meta-analyses cannot achieve full standardization of the data.[9] Most past meta-analyses have not communicated with the primary investigators,[35] and even those that have, have not been able to retrieve standardised data for most studies.[9] Moreover, in our experience,[9] inclusion of a few sets of unpublished data can totally eliminate the statistical significance of prognostic effects based on the published literature. Selecting the studies based on their apparent quality of design and conduct is also not informative, since reporting of these articles[19] is suboptimal and reported quality does not seem to correlate with effect sizes.[10]

Articles that did not report or imply prognostic effects in the abstract were excluded from Database 2. These articles might have some prognostic associations hidden in the full text and this information might have been 'negative'. However, in an effort to retrieve the Database 1 articles using the Database 2 algorithm, we found no strong evidence for such a differential retrieval bias against 'negative' articles. Small bias would not affect the conclusion that most of this prognostic literature is 'positive'.

We should also acknowledge that one cannot tell what is the expected proportion of prognostic results that should be 'positive', if no bias exists in the conduct and reporting of these studies. It is conceivable that for many prognostic investigations, researchers pick their targets based on some prior evidence, and therefore, one would expect that the

proportion of nominally statistically significant findings should be much higher than the 5% expected by chance. However, the almost ubiquitous presence of 'positive' studies seems to be too excessive even under very optimistic assumptions about the ability of investigators to select important targets for prognostic studies.

The results of the current study may lead to some recommendations on how to improve this situation. The recently proposed REMARK consensus[19] is a step forward for the standardization of the reporting of cancer prognostic marker studies. The authors should avoid highlighting only the significant associations and they should try to present or at least alert readers to all of the examined associations and all the different definitions of outcomes, markers, and covariates that they did consider a priori versus post hoc. Additionally, journals should encourage the publication of well designed, executed and reported prognostic marker studies, regardless of the 'significant' or 'non-significant' findings. The development of collaborations and networks between investigators may be beneficial, if such networks focus also on minimising selective reporting and publication bias.[36,37] Transparency and public availability of protocols, data, analyses and results would also help.[36–38] Some fields, such as molecular profiling with microarrays, have made important progress in this regard.[39] In the meanwhile, readers should also be advised to interpret cautiously the postulated prognostic associations. While we limited our survey to cancer, the most prolific field of prognostic markers, similar considerations may apply also to prognostic markers in other fields across medicine. Given the potential clinical importance of prognostic information, rigorous efforts to improve the design and reporting of these studies are warranted. At a different level, the community of researchers is dependent also on funding groups. Funding groups should also realise that investigators should not be supported primarily for their ability to produce statistically significant results, but they should reward novel ideas, rigorous design, implementation and transparent reporting of results, regardless of their statistical significance. Perhaps there should be also disincentives for investigators and teams that report exclusively only statistically significant results in their careers.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding this submission.

Appendix

See Tables 3–6.

Table 3 – Statements made in the Abstract of 'negative' prognostic studies that (1) claim significance for other (non-prognostic) analyses, (2) discuss on non-significant trends, or (3) offer apologies for the non-statistical significance of the observed findings, (Database 1)

Author/Year/Journal	Statement	Type of statement
Bigner/1988/J Neuropathol Exp Neurol	Although the patients with amplified genes in their tumours survived slightly longer than patients whose tumours had no detectable gene amplification, these differences were not statistically significant ($p = 0.21$)... ...Although prominent perivascular lymphocytic infiltrates were more frequent in tumours without amplification, this association was of borderline significance statistically	2
Burak/2001/Eur J Nucl Med	We observed a positive correlation between WR% and Pgp status ($r = 0.61$, $p < 0.01$), and the wash-out rate of 99mTc-MIBI was significantly higher in patients with high Pgp expression than in those with a low Pgp score (33 ± 9% versus 17 ± 9%)	1
Caleffi/1994/Cancer	p53 mutations were found more often in tumours of younger women ($p = 0.002$), Afro-American women ($p = 0.05$), and in tumours lacking ER ($p = 0.03$), PR ($p = 0.04$), or both ($p = 0.06$)	1
Cheon/1993/Yonsei Med J	–	–
Costello/1995/Hum Pathol	This problem could be addressed in a prospective study involving more extensive tumour sampling	3
denTonkelaar/1995/Breast Cancer Res Treat	Results of the stratified analyses were suggestive of a modifying effect of these factors. The absence of an association between obesity and survival time might be explained by two counteracting mechanisms. On the one hand obesity might be related to impaired survival, due to a tumour growth promoting effect of extra-ovarian oestrogens. On the other hand obesity might be related to improved survival in a screened population, because obese patients profit more from screening by earlier detection of tumours than leaner counterparts	2, 3
Dunphy/1997/Arch Otolaryngol Head Neck Surg	–	–

Table 3 – *continued*

Author/Year/Journal	Statement	Type of statement
Frank/1994/Cancer	Patients whose tumours stained strongly for p53 were significantly younger, presented at a more advanced clinical disease stage, and tended to have increased expression of epidermal growth factor receptor ($p = 0.056$)	1, 2
Fridman/2000/Virchows Arch	–	–
Galanis/1998/Int J Oncol	Oncogene amplification events were significantly more frequent in grade 4 than in grade 3 astrocytomas, mixed gliomas or oligodendrogliomas ($p < 0.001$). With respect to EGFR, there was a significant difference in the frequency of amplification between primary and secondary gliomas ($p = 0.001$)... ...There was no apparent correlation between the occurrence of gene amplification and patient survival, possibly because the genes amplified in human gliomas are part of larger signalling pathways	1, 3
Geradts/1999/Clin Cancer Res	...with the exception that pRB/pl6 abnormalities were more common in older patients ($p = 0.0005$). pRB and p16 expression showed a strong inverse correlation ($p = 0.002$)... Abnormal expression of any of the three genes inversely correlated with K-ras codon 12 mutations ($p = 0.004$)...	1
Hirch/2002/Br J Cancer	No statistical difference in survival was observed comparing patients with positive (2+/3+) and negative tumours (0/1+), although 3+ patients showed a tendency to shorter survival... ... The therapeutic implications of protein expression and gene amplification in lung cancer need to be examined in prospective clinical trials	2, 3
Kazkayasi/2001/Eur Arch Otolaryngol	There was a statistically significant correlation between immunostaining of p53 and c-erbB-2 proteins ($p = 0.037$). While it was found that over-expression of p53 was significantly associated with the presence of lymph node metastasis ($p = 0.006$), there was no association between the expression of c-erbB-2 and lymph node status	1
Keohavong/1996/Clin Cancer Res	However, the substitution of the wild-type GGT (glycine) at codon 12 with a GTT (valine) or a CGT (arginine) showed a strong trend ($p = 0.07$) towards a poorer prognosis compared with wild-type or other amino acid substitutions. Substitution of the wild-type glycine for aspartate (GAT) showed a strong trend ($p = 0.06$) for a better outcome than the valine or arginine substitution. Although these trends will require larger patient populations for verification, these data suggest that the prognostic significance of K-ras mutations may depend on the amino acid substitution in the p21(ras) protein	2, 3
McLaren/1992/Br J Cancer	This indicates that although p53 may be of considerable importance in the initiation of malignancy it is probably of little significance once a tumour has developed	3
Molino/1999/Breast Cancer Res Treat	No significant association was found between bone marrow evolution and relapse or death, but the relatively high probability of a change in status over time cannot exclude the possibility that a positive aspirate during the course of breast cancer may be a negative prognostic factor	3
Nadal/1995/J Pathol	These findings indicate that p53 may play a role in an early stage of malignant transformation of a subset of squamous cell carcinomas of the larynx, but seems not to be associated with further progression of the tumours	3
O'Neill/1996/Histopathology	There was a significant linear correlation between apoptotic indices and mitotic indices. bcl-2 over-expression and p53 over-expression were not associated with attenuated apoptosis, or altered mitotic or Ki-67 labelling indices in either tumour type... It is likely that the effects on apoptosis of bcl-2 and p53 are countered by those of other oncogene products and/or additional factors that regulate apoptosis *in vivo*	1, 3
Pfeiffer/1998/Br J Cancer	Correlation between results obtained by the two different techniques was highly significant ($r(s) = 0.63$, $p < 0.001$, $n = 190$). This correlation improved even further ($r(s) = 0.76$) when sections were estimated using an IHC score that took into account percentage staining, intensity and relative tumour area...	1

(*continued on next page*)

Table 3 – *continued*

Author/Year/Journal	Statement	Type of statement
	...The expression of EGFR was highest in squamous cell carcinomas...	
Quantin/1997/Cancer Det Prev	–	–
Radig/1998/Hum Pathol	Therefore, we suggest that alterations in p53 gene are an early event in the tumourigenesis of malignant osteoblastic tumours without impact on progression of these tumours	3
Ravdin/1994/J Clin Oncol	...the levels of cathepsin D expression as measured by Western blotting and IHC correlated with each other and with levels of cathepsin D measured in previous work using Western blotting with the polyclonal antiserum...	1
Riethdorf/1998/Mund Kiefer Gesichtschir	The absence of statistically significant correlations between p53 gene mutations and progressive disease, however, does not exclude its putative relevance in early phases of tumour development	3
Rodenhuis/1997/J Clin Oncol	Patients with a ras mutation in their tumour were more likely to have a close relative with lung cancer... Patients with advanced lung adenocarcinoma who harbour a ras mutation may have major responses to chemotherapy and have similar progression-free and overall survival as patients with ras mutation-negative tumours. K-ras mutations may represent one of several ways in which early tumours are enabled to metastasise to distant sites	1, 3
Salven/1997/Mod Pathol	...in addition to being expressed by cancer cells VEGF is frequently expressed by tumour infiltrating inflammatory cells and by cells of histologically normal adjacent tissues; this suggests a possible role in tumour angiogenesis. Our results also suggest that angiogenic factors other than VEGF might provide the positive regulatory signals needed for tumour angiogenesis	3
Sommer/1997/Laryngo-Rhino-Otol	–	–
Stoll/1998/Virchows Arch	In this latter epithelium there was a significant correlation between grade of dysplasia and staining for p53 ($p < 0.01$). In the dysplastic epithelium a significant correlation between p53, waf1, and mdm2 was shown ($p < 0.05$)... It seems that p53 and associated factors are important in the early stages of cancerogenesis but not in further tumour progression and metastatic spread	1, 3
Taylor/1999/Hum Pathol	The overall correlation rate between IHC and sequencing was 59% ($p < .04$, χ^2)... Specific types of alterations (e.g. truncating mutations) and other factors may contribute to this poor correlation...	1, 3
Tagawa/1998/Cancer Lett	Frequent mutations were observed among younger patients (less than 65 years old)... We observed that Arg/Arg homozygotes were frequently found in non-smoking patients with NSCLC but Arg/Pro heterozygotes were infrequent in the group... Thus, the polymorphism of the p53 gene affects the predisposition of non-smokers to NSCLC, but the alteration of the p53 gene is independent of tumour progression and histopathology	3
Wang/1998/J Cancer Res Clin Oncol	All mutations occurred in male patients who were smokers... Patients with K-ras gene mutation survived for shorter periods than those without mutations ($p = 0.08$, by the log-rank test)...	2
Yokoyama/1998/Pathol Res Pract	MDM2 amplification and p53 mutation may reflect tumour progression, although no correlation between alteration and response to chemotherapy or patient survival was demonstrated	3
Oda/2000/Hum pathol	MIB-1 LI was significantly higher in the metastatic site than in the primary site (primary, 20.02; metastatic, 26.72; $p = .0209$)... nm23 expression was significantly increased in the metastatic site, compared with the primary site ($p = .0009$)... Among the overall tumours, c-MET-positive tumours showed significantly higher MIB-1 LI, compared with c-MET-negative tumours (negative, 20.99; positive, 27.65; $p = .0292$)... Positive correlation between c-MET expression and proliferative activity also suggests that c-MET expression may play an important role in tumour progression in osteosarcomas	1, 3

Table 4 – Statements made in the Abstract of 'negative' prognostic studies that (1) claim significance for other (non-prognostic) analyses, (2) discuss on non-significant trends, or (3) offer apologies for the non-statistical significance of the observed findings (Database 2)

Author/Year/Journal	Statement	Type of statement
Nakopoulou/2005/Pathobiology	Cytoplasmic expression of COX-2 was detected in 66.9% of breast carcinoma samples and was inversely correlated with both nuclear and histological grade ($p < 0.0001$ and $p = 0.039$, respectively), whereas its association with PR was found to be positive ($p = 0.016$). COX-2 expression was inversely correlated with topoIIalpha and p53 ($p = 0.033$ and $p = 0.002$, respectively), whereas its association with PPARgamma was parallel ($p < 0.0001$). In addition, c-erbB-2 of tumour cells was inversely correlated with COX-2 in stromal cells of the tumour ($p = 0.011$)... ...increased expression of COX-2 may be related to breast carcinomas with less aggressive phenotype. This suggestion is further supported by the positive correlation between COX-2 and PPARgamma...	1, 3
Lee/2005/J Surg Oncol	The presence of ITC was not related to clinicopathologic factors such as age, sex, location of tumour, tumour size, tumour depth, differentiation, lymphovascular invasion and the preoperative CEA level,except for the tumour gross type ($p = 0.002$)	1
Ozkara/2005/Int J Gynecol Cancer	–	–
Chang/2005/J Clin Neurosci	Relatively more severe peri-focal oedema on imaging was also noted in the glioblastomas with IL-6 expression. IL-6 was also found in the cytoplasm of endothelial cells of newly formed vessels and infiltrating inflammatory cells. These preliminary results implicate IL-6 expression as a possible prognostic indicator in glioblastoma	2, 3
Chang/2005/Leuk Lymphoma	CD56 negative myeloma was associated with bone lesions ($p = 0.032$...) Melphalan-based high-dose chemotherapy and ASCT may overcome the adverse influence of CD56 negative myeloma	1, 3
Watwe/2005/Am J Clin Oncol	Prognostic significance of this induction remains to be defined in a larger cohort	3
Jesus/2005/Acta Cir Braz	–	–
Siegelmann-Danieli/2005/Tumouri	Despite a trend of a younger age at diagnosis in P53-altered tumours, results did not reach statistically significant differences. A trend of a worse clinical outcome with P53 alteration was noted	2
Ikeguchi/2005/J Exp Clin Cancer Res	The mean AI of 29 tumours with normal expression levels of TGF-beta gene (4%) was significantly higher than that of 30 tumours with low expression levels of TGF-beta gene (2.5%, $p = 0.03$). Thirteen out of 30 tumours (43%) with low expression level of TGF-P gene showed surviving positive, while only 4 out of 29 tumours (14%) with preserved expression of TGF-beta gene showed survivin positive. This difference was significant ($p = 0.012$)	1
Saiz-Bustillo/2005/Med Oral Patol Oral Cir Bucal	–	–
Sheehan/2005/Hum Pathol	Nuclear Smad4 over-expression correlated with tumour grade ($p = .02$), stage ($p = .04$), and DNA ploidy ($p = .04$)... Cytoplasmic over-expression correlated with tumour grade ($P = .04$) and DNA ploidy ($p = .04$) while showing a trend for correlation with tumour stage ($p = .08$)... Smad4 protein expression persists in PACs compared with benign glands, with both nuclear and cytoplasmic over-expression correlating with prognostic variables indicative of aggressive tumour behaviour. Given the significant reported variability of Smad4 in several different cancers, further studies in prostate and other tumours are warranted to elucidate its role in tumourigenesis	1, 2, 3
Kindler/2005/J Clin Oncol	–	–
Odegaard/2005/Gynecol Oncol	AP-2gamma was detected in the nucleus of tumour cells in 28/75 (37%) borderline tumours, 13/22 (59%) FIGO stage I carcinomas, and 255/306 (83%) advanced-stage carcinomas ($p < 0.001$, χ^2 test)... ...The lack of predictive value for this transcription factor in advanced-stage disease may be related to its frequent expression	1, 3

(continued on next page)

Table 4 – *continued*

Author/Year/Journal	Statement	Type of statement
Nyman/2006/Lung Cancer	–	–
Haberler/2006/J Neurooncol	The value of anti-tyrosine kinase immunolabelling as predictive factor for patient selection remains to be clarified by comparative analysis of tumour tissue of therapy-responders versus non-responders	3
Lustosa/2005/Acta Cir Braz	–	–
Klabatsa/2005/Lung Cancer	HIF-1 alpha does not appear to predict survival; however, this study suggests that bioreductive drugs should be investigated in clinical trials of MPM	3
Yumac/2005/Pathol Res Pract	–	–
Wang/2005/Anticancer Res	–	–
Suzuki/2005/Tokai J Exp Clin Med	PTHrP receptor correlated MIB-1 index alone ($p < 0.044$). *Conclusions*: This findings suggest PTHrP receptor is related to the tumour proliferation of breast cancer	1
Camps/2005/Lung Cancer	There was a tendency towards a higher response rate for patients with K-ras mutations versus wild-type K-ras in serum, however not statistically significant ($p = 0.37$)	2
Hasengaowa/2005/Eur J Gynaecol Oncol	The HS-GAG expression index was significantly lower in cases of advanced stage, high-grade, deep myometrial invasion, positive peritoneal cytology, lymph vascular space invasion and lymph node metastasis	1
Sturm/2005/BMC Cancer	–	–
Filiberti/2005/Tumour Biol	Survival was evaluated in 82 PM patients. At the end of the follow-up (median 9.8 months) 80.5% of patients had died. Median survival was 13.1 and 7.9 months for patients with PDGF-AB lower and higher than the cut-off, respectively. Adjusting for age, sex, histology and platelet count, positive PDGF-AB levels were associated with lower survival (OR = 1.2, 95% CI: 0.9–1.6), even if not significantly so. In conclusion, serum PDGF may represent a useful additional parameter to prognostic factors already available for PM	2
Zafirellis/2005/Anticancer Res	p53 expression was observed in 34 patients (65.4%) and was significantly correlated with the intestinal type of cancer ($p = 0.018$). Bcl-2 expression was detected in 12 patients (23.1%) and inversely correlated with lymph node metastasis ($p = 0.042$) and tumour grade ($p = 0.024$). There was a statistically significant inverse relationship between p53 and bcl-2 expression ($p = 0.014$)	1
Blonski/2005/Anticancer Res	More strikingly, however, aviscumine binds to malignant cells in 92.5% of the patients. This is an indicator for the use of aviscumine as a possible target for tumour therapy	3
Kato/2005/Anticancer Res	Serum p53-Ab levels in either vein did not correlate with prognosis in the univariate survival analysis, although the levels in the two veins were significantly correlated	1
Akslen/2005/J Invest Dermatol	...although BRAF and NRAS mutations are likely to be important for the initiation and maintenance of some melanomas	3
Ek/2005/Acta Pediatr	IFNgamma, and possibly also TNFalpha, were related to anaemia in children with solid tumours	1, 2
Jones/2005/Hum Pathol	–	–
Swiatoniowski/2005/ Anticancer Res	Further studies, on other uniform populations, with tumour features different from those described here, are necessary in order to reveal the prognostic significance of the molecules discussed	3

Table 4 – *continued*

Author/Year/Journal	Statement	Type of statement
Hernandez/2005/Clin Cancer Res	–	–
Hermsen/2005/Cell Oncol	The only aberration that correlated to one of the clinico-pathological parameters was amplification 11q13, that occurred solely in lymph node positive, stage IV tumours	1
Hantschmann/2005/ Anticancer Res	Twenty-nine percent showed high microvessel densitiy. These tumours were more likely to have vascular space involvement ($p = 0.02$). In carcinomas with TGF-alpha expression in >50% of the tumour cells, microvessel density was increased ($p = 0.05$). Overall and disease-free survival tended to be reduced for tumours with high TGF-alpha expression and microvessel density, but differences were not significant	1, 2
Kantarjian/2005/Leuk Lymphoma	We conclude that the previously established poor prognostic significance of marrow fibrosis in CML is less relevant with imatinib therapy	3
Olson/2005/Leuk Lymphoma	A small number of patients expressed functional Pgp (1%, 3/295) and some overexpressed functional MRP1 (10%, 19/295), with a statistically significant number of the latter being of T-lineage as opposed to pre-B ($p < 0.001$)	1
Wild/2005/Int J Oncol	Positive COX2 staining was seen in 77.8% (140/182) of muscle invasive urothelial BC, compared to 35% (7/20) of muscle invasive squamous cell carcinomas ($p < 0.001$). COX2 protein expression was associated with advanced tumour stage ($p < 0.0001$), high-grade histology ($p < 0.0001$), solid growth pattern in invasive BC (pT1-4, $p = 0.02$), high Ki-67 labelling index ($p < 0.0001$), and positive P53 IHC ($p < 0.001$). COX2 expression was not associated with survival, recurrence, and progression in clinically relevant subgroups (pTa, pT1, pT2-4). Expression of COX2 is common in advanced BC with poor prognostic characteristics, supporting efforts to initiate clinical trials on the efficacy of COX2 inhibitors in the adjuvant treatment of high-risk urinary BC	1, 3
Khor/2005/Cancer	In the manual count analysis, there was no significant relation between MDM2 over-expression and outcome. The ACIS index, using a cut-off point defined by the median value, < or =3% versus >3%, was related to 5-year DM rates in univariate analyses (32.6% versus 45.8%; $p = 0.057$) and MVA ($p = 0.06$). The intensity of MDM2 staining was not significant. *Conclusions*: MDM2 expression quantified by image analysis was weakly associated with DM. The cohort examined was relatively small and with larger patient numbers, MDM2 over-expression may emerge as a more significant covariate	2, 3
Skolarikos/2005/Int J Urol	Bcl-2 protein expression was higher in RCC compared to normal renal tissue ($p < 0.0001$). Aneuploid tumours had higher bcl-2 expression compared to diploid tumours ($p = 0.015$)... Tumour stage was the only statistically important prognostic factor ($p = 0.0045$)	1
Boyapati/2005/Breast Cancer Res Treat	–	–
Tas/2005/Med Oncol	Further studies are necessary to determine the potential prognostic importance of this observation	3
Berdjis/2005/BJU Int	The mean (range) Ki-67 LI was 40.5(6.4–93.0)%; a high mean Ki-67 LI was significantly inversely correlated with tumour differentiation ($p < 0.005$) and there was a tendency for a high Ki-67 LI to be associated with advanced local tumour stage, nodal metastasis and clinical disease progression, but these correlations were not statistically significant ($p = 0.07$, 0.07 and 0.06, respectively)	1, 2
Iwata/2005/Lung Cancer	–	–
Watanabe/2005/J Urol	In upper urinary tract tumours the prevalence of S-p53Abs significantly correlated with higher grade ($p < 0.01$), higher stage ($p = 0.02$), positive lymph nodes ($p = 0.03$) and p53 nuclear accumulation ($p < 0.01$)...	1, 3

(*continued on next page*)

Table 4 – *continued*

Author/Year/Journal	Statement	Type of statement
	. . .Our data suggest the possibility of the clinical application of S-p53Abs, especially for the detection of high grade or high stage tumours in the upper urinary tract	
Antunes/2004/Acta Med Port	–	–
de Jong/2005/Clin Cancer Res	TP53 mutations were detected in 36% of the metastases and occurred more frequently in liver metastases from left-sided colon tumours than from right-sided colon tumours ($p = 0.04$). In metastases with TP53 mutations, microvessel density was higher compared with tumours with wild-type p53	1
Roessler/2005/World J Gastroenterol	CDX2 correlated with a lower pT and pN stage in the subgroups of intestinal and stage I cancers and was associated with MUC2 positivity. A prognostic impact of CDX2 or MUC2 was not observed. . . . . .*Conclusion*: CDX2 and MUC2 play an important role in the differentiation of normal, inflamed, and neoplastic gastric tissues. According to our results, loss of CDX2 may represent a marker of tumour progression in early gastric cancer and carcinomas with an intestinal phenotype	1, 3
Nakaya/2005/Br J Cancer	–	–
Chakravarti/2005/Int J Radiat Oncol Biol Phys	. . .the RTOG is conducting additional investigations into the prognostic value of activation patterns of EGFR signalling, both at the level of the receptor (e.g. EGFRvIII, phospho-EGFR) and at the level of downstream signal transduction pathways (e.g. PI3K, Ras/MAPK pathways)	3
Schindlbeck/2005/J Cancer Res Clin Oncol	Patients with HER2 (IHC, $p = 0.29$) and TOP IIa (FISH, $p = 0.16$) positive tumours tended to stay or become negative in BM status after abCTX and vice versa. After a median follow-up of 44 months (6–127), none of the factors reached significance for overall survival. Yet, patients with HER2 ($p = 0.16$) and TOP IIa ($p = 0.09$) positive tumours showed a trend towards prolonged disease-free survival. Remarkably, none of the TOP IIa FISH-positive patients developed distant metastases ($p = 0.099$) or died ($p = 0.19$) after CTX so far. *Conclusions*: HER2- and TOP IIa positivity seem to improve the effect of abCTX. The combination of the prognostic value of ITC-BM and the predictive capacity of HER2 and TOP IIa could help to stratify patients for certain therapies. The direct examination of those factors on ITC-BM is the focus of ongoing studies	2, 3
Talvensaari-Mattila/2005/Tumour Biol	There was a significant correlation between VEGF and both its receptors. Furthermore, this receptor expression was correlated between the two types of receptors	1
Esteva/2005/Clin Cancer Res	However, a high concordance between RT-PCR and immunohistochemical assays for oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 status was noted. . . . . . However, further work needs to be done to develop an assay to identify the likelihood of recurrent disease in patients with node-negative breast cancer who do not receive adjuvant tamoxifen or chemotherapy	1, 3
Ribas/2005/Cancer Lett	Additional studies are needed to clarify the correspondence between the epigenetic alteration of the p16 gene and its protein immunexpression, and the clinical relevance of p16 methylation in MM patients	3
Benitah/2005/Radiology	–	–
Sagol/2005/Pancreas	–	–
Carlinfante/2005/Pathol Res Pract	We found no relation to the histologic types, clinical staging and survival; however, the low proliferation rate could explain the natural course of tumour	3

Table 4 – *continued*

Author/Year/Journal	Statement	Type of statement
Goh/2005/Med J Malaysia	Long-term follow-up may give a better evaluation on the prognostic value of P53 over-expression in colorectal carcinoma	3
Polin/2005/J Neurosurg	–	–
Li/2005/Dis Markers	–	–
Wu/2005/Appl Immunohistochem Mol Morphol	–	–
Abraham/2005/Clin Cancer Res	Our findings suggest that the prevalence of CD44(+)/CD24(-/low) tumour cells in breast cancer may not be associated with clinical outcome and survival but may favor distant metastasis	2
Stein/2005/Am J Clin Oncol	Further prospective, randomised studies are required to fully elucidate the benefits of adjuvant radiotherapy	3
Cohen/1998/Rom J Morphol Embryol	At stages III–IV, we found a trend, which, however, was not statistically significant, between positive immunostains of p53 and p21 proteins and longer survival... ...*Conclusions*: These results vary from our previous study on the expression of the differentiation marker cytokeratin 18, which showed that positive staining of tumour cells was associated with a statistically significant poorer prognosis at stage I regardless of histological types	2, 3
Lee/2005/BMC Cancer	...perineural invasion was more common in surviving positive and venous invasion was more common in survivin negative ($p = 0.041$ and 0.040, respectively)... Responsiveness to chemotherapy appeared to be slightly better in patients with low survivin expression...seems to have a potential as a predictive marker for chemotherapy. Further study of large scale is required to determine the clinical significance of survivin expression in pancreatic cancer	1, 2, 3
Wong/2005/Appl Immunohistochem Mol Morphol	...those 2 patients had a much shorter survival of 6 months than the remaining 15 patients, who had around 24 months... the involvement of it may indicate a worse prognosis with shorter survival	2
Eichholzer/2005/Swiss Med Wkly	- -	–

Table 5 – Distribution of the articles in journals (alphabetical list; the impact factor was derived from ISI-Thompson Scientific, Journal Citation Reports, 2005 – Database 1)

Journal	Articles	Impact factor	Journal	Articles	Impact factor
Acta Neurochir (Wien)	1	1.1	Br J Cancer	23	4.1
Acta Otolaryngol	1	0.8	Breast Cancer Res Treat	10	4.6
Acta Pathol Jpn	1	–	Bull Cancer	1	–
Am J Clin Oncol	1	1.6	Cancer	27	4.8
Am J Clin Pathol	1	2.9	Cancer Causes Control	1	3.2
Am J Pathol	1	5.8	Cancer Detect Prev	1	1.6
Am J Respir Crit Care Med	2	8.7	Cancer Epidemiol Biomarkers Prev	1	4.5
Am J Surg Pathol	1	4.4	Cancer Genet Cytogenet	1	3
Am Rev Respir Dis	1	–	Cancer Lett	5	3
Anal Quant Cytol Histol	1	0.6	Cancer Res	16	7.6
Anatomic Pathol	1	–	Chest	3	4
Ann Histochem	1	–	Clin Cancer Res	24	5.7
Ann Surg	1	6.3	Clin Orthop Relat Res	1	1.5
Ann Surg Oncol	1	3.5	Clin Otolar Allied Sciences	1	1
Ann Thorac Surg	4	2.2	Cytometry	3	2.1
Anticancer Res	8	1.6	Eur Arch Otorhinolaryngol	1	0.9
APMIS	1	2.1	Eur J Cancer	11	3.7
Arch Otolaryngol Head Neck Surg	1	1.6	Eur J Nucl Med	1	3.9
Auris Nasus Larynx	1	–	Eur J Surg Oncol	2	3.2

(*continued on next page*)

Table 5 – *continued*

Journal	Articles	Impact factor	Journal	Articles	Impact factor
Fukuoka Igaku Zasshi	1	–	Lancet	5	23.9
Gen Diagn Pathol	2	–	Laryngorhinootologie	2	0.6
Head Neck	2	1.9	Laryngoscope	3	1.6
Histopathology	1	2.6	Lung Cancer	6	3.2
Hum Pathol	10	2.6	Mod Pathol	6	3.4
Int J Cancer	17	4.7	Mol Med	1	3.4
Int J Clin Oncol	1	–	Mund Kiefer Gesichtschir	1	–
Int J Mol Med	1	2.1	N Engl J Med	4	44
Int J Oncol	5	2.7	Nat Med	1	28.9
Int J Radiat Oncol Biol Phys	4	4.5	Neoplasma	2	0.7
Int Orthop	2	0.7	Nippon Hinyokika Gakkai Zasshi	4	–
J Cancer Res Clin Oncol	1	2.5	Nippon Kyobu Geka Gakkai Zasshi	1	–
J Chemother	1	1.9	Oncogene	5	6.9
J Clin Invest	1	15	Oncol Rep	2	1.6
J Clin Oncol	22	11.8	Oral Oncol	4	2.3
J Clin Pathol	3	2.1	Otolaryngol Head Neck Surg	1	1.2
J Jpn Assn Thorac Surg	1	–	Pathol Int	1	0.9
J Korean Med Sci	1	0.6	Pathol Oncol Res	1	1.2
J Natl Cancer Inst	7	15.1	Pathol Res Pract	4	1.1
J Neurol	1	2.8	Pathology	1	1.5
J Neuropathol Exp Neurol	1	4.4	Prev Med	1	2.2
J Neurosurg	1	2.5	Proc Natl Acad Sci U S A	1	10.2
J Oral Pathol Med	1	1.7	Radiother Oncol	2	3.3
J Pathol	4	6.2	Respir Med	1	1.7
J Pediatr Hematol Oncol	1	1.3	Surg Oncol	1	2.1
J Surg Oncol	5	1.8	Thorax	1	6.2
J Thorac Cardiovasc Surg	7	3.7	Virchows Arch	4	2.2
JAMA	1	23.5	World J Surg	1	1.6
Jpn J Cancer Chemother	1	–	Yonsei Med J	1	0.6
Jpn J Cancer Res	3	–			

Table 6 – Distribution of the articles in journals (alphabetical list; the impact factor was derived from ISI-Thompson Scientific, Journal Citation Reports, 2005 – Database 2)

Journal	Articles	Impact factor	Journal	Articles	Impact factor
Acta Chir Belg	2	0.3	Am J Surg	3	1.9
Acta Cir Bras	2	–	Am J Surg Pathol	7	4.4
Acta Haematol	1	1.3	Am Surg	2	1.3
Acta Med Port	1	–	An Med Interna	1	–
Acta Neuropathol (Berl)	1	2.5	An Otorrinolaringol Ibero Am	4	–
Acta Oncol	4	2.4	Anal Quant Cytol Histol	2	0.6
Acta Orthop Scand Suppl	1	–	Ann Hematol	2	2.2
Acta Otolaryngol	1	0.8	Ann Neurol	3	7.6
Acta Otorhinolaryngol Ital	1	–	Ann Oncol	21	4.3
Acta Paediatr	1	1.3	Ann Otol Rhinol Laryngol	1	1
Actas Urol Esp	3	–	Ann Plast Surg	1	0.9
Ai Zheng	5	–	Ann Saudi Med	1	–
AJNR Am J Neuroradiol	1	2.5	Ann Surg	9	6.3
AJR Am J Roentgenol	2	2.2	Ann Surg Oncol	10	3.5
Aliment Pharmacol Ther	2	3.4	Ann Thorac Surg	3	2.2
Am J Clin Oncol	3	1.6	Anticancer Res	46	1.6
Am J Clin Pathol	6	2.9	ANZ J Surg	1	0.8
Am J Dermatopathol	1	1.4	APMIS	1	2.1
Am J Epidemiol	4	5.1	Appl Immunohistochem Mol Morphol	3	1.4
Am J Gastroenterol	2	5.1			
Am J Hematol	2	1.6	Arch Dermatol	2	3.4
Am J Obstet Gynecol	3	3.1	Arch Esp Urol	1	–
Am J Otolaryngol	3	0.6	Arch Pathol Lab Med	2	1.6

Table 6 – *continued*

Journal	Articles	Impact factor	Journal	Articles	Impact factor
Arch Surg	2	3.1	Ethn Dis	1	1.6
Arkh Patol	1	–	Eur J Cancer	19	3.7
Australas Radiol	1	–	Eur J Cardiothorac Surg	4	1.8
Biochem Biophys Res Commun	3	3	Eur J Epidemiol	4	1.3
Biol Blood Marrow Transplant	1	3.6	Eur J Gynaecol Oncol	4	0.6
Biomed Res	1	–	Eur J Haematol	10	2
BJU Int	9	2.5	Eur J Histochem	1	1
Blood	24	10.1	Eur J Nucl Med Mol Imaging	2	3.9
BMC Cancer	8	2	Eur J Surg Oncol	6	3.2
Bone Marrow Transplant	1	2.6	Eur Respir J	2	3.9
Bosn J Basic Med Sci	1	–	Eur Surg Res	1	0.8
Br J Cancer	35	4.1	Eur Urol	12	3.5
Br J Dermatol	1	3	Exp Oncol	2	0.8
Br J Haematol	12	4.1	FEBS Lett	1	3.4
Br J Ophthalmol	1	2.5	Folia Histochem Cytobiol	2	0.8
Br J Surg	4	3.7	Gastric Cancer	4	–
Brain Tumor Pathol	1	–	Gastroenterology	2	2.2
Breast	2	1.7	Gend Med	1	–
Breast Cancer Res	13	4	Georgian Med News	2	–
Breast Cancer Res Treat	10	4.6	Graefes Arch Clin Exp Ophthalmol	1	–
Breast J	1	–	Gut	8	7.7
Bull Cancer	2	–	Gynecol Oncol	35	2.5
Cancer	62	4.8	Haematologica	2	4.5
Cancer Biol Ther	2	3	Hamostaseologie	1	–
Cancer Causes Control	4	3.2	Head Neck	4	1.9
Cancer Chemother Pharmacol	2	2.3	Hematology	3	–
Cancer Detect Prev	2	1.6	Hepatobiliary Pancreat Dis Int	1	–
Cancer Epidemiol Biomarkers Prev	9	4.5	Hepatogastroenterology	10	0.7
Cancer Genet Cytogenet	2	3	Hepatology	1	9.8
Cancer Immunol Immunother	1	4.1	Histol Histopathol	3	2.1
Cancer Invest	2	1.9	Histopathology	10	2.6
Cancer J	2	2.5	Hum Pathol	22	2.6
Cancer Lett	16	3	In Vivo	4	1.1
Cancer Res	20	7.6	Indian J Cancer	1	–
Cancer Sci	6	3.8	Indian J Med Res	1	0.9
Carcinogenesis	1	5.1	Indian J Pathol Microbiol	1	–
Cell Cycle	3	–	Int Braz J Urol	1	–
Cell Oncol	2	4.2	Int J Biochem Cell Biol	1	3.8
Cell Prolif	1	4.5	Int J Biol Markers	8	1.1
Chang Gung Med J	1	–	Int J Cancer	34	4.7
Chest	4	4	Int J Clin Pract	1	1.1
Childs Nerv Syst	1	0.9	Int J Colorectal Dis	1	1.8
Chin Med J (Engl)	1	0.5	Int J Gynaecol Obstet	1	1.1
Clin Biochem	1	2.4	Int J Gynecol Cancer	13	1.4
Clin Breast Cancer	3	–	Int J Gynecol Pathol	1	1.8
Clin Cancer Res	127	5.7	Int J Hematol	1	1.7
Clin Endocrinol (Oxf)	2	3.4	Int J Immunopathol Pharmacol	2	3.4
Clin Exp Metastasis	4	2.8	Int J Mol Med	1	2.1
Clin Lab Haematol	1	0.8	Int J Oncol	14	2.7
Clin Neuropathol	1	0.9	Int J Oral Maxillofac Surg	3	1.1
Clin Oncol (R Coll Radiol)	3	1.3	Int J Radiat Oncol Biol Phys	31	4.5
Clin Orthop Relat Res	2	1.5	Int J Urol	6	0.6
Clin Transl Oncol	2	–	Int Urol Nephrol	4	–
Clinics	1	–	Intern Med	4	0.6
Colorectal Dis	1	–	Invest Ophthalmol Vis Sci	3	3.6
Croat Med J	4	0.8	J Am Coll Surg	5	2.6
Cytokine	1	2	J Cancer Res Clin Oncol	13	2.5
Dig Dis Sci	1	1.4	J Cell Mol Med	1	3.6
Dig Liver Dis	2	1.8	J Cell Physiol	2	4.4
Dis Colon Rectum	5	2.3	J Chemother	1	1.9
Dis Esophagus	1	0.9	J Clin Endocrinol Metab	4	6
Dis Markers	1	2.6	J Clin Gastroenterol	2	2.3
Endocr Pathol	2	1.1	J Clin Invest	1	15
Endocr Relat Cancer	2	4.9	J Clin Neuroscience	1	0.7

(*continued on next page*)

Table 6 – *continued*

Journal	Articles	Impact factor	Journal	Articles	Impact factor
J Clin Oncol	75	11.8	Med Oncol	5	1
J Clin Pathol	9	2.1	Med Oral Patol Oral Cir Bucal	2	–
J Craniomaxillofac Surg	3	0.8			
J Cutan Pathol	1	1.3	Med Pregl	1	–
J Dermatol	1	0.5	Med Sci Monit	2	–
J Endocrinol Invest	1	1.5	Med Wieku Rozwoj	3	–
J Exp Clin Cancer Res	6	0.7	Melanoma Res	5	1.5
J Formos Med Assoc	1	0.5	Mod Pathol	20	3.4
J Gastroenterol	1	1.5	Mol Cancer Ther	1	5.2
J Gastrointest Surg	2	2.3	Mol Carcinog	1	2.4
J Hepatol	1	4.9	Mol Cell Proteomics	1	9.9
J Histochem Cytochem	1	2.2	Mol Diagn	1	–
J Huazhong Univ Sci Technolog Med Sci	2	–	N Engl J Med	1	44
			Neoplasia	2	3.9
J Int Med Res	2	0.7	Neoplasma	11	0.7
J Intern Med	1	4	Nephron Clin Pract	1	1.4
J Invest Dermatol	1	4.4	Neuro Endocrinol Lett	1	1
J Korean Med Sci	1	0.6	Neuroendocrinology	1	2.6
J Mol Diagn	1	2.9	Neurol Med Chir (Tokyo)	1	0.4
J Mol Med	1	4.7	Neurology	1	5.1
J Natl Cancer Inst	5	15.1	Neuro-oncol	1	4.2
J Natl Cancer Inst Monogr	1	–	Neuropathol Appl Neurobiol	1	3.3
J Neurol	2	2.8	Neuropathology	1	1.2
J Neurooncol	8	2.3	Neuropediatrics	1	1.4
J Neurosurg	3	2.5	Neurosurgery	2	2.6
J Neurosurg Spine	1	1.2	Nippon Hinyokika Gakkai Zasshi	1	–
J Nippon Med Sch	2	–			
J Nucl Med	1	4.7	Nippon Igaku Hoshasen Gakkai Zasshi	1	–
J Obstet Gynaecol Res	1	0.7			
J Oral Maxillofac Surg	1	1.3	Oncogene	6	6.9
J Oral Pathol Med	3	1.7	Oncol Rep	26	1.6
J Otolaryngol	1	0.5	Oncol Res	3	1.9
J Pathol	10	6.2	Oncology	14	2
J Pediatr Endocrinol Metab	1	0.8	Onkologie	6	1.2
J Soc Gynecol Investig	1	2.9	Oral Oncol	12	2.3
J Steroid Biochem Mol Biol	1	2.9	Orthopedics	1	0.5
J Surg Oncol	11	1.8	Otolaryngol Head Neck Surg	2	1.2
J Surg Res	2	2	Otolaryngol Pol	3	–
J Thorac Cardiovasc Surg	6	3.7	Pancreas	3	2.3
J Urol	16	3.6	Pancreatology	1	1.6
JAMA	3	23.5	Pathobiology	1	1.5
Jpn J Clin Oncol	8	1.3	Pathol Int	1	0.9
Jpn J Thorac Cardiovasc Surg	1	–	Pathol Oncol Res	2	1.2
Klin Lab Diagn	1	–	Pathol Res Pract	4	1.1
Korean J Gastroenterol	2	–	Pathologica	1	–
Korean J Hepatol	1	–	Pathology	3	1.5
Korean J Intern Med	1	–	Pediatr Blood Cancer	3	1.5
Lancet	2	23.9	Pediatr Dev Pathol	1	1
Lancet Oncol	1	9.6	Pediatr Hematol Oncol	1	0.5
Laryngoscope	3	1.6	Pediatr Neurosurg	1	1.1
Leuk Lymphoma	10	1.3	Pharmacogenet Genomics	1	–
Leuk Res	5	2.4	Pol Arch Med Wewn	2	–
Leukemia	8	6.6	Pol J Pathol	1	–
Lijec Vjesn	1	–	Proc Natl Acad Sci USA	1	10.2
Lin Chuang Er Bi Yan Hou Ke Za Zhi	3	–	Prostaglandins Leukot Essent Fatty Acids	2	1.8
Liver Int	1	1.8	Prostate	5	3.6
Liver Transpl	1	4.5	Prostate Cancer Prostatic Dis	1	1.1
Lung	2	0.9	Proteomics	1	6.1
Lung Cancer	21	3.2	Przegl Epidemiol	2	–
Magy Seb	1	–	Quintessence Int	1	0.5
Med Arh	1	–	Radiology	1	5.4
Med Clin (Barc)	2	1.1	Radiother Oncol	4	3.3
Med J Malaysia	1	–	Ren Fail	2	0.5

Table 6 – *continued*

Journal	Articles	Impact factor	Journal	Articles	Impact factor
Respiration	1	1.3	Thyroid	1	2.2
Respirology	1	1.3	Tokai J Exp Clin Med	1	–
Rev Esp Enferm Dig	1	0.5	Transplant Proc	1	0.8
Rev Mal Respir	1	0.6	Transplantation	1	3.9
Rev Med Chil	1	0.4	Tuberk Toraks	1	–
Rev Med Panama	1	–	Tumori	6	0.8
Rinsho Byori	1	–	Tumour Biol	11	1.2
Rocz Akad Med Bialymst	2	–	Urol Oncol	2	1.1
Rom J Morphol Embryol	1	–	Urology	13	2.1
Sao Paulo Med J	1	–	Virchows Arch	8	2.2
Saudi Med J	2	0.3	Virus Res	1	2.6
Scand J Gastroenterol	2	1.8	Vopr Onkol	7	–
Scand J Urol Nephrol	2	0.7	Wien Klin Wochenschr	1	0.6
ScientificWorldJournal	1	–	World J Gastroenterol	31	–
Sichuan Da Xue	1	–	World J Surg	9	1.6
Xue Bao Yi Xue Ban			World J Urol	1	2.3
Singapore Med J	2	–	Yonsei Med J	4	0.6
Soc Sci Med	1	–	Zentralbl Chir	1	–
Strahlenther Onkol	2	3.5	Zentralbl Gynakol	1	–
Support Care Cancer	1	1.6	Zhong Nan Da Xue	1	–
Surg Endosc	3	1.8	Xue Bao Yi Xue Ban		
Surgery	4	2.6	Zhong Xi Yi Jie He Xue Bao	1	–
Swiss Med Wkly	1	–	Zhonghua Nei Ke Za Zhi	2	–
Ter Arkh	1	0.2	Zhonghua Yi Xue Za Zhi	4	–
Thorac Cardiovasc Surg	1	0.9	Zhonghua Zhong Liu Za Zhi	4	–

Specific search algorithm

(Tumour marker OR prognostic marker OR prong* marker OR molecular marker OR tumour protein OR prognostic factor OR prong* factor OR p53 OR VEGF OR MVD OR K-ras OR c-myc OR Cathepsin OR PgP OR cox OR HIF OR bcl-2 OR EGFR OR ki-67 OR c-erbB-2 OR BMI OR BMM OR DNA ploidy) AND (malign* OR neoplasm* OR cancer OR haematological malignancy OR leukaemia OR tumour) NOT (review OR meta-analysis).

REFERENCES

1. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;**323**:224–8.
2. Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology. *Br J Cancer* 1994;**69**:979–85.
3. Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst* 1996;**88**: 1456–66.
4. Schilsky RL, Taube SE. Tumor markers as clinical cancer tests–are we there yet? *Semin Oncol* 2002;**29**:211–2.
5. Bast RC, Ravdin P, Hayes DF, et al. update of recommendations for the use of tumor markers in breast and colorectal cancer:clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;**19**:1865–78.
6. Ioannidis JP. Is molecular profiling ready for use in clinical decision making? *Oncologist* 2007;**12**:301–11.
7. Altman DG, Lyman GH. Methodological challenges in the evaluation of prognostic factors in breast cancer. *Breast Cancer Res Treat* 1998;**52**:289–303.
8. Burton A, Altman DG. Missing covariate data within cancer prognostic studies:a review of current reporting and proposed guidelines. *Br J Cancer* 2004;**91**:4–8.
9. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. *J Natl Cancer Inst* 2005;**97**:1043–55.
10. Kyzas PA, Denaxa-Kyza D, Ioannidis JP. Quality of reporting of cancer prognostic marker studies:association with reported prognostic effect. *J Natl Cancer Inst* 2007;**99**:236–43.
11. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* 1992;**267**:374–8.
12. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. *Lancet* 1991;**337**:867–72.
13. Chan AW, Hrobjartsson A, Haahr MT, et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**:2457–65.
14. Chan AW, Krleza-Jeric K, Schmid I, et al. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004;**171**:735–40.
15. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet* 2004;**364**:911–2.
16. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007;**4**:245–53.
17. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005;**2**:e124.
18. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;**2**:23.
19. McShane LM, Altman DG, Sauerbrei W, et al. Reporting recommendations for tumor marker prognostic studies (REMARK). *Eur J Cancer* 2005;**41**:1690–6.
20. Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical

expression in head and neck squamous cell carcinoma: a meta-analysis. *Clin Cancer Res* 2005;**11**:1434–40.
21. Pakos EE, Kyzas PA, Ioannidis JP. Prognostic significance of TP53 tumor suppressor gene expression and mutations in human osteosarcoma:a meta-analysis. *Clin Cancer Res* 2004;**10**:6208–14.
22. Pakos EE, Ioannidis JP. The association of P-glycoprotein with response to chemotherapy and clinical outcome in patients with osteosarcoma. A meta-analysis. *Cancer* 2003;**98**:581–9.
23. Lee MA, Park GS, Lee HJ, et al. Survivin expression and its clinical significance in pancreatic cancer. *BMC Cancer* 2005;**5**:127.
24. Wong SC, Chan AT, Lo ES, et al. Nuclear beta-catenin expression is rare and its potential association with short survival in colorectal signet-ring cell carcinoma. *Appl Immunohistochem Mol Morphol* 2005;**13**:248–51.
25. Galanis E, Buckner J, Kimmel D, et al. Gene amplification as a prognostic factor in primary and secondary high-grade malignant gliomas. *Int J Oncol* 1998;**13**:717–24.
26. Swiatoniowski G, Matkowski R, Suder E, et al. E-cadherin and fibronectin expressions have no prognostic role in stage II ductal breast cancer. *Anticancer Res* 2005;**25**:2879–83.
27. Khor LY, Desilvio M, Al-Saleem T, et al. MDM2 as a predictor of prostate carcinoma outcome: an analysis of Radiation Therapy Oncology Group Protocol 8610. *Cancer* 2005;**104**:962–7.
28. Riethdorf S, Friedrich RE, Suhwold J, et al. p53 mutations and HPV infections in squamous epithelial carcinomas of the head–neck region. Long-term follow-up. *Mund Kiefer Gesichtschir* 1998;**2**:30–4 [in German].
29. Klabatsa A, Sheaff MT, Steele JP, et al. Expression and prognostic significance of hypoxia-inducible factor 1alpha (HIF-1alpha) in malignant pleural mesothelioma (MPM). *Lung Cancer* 2006;**51**:53–9.
30. Cohen R, Guber A, Koren R, et al. Prognostic significance of p53 and ras p21 protein expression in surgically treated non-small cell lung carcinoma. *Rom J Morphol Embryol* 1998;**44**:117–23.
31. Kavvoura FK, Liberopoulos G, Ioannidis JP. Selection in reported epidemiological risks: an empirical assessment. *PLoS Med* 2007;**4**:e79.
32. Goodman SN. Toward evidence-based medical statistics. 1: The *P* value fallacy. *Ann Intern Med* 1999;**130**:995–1004.
33. Wacholder S, Chanock S, Garcia-Closas M, et al. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004;**96**:434–42.
34. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;**316**:140–4.
35. Devereaux PJ, Choi PT, El-Dika S, et al. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. *J Clin Epidemiol* 2004;**57**:1232–6.
36. Ioannidis JP, Gwinn M, Little J, et al. A road map for efficient and reliable human genome epidemiology. *Nat Genet* 2006;**38**:3–5.
37. Bogardus Jr ST, Concato J, Feinstein AR. Clinical epidemiological quality in molecular genetic research:the need for methodological standards. *JAMA* 1999;**281**:1919–26.
38. Ioannidis JP. Molecular evidence-based medicine. *Eur J Clin Invest* 2007;**37**:340–9.
39. Brazma A, Hingamp P, Quackenbush J, et al. Minimum information about a microarray experiment (MIAME)-toward standards for microarray data. *Nat Genet* 2001;**29**:365–71.

REFERENCES OF THE 'NEGATIVE' ARTICLES LISTED IN TABLES 3 AND 4

1. Bigner SH, Burger PC, Wong AJ, Werner MH, Hamilton SR, Muhlbaier LH, et al. Gene amplification in malignant human gliomas:clinical and histopathologic aspects. J Neuropathol Exp Neurol 1988;47: 191–205.
2. Burak Z, Ersoy O, Moretti JL, Erinc R, Ozcan Z, Dirlik A, et al. The role of 99mTc-MIBI scintigraphy in the assessment of MDR1 over-expression in patients with musculoskeletal sarcomas:comparison with therapy response. Eur J Nucl Med 2001;28:1341–50.
3. Caleffi M, Teague MW, Jensen RA, Vnencak-Jones CL, Dupont WD, Parl FF. p53 gene mutations and steroid receptor status in breast cancer. Clinicopathologic correlations and prognostic assessment. Cancer 1994;73:2147–56.
4. Cheon SH, Sohn HY, Chang J, Kim SK, Ko EH, Kim SK, et al. Flow cytometric analysis of DNA ploidy in primary non-small cell carcinoma of the lung in Korea. Yonsei Med J 1993;34:365–70.
5. Costello P, McCann A, Carney DN, Dervan PA. Prognostic significance of microvessel density in lymph node negative breast carcinoma. Hum Pathol 1995;26:1181–4.
6. den Tonkelaar I, de Waard F, Seidell JC, Fracheboud J. Obesity and subcutaneous fat patterning in relation to survival of postmenopausal breast cancer patients participating in the DOM-project. Breast Cancer Res Treat 1995;34:129–37.
7. Dunphy CH, Dunphy FR, Boyd JH, Varvares MA, Kim HJ, Lowe V, et al. Expression of p53 protein in advanced head and neck squamous cell carcinoma before and after chemotherapy. Arch Otolaryngol Head Neck Surg 1997;123: 1223–5.
8. Frank JL, Bur ME, Garb JL, Kay S, Ware JL, Sismanis A, et al. p53 tumor suppressor oncogene expression in squamous cell carcinoma of the hypopharynx. Cancer 1994;73:181–6.
9. Fridman V, Humblet C, Bonjean K, Boniver J. Assessment of tumor angiogenesis in invasive breast carcinomas:absence of correlation with prognosis and pathological factors. Virchows Arch 2000;437:611–7.
10. Galanis E, Buckner J, Kimmel D, Jenkins R, Alderete B, O'Fallon J, et al. Gene amplification as a prognostic factor in primary and secondary high-grade malignant gliomas. Int J Oncol 1998;13:717–24.
11. Geradts J, Fong KM, Zimmerman PV, Maynard R, Minna JD. Correlation of abnormal RB, p16ink4a, and p53 expression with 3p loss of heterozygosity, other genetic abnormalities, and clinical features in 103 primary non-small cell lung cancers. Clin Cancer Res 1999;5:791–800.
12. Hirsch FR, Varella-Garcia M, Franklin WA, Veve R, Chen L, Helfrich B, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer 2002;86:1449–56.
13. Kazkayasi M, Hucumenoglu S, Siriner GI, Hucumenoglu M. Overexpression of p53 and c-erbB-2 oncoproteins in laryngeal carcinoma. Eur Arch Otorhinolaryngol 2001;258:329–35.

14. Keohavong P, DeMichele MA, Melacrinos AC, Landreneau RJ, Weyant RJ, Siegfried JM. Detection of K-ras mutations in lung carcinomas:relationship to prognosis. Clin Cancer Res 1996;2:411–8.
15. McLaren R, Kuzu I, Dunnill M, Harris A, Lane D, Gatter KC. The relationship of p53 immunostaining to survival in carcinoma of the lung. Br J Cancer 1992;66:735–8.
16. Molino A, Pelosi G, Micciolo R, Turazza M, Nortilli R, Pavanel F, et al. Bone marrow micrometastases in breast cancer patients. Breast Cancer Res Treat 1999;58:123–30.
17. Nadal A, Campo E, Pinto J, Mallofre C, Palacin A, Arias C, et al. p53 expression in normal, dysplastic, and neoplastic laryngeal epithelium. Absence of a correlation with prognostic factors. J Pathol 1995;175:181–8.
18. O'Neill AJ, Staunton MJ, Gaffney EF. Apoptosis occurs independently of bcl-2 and p53 over-expression in non-small cell lung carcinoma. Histopathology 1996;29: 45–50.
19. Pfeiffer P, Nexo E, Bentzen SM, Clausen PP, Andersen K, Rose C. Enzyme-linked immunosorbent assay of epidermal growth factor receptor in lung cancer:comparisons with immunohistochemistry, clinicopathological features and prognosis. Br J Cancer 1998;78:96–9.
20. Quantin X, Pujol JL, Lehmann M, Simony J, Serre I, Michel FB. Immunohistochemical detection of p53 protein and prognosis of surgically resected non-small-cell lung cancer. Cancer Detect Prev 1997;21:418–25.
21. Radig K, Schneider-Stock R, Haeckel C, Neumann W, Roessner A. p53 gene mutations in osteosarcomas of low-grade malignancy. Hum Pathol 1998;29:1310–6.
22. Ravdin PM, Tandon AK, Allred DC, Clark GM, Fuqua SA, Hilsenbeck SH, et al. Cathepsin D by western blotting and immunohistochemistry:failure to confirm correlations with prognosis in node-negative breast cancer. J Clin Oncol 1994;12:467–74.
23. Riethdorf S, Friedrich RE, Suhwold J, Ostwald C, Barten M, Gogacz P, et al. [p53 mutations and HPV infections in squamous epithelial carcinomas of the head–neck region. Long-term follow-up] Mund Kiefer Gesichtschir 1998;2:30–4. German.
24. Rodenhuis S, Boerrigter L, Top B, Slebos RJ, Mooi WJ, van't Veer L, et al. Mutational activation of the K-ras oncogene and the effect of chemotherapy in advanced adenocarcinoma of the lung:a prospective study. J Clin Oncol 1997;15:285–91.
25. Salven P, Heikkila P, Anttonen A, Kajanti M, Joensuu H. Vascular endothelial growth factor in squamous cell head and neck carcinoma:expression and prognostic significance. Mod Pathol 1997;10:1128–33.
26. Sommer T, Olofsson J. [Significance of p53, PCNA and Ki-67 in the prognosis of squamous cell carcinoma of the oral cavity] Laryngorhinootologie 1997;76:189–96. German.
27. Stoll C, Baretton G, Lohrs U. The influence of p53 and associated factors on the outcome of patients with oral squamous cell carcinoma. Virchows Arch 1998;433:427–33.
28. Taylor D, Koch WM, Zahurak M, Shah K, Sidransky D, Westra WH. Immunohistochemical detection of p53 protein accumulation in head and neck cancer:correlation with p53 gene alterations. Hum Pathol 1999;30:1221–5.
29. Tagawa M, Murata M, Kimura H. Prognostic value of mutations and a germ line polymorphism of the p53 gene in non-small cell lung carcinoma:association with clinicopathological features. Cancer Lett 1998;128:93–9.
30. Wang YC, Lee HS, Chen SK, Yang SC, Chen CY. Analysis of K-ras gene mutations in lung carcinomas:correlation with gender, histological subtypes, and clinical outcome. J Cancer Res Clin Oncol 1998;124:517–22.
31. Yokoyama R, Schneider-Stock R, Radig K, Wex T, Roessner A. Clinicopathologic implications of MDM2, p53 and K-ras gene alterations in osteosarcomas:MDM2 amplification and p53 mutations found in progressive tumors. Pathol Res Pract 1998;194:615–21.
32. Oda Y, Naka T, Takeshita M, Iwamoto Y, Tsuneyoshi M. Comparison of histological changes and changes in nm23 and c-MET expression between primary and metastatic sites in osteosarcoma:a clinicopathologic and immunohistochemical study. Hum Pathol 2000;31:709–16.
33. Nakopoulou L, Mylona E, Papadaki I, Kapranou A, Giannopoulou I, Markaki S, et al. Overexpression of cyclooxygenase-2 is associated with a favorable prognostic phenotype in breast carcinoma. Pathobiology 2005;72: 241–9.
34. Lee MR, Hong CW, Yoon SN, Lim SB, Park KJ, Lee MJ, et al. Isolated tumor cells in lymph nodes are not a prognostic marker for patients with stage I and stage II colorectal cancer. J Surg Oncol 2006;93:13-8;discussion 18–9.
35. Ozkara SK, Corakci A. FHIT expression in neoplastic, hyperplastic, and normal endometrium. Int J Gynecol Cancer 2005;15:1081–8.
36. Chang CY, Li MC, Liao SL, Huang YL, Shen CC, Pan HC. Prognostic and clinical implication of IL-6 expression in glioblastoma multiforme. J Clin Neurosci 2005;12:930–3.
37. Chang H, Samiee S, Yi QL. Prognostic relevance of CD56 expression in multiple myeloma:a study including107 cases treated with high-dose melphalan-based chemotherapy and autologous stem cell transplant. Leuk Lymphoma 2006;47:43–7.
38. Watwe V, Javle M, Lawrence D, Groth J, Iyer R, El-Hajjar D, et al. Cyclooxygenase-2 (COX-2) levels before and after chemotherapy:a study in rectal cancer. Am J Clin Oncol 2005;28:560–4.
39. Jesus EC, Matos D, Artigiani R, Waitzberg AF, Goldenberg A, Saad SS. Assessment of staging, prognosis and mortality of colorectal cancer by tumor markers:receptor erbB-2 and cadherins. Acta Cir Bras 2005;20:422–7 [Epub 2005 Nov 8].
40. Siegelmann-Danieli N, Ben-Izhack O, Hanlon A, Ridge JA, Stein ME, Khandelwal V, et al. P53 alteration in oral tongue cancer is not significantly associated with age at diagnosis or tobacco exposure. Tumori 2005;91:346–50.
41. Ikeguchi M, Iwamoto A, Taniguchi K, Katano K, Hirooka Y. The gene expression level of transforming growth factor-beta (TGF-beta) as a biological prognostic marker of hepatocellular carcinoma. J Exp Clin Cancer Res 2005;24:415–21.
42. Saiz-Bustillo R, Corchero-Martin G, Garcia-Montesinos-Perea B, Gonzalez-Teran T, Sanchez-Santolino S. Oral squamous cell carcinoma. Cytometric parameters of prognostic interest. Med Oral Patol Oral Cir Bucal 2005;10: 462–7.

43. Sheehan GM, Kallakury BV, Sheehan CE, Fisher HA, Kaufman RP Jr, Ross JS. Smad4 protein expression correlates with grade, stage, and DNA ploidy in prostatic adenocarcinomas. Hum Pathol 2005;36: 1204–9.
44. Kindler HL, Friberg G, Singh DA, Locker G, Nattam S, Kozloff M, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2005;23:8033–40.
45. Odegaard E, Staff AC, Kaern J, Florenes VA, Kopolovic J, Trope CG, et al. The AP-2gamma transcription factor is upregulated in advanced-stage ovarian carcinoma. Gynecol Oncol 2006;100:462–8.
46. Nyman J, Johansson KA, Hulten U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer – mature results for medically inoperable patients. Lung Cancer 2006;51:97–103.
47. Haberler C, Gelpi E, Marosi C, Rossler K, Birner P, Budka H, et al. Immunohistochemical analysis of platelet-derived growth factor receptor-alpha, -beta, c-kit, c-abl, and arg proteins in glioblastoma:possible implications for patient selection for imatinib mesylate therapy. J Neurooncol 2006;76:105–9.
48. Lustosa SA, Logullo A, Artigiani R, Saad SS, Goldenberg A, Matos D. Analysis of the correlation between p53 and bcl-2 expression with staging and prognosis of the colorectal adenocarcinoma. Acta Cir Bras 2005;20: 353–7.
49. Klabatsa A, Sheaff MT, Steele JP, Evans MT, Rudd RM, Fennell DA. Expression and prognostic significance of hypoxia-inducible factor 1alpha (HIF-1alpha) in malignant pleural mesothelioma (MPM). Lung Cancer 2006;51:53–9.
50. Yamac D, Celenkoglu G, Coskun U, Akyurek N, Akcali Z, Dursun A, et al. Prognostic importance of COX-2 expression in patients with colorectal cancer. Pathol Res Pract 2005;201:497–502.
51. Wang X, Jones TD, Maclennan GT, Yang XJ, Lopez-Beltran A, Eble JN, et al. P53 expression in small cell carcinoma of the urinary bladder:biological and prognostic implications. Anticancer Res 2005;25:2001–4.
52. Suzuki Y, Tokuda Y, Saito Y, Umemura S, Osamura RY. Clinicopathological correlation between expression of PTHrP receptor and various prognostic factors in breast cancer without axillary lymph node metastasis. Tokai J Exp Clin Med 2005;30:127–32.
53. Camps C, Sirera R, Bremnes R, Blasco A, Sancho E, Bayo P, et al. Is there a prognostic role of K-ras point mutations in the serum of patients with advanced non-small cell lung cancer? Lung Cancer 2005;50:339–46.
54. Hasengaowa, Kodama J, Kusumoto T, Shinyo Y, Seki N, Nakamura K, et al. Loss of basement membrane heparan sulfate expression is associated with tumor progression in endometrial cancer. Eur J Gynaecol Oncol 2005;26:403–6.
55. Sturm I, Bosanquet AG, Hummel M, Dorken B, Daniel PT. In B-CLL, the codon 72 polymorphic variants of p53 are not related to drug resistance and disease prognosis. BMC Cancer 2005;5:105.
56. Filiberti R, Marroni P, Neri M, Ardizzoni A, Betta PG, Cafferata MA, et al. Serum PDGF-AB in pleural mesothelioma. Tumour Biol 2005;26:221–6.
57. Zafirellis K, Karameris A, Milingos N, Androulakis G. Molecular markers in gastric cancer:can p53 and bcl-2 protein expressions be used as prognostic factors? Anticancer Res 2005;25:3629–36.
58. Blonski K, Schumacher U, Burkholder I, Edler L, Nikbakht H, Boeters I, et al. Binding of recombinant mistletoe lectin (aviscumine) to resected human adenocarcinoma of the lung. Anticancer Res 2005;25: 3303–7.
59. Kato H, Nakajima M, Fukuchi M, Miyazaki T, Manda R, Kimura H, et al. Serum p53 antibodies in drainage blood from the azygos vein in patients with esophageal carcinoma. Anticancer Res 2005;25:3231–5.
60. Akslen LA, Angelini S, Straume O, Bachmann IM, Molven A, Hemminki K, et al. BRAF and NRAS mutations are frequent in nodular melanoma but are not associated with tumor cell proliferation or patient survival. J Invest Dermatol 2005;125:312–7.
61. Ek T, Mellander L, Abrahamsson J. Interferon gamma and tumour necrosis factor alpha in relation to anaemia and prognosis in childhood cancer. Acta Paediatr 2005;94: 435–7.
62. Jones TD, Kernek KM, Yang XJ, Lopez-Beltran A, MacLennan GT, Eble JN, et al. Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder:an immunohistochemical profile of 44 cases. Hum Pathol 2005;36:718–23.
63. Swiatoniowski G, Matkowski R, Suder E, Bruzewicz S, Setta M, Kornafel J, et al. E-cadherin and fibronectin expressions have no prognostic role in stage II ductal breast cancer. Anticancer Res 2005;25:2879–83.
64. Hernandez S, Lopez-Knowles E, Lloreta J, Kogevinas M, Jaramillo R, Amoros A, et al. FGFR3 and Tp53 mutations in T1G3 transitional bladder carcinomas:independent distribution and lack of association with prognosis. Clin Cancer Res 2005;11:5444–50.
65. Hermsen M, Alonso Guervos M, Meijer G, van Diest P, Suarez Nieto C, Marcos CA, et al. Chromosomal changes in relation to clinical outcome in larynx and pharynx squamous cell carcinoma. Cell Oncol 2005;27: 191–8.
66. Hantschmann P, Jeschke U, Friese K. TGF-alpha, c-erbB-2 expression and neoangiogenesis in vulvar squamous cell carcinoma. Anticancer Res 2005;25:1731–7.
67. Kantarjian HM, Bueso-Ramos CE, Talpaz M, O'Brien S, Giles F, Rios MB, et al. The degree of bone marrow fibrosis in chronic myelogenous leukaemia is not a prognostic factor with imatinib mesylate therapy. Leuk Lymphoma 2005;46:993–7.
68. Olson DP, Taylor BJ, La M, Sather H, Reaman GH, Ivy SP. The prognostic significance of P-glycoprotein, multidrug resistance-related protein 1 and lung resistance protein in pediatric acute lymphoblastic leukaemia:a retrospective study of 295 newly diagnosed patients by the Children's Oncology Group. Leuk Lymphoma 2005;46:681–91.
69. Wild PJ, Kunz-Schughart LA, Stoehr R, Burger M, Blaszyk H, Simon R, et al. High-throughput tissue microarray analysis of COX2 expression in urinary bladder cancer. Int J Oncol 2005;27:385–91.

70. Khor LY, Desilvio M, Al-Saleem T, Hammond ME, Grignon DJ, Sause W, et al. Radiation Therapy Oncology Group. MDM2 as a predictor of prostate carcinoma outcome:an analysis of Radiation Therapy Oncology Group Protocol 8610. Cancer 2005;104:962–7.
71. Skolarikos A, Alivizatos G, Bamias A, Mitropoulos D, Ferakis N, Deliveliotis C, et al. Bcl-2 protein and DNA ploidy in renal cell carcinoma:do they affect patient prognosis? Int J Urol 2005;12:563–9.
72. Boyapati SM, Shu XO, Ruan ZX, Dai Q, Cai Q, Gao YT, et al. Soyfood intake and breast cancer survival:a followup of the Shanghai Breast Cancer Study. Breast Cancer Res Treat 2005;92:11–7.
73. Tas F, Duranyildiz D, Argon A, Oguz H, Camlica H, Yasasever V, et al. Apoptosis of lymphocytes in peripheral blood of patients with melanoma. Med Oncol 2005;22:177–81.
74. Berdjis N, Meye A, Nippgen J, Dittert D, Hakenberg O, Baretton GB, et al. Expression of Ki-67 in squamous cell carcinoma of the penis. BJU Int 2005;96:146–8.
75. Iwata T, Uramoto H, Sugio K, Fujino Y, Oyama T, Nakata S, et al. A lack of prognostic significance regarding DeltaNp63 immunoreactivity in lung cancer. Lung Cancer 2005;50:67–73.
76. Watanabe J, Nishiyama H, Kawanishi H, Ito M, Kamoto T, Ogawa O. Clinical evaluation of serum p53 antibodies in patients with upper urinary tract tumors. J Urol 2005;174:73–5.
77. Antunes A, Silva T, Godinho I, Amaral N, Oliveira C. [Prognostic value of c-erb-2 immunohistochemistry expression in patients with primary breast cancer and adjuvant treatment with tamoxifen] Acta Med Port 2004;17:271–6.
78. de Jong KP, Gouw AS, Peeters PM, Bulthuis M, Menkema L, Porte RJ, et al. P53 mutation analysis of colorectal liver metastases:relation to actual survival, angiogenic status, and p53 overexpression. Clin Cancer Res 2005;11: 4067–73.
79. Roessler K, Monig SP, Schneider PM, Hanisch FG, Landsberg S, Thiele J, et al. Co-expression of CDX2 and MUC2 in gastric carcinomas:correlations with clinico-pathological parameters and prognosis. World J Gastroenterol 2005;11:3182–8.
80. Nakaya N, Tsubono Y, Nishino Y, Hosokawa T, Fukudo S, Shibuya D, et al. Personality and cancer survival:the Miyagi cohort study. Br J Cancer 2005;92:2089–94.
81. Chakravarti A, Seiferheld W, Tu X, Wang H, Zhang HZ, Ang KK, et al. Immunohistochemically determined total epidermal growth factor receptor levels not of prognostic value in newly diagnosed glioblastoma multiforme:report from the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2005;62:318–27.
82. Schindlbeck C, Janni W, Shabani N, Kornmeier A, Rack B, Rjosk D, et al. Isolated tumor cells in the bone marrow (ITC-BM) of breast cancer patients before and after anthracyclin based therapy:influenced by the HER2- and Topoisomerase IIalpha-status of the primary tumor? J Cancer Res Clin Oncol 2005;131:539–46.
83. Talvensaari-Mattila A, Soini Y, Santala M. VEGF and its receptors (flt-1 and KDR/flk-1) as prognostic indicators in endometrial carcinoma. Tumour Biol 2005;26:81–7.
84. Esteva FJ, Sahin AA, Cristofanilli M, Coombes K, Lee SJ, Baker J, et al. Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. Clin Cancer Res 2005;11:3315–9.
85. Ribas C, Colleoni GW, Felix RS, Regis Silva MR, Caballero OL, Brait M, et al. p16 gene methylation lacks correlation with angiogenesis and prognosis in multiple myeloma. Cancer Lett 2005;222:247–54 [Epub 2004 Nov 11].
86. Benitah N, Yeh BM, Qayyum A, Williams G, Breiman RS, Coakley FV. Minor morphologic abnormalities of adrenal glands at CT: prognostic importance in patients with lung cancer. Radiology 2005;235:517–22.
87. Sagol O, Yavuzsen T, Oztop I, Ulukus C, Ylmaz U, Alakavuklar M, et al. The effect of apoptotic activity, survivin, Ki-67, and P-glycoprotein expression on prognosis in pancreatic carcinoma. Pancreas 2005;30:343–8.
88. Carlinfante G, Lazzaretti M, Ferrari S, Bianchi B, Crafa P. P53, bcl-2 and Ki-67 expression in adenoid cystic carcinoma of the palate. A clinico-pathologic study of 21 cases with long-term follow-up. Pathol Res Pract 2005;200:791–9.
89. Goh KS, Ong TA, Peh SC, Yuen HL, Naicker M. P53 expression in colorectal carcinoma:the University of Malaya Medical Centre's experience. Med J Malaysia 2004;59:515–21.
90. Polin RS, Marko NF, Ammerman MD, et al. Functional outcomes and survival in patients with high-grade gliomas in dominant and nondominant hemispheres. J Neurosurg 2005;102:276–83.
91. Li HC, Cai QY, Shinohara ET, Cai H, Cao C, Wang ZF, et al. Endostatin polymorphism 4349G/A(D104N) is not associated with aggressiveness of disease in prostate [corrected] cancer. Dis Markers 2005;21:37–41.
92. Wu JT, Kakar S, Nelson RL, Mihalov ML, Hayward B, Gilbert PB, et al. Prognostic significance of DCC and p27Kip1 in colorectal cancer. Appl Immunohistochem Mol Morphol 2005;13:45–54.
93. Abraham BK, Fritz P, McClellan M, Hauptvogel P, Athelogou M, Brauch H. Prevalence of CD44+/CD24-/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. Clin Cancer Res 2005;11:1154–9.
94. Stein DE, Heron DE, Rosato EL, Anne PR, Topham AK. Positive microscopic margins alter outcome in lymph node-negative cholangiocarcinoma when resection is combined with adjuvant radiotherapy. Am J Clin Oncol 2005;28:21–3.
95. Cohen R, Guber A, Koren R, Marom Z, Siegal A. Prognostic significance of p53 and ras p21 protein expression in surgically treated non-small cell lung carcinoma. Rom J Morphol Embryol 1998;44:117–23.
96. Lee MA, Park GS, Lee HJ, Jung JH, Kang JH, Hong YS, et al. Survivin expression and its clinical significance in pancreatic cancer. BMC Cancer 2005;5:127.
97. Wong SC, Chan AT, Lo ES, Lo YM. Nuclear beta-catenin expression is rare and its potential association with short survival in colorectal signet-ring cell carcinoma. Appl Immunohistochem Mol Morphol 2005;13: 248–51.
98. Eichholzer M, Bernasconi F, Jordan P, Stahelin HB. Body mass index and the risk of male cancer mortality of various sites:17-year follow-up of the Basel cohort study. Swiss Med Wkly 2005;135:27–33.