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A Meta-analysis of Reported Correlations between Prognostic Factors in Breast Cancer: Does Axillary Lymph Node Metastasis Represent Biology or Chronology?

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A statistical overview of published results on correlations between various prognostic factors in breast cancer was undertaken. A distinction was made between clinical (or anatomical) prognostic factors—namely, axillary lymph node status and tumour size—and eight different biological prognostic factors. The latter included: tumour grade, oestrogen and progesterone receptor status, thymidine labelling index, DNA ploidy, S-phase fraction, epidermal growth factor receptor expression and c-*erb*B-2 gene amplification (or overexpression). 139 articles were eligible for review which reported a total of 432 individual correlations. A simple form of meta-analysis was employed: the counting method, in which the number of studies achieving a statistically significant correlation or not were counted. For each possible correlation examined, the proportion of studies showing a statistically significant correlation was calculated and an exact binomial 99% confidence interval determined for that proportion. If the 99% confidence interval included 5% (the proportion of correlations that would be expected to be statistically significant if the null hypothesis was true), it was taken as failing to exclude the null hypothesis of a zero correlation, while if it excluded 5% it was taken as rejecting the null hypothesis of a zero correlation. A broad agreement was found among published reports on the existence of a statistically significant correlation between the various biological prognostic factors in breast cancer. Of the 20 correlations examined, 18 had a 99% confidence interval excluding 5%, thus rejecting the null hypothesis of a zero correlation. On the other hand, a completely different result was obtained when reports on possible correlations between lymph node status and tumour size on the one hand and the eight biological prognostic factors on the other were analysed. Of the 16 correlations examined, 13 had a 99% confidence interval including 5%, failing to reject the null hypothesis of a zero correlation. These observations suggest the hypothesis that the prognostic influence of node status and tumour size cannot be explained by an analysis of the biology of breast cancer; and is compatible with the contention that axillary node status is merely a reflection of the relative chronological age of breast cancer.
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INTRODUCTION

AXILLARY NODE status has been the traditional prognostic factor used in the clinical management of breast cancer [1]. In recent years, several biological factors have been identified which have been shown to influence the clinical course of the disease, and these are being increasingly used to make treatment decisions [2]. Nevertheless, lymph node status remains the gold standard against which the predictive power of biological prognostic factors are evaluated [2].

The existence of a strong direct relationship between the two major clinical prognostic factors, namely, the size of a tumour and (the risk of) axillary lymph node metastasis is well established [3]. A recent analysis of data on 24740 cases of breast cancer recorded in the Surveillance, Epidemiology, and End Results Programme of the National Cancer Institute has demonstrated this relationship to be strictly linear [4]. On the other hand, results of published reports on correlations between various biological prognostic factors, and those between biological prognostic factors and lymph node status and tumour size, are conflicting. It is not clear to what extent the various prognostic factors are interrelated, and no systematic review of this vast and scattered literature is available. One purpose of this study was to undertake such a review, and to subject the results that have been reported in the literature to a statistical meta-analysis to establish reliably the extent to which the various prognostic factors in breast cancer might be correlated.

The second purpose of this statistical overview is the following. It is generally held that the relatively poor prognosis of patients with breast cancer that have spread to the axillary lymph nodes is due in part to a relatively greater biological aggressiveness and/or metastatic potential of the tumour, and in part to the relatively advanced chronological age at which the tumour is diagnosed [5]. On the other hand, some investigators have presented evidence which suggests that presence (and extent) of lymph node metastasis has little to do with tumour aggressiveness or metastatic potential, but is entirely a reflection of the relatively advanced chronological age of breast cancer [6–8]. One way to investigate which of the two views might be more appropriate could be to examine whether any interrelationships exist between clinical (or anatomical) prognostic factors—lymph node status and tumour size—and several of the well established biological prognostic factors in breast cancer. If a significant correlation between clinical and biological factors is found, the argument could be made that the poor prognosis of patients with lymph node metastasis is due, at least in part, to adverse biological properties of the tumour. If on the other hand, no significant correlation is found, this might be compatible with the suggestion that the presence of lymph node metastasis might entirely be a reflection of chronologically more advanced breast cancer.

METHODS

A literature search was made for articles published in English listed in the *Index Medicus*, and more recently in *Oncodisc* (Lippincott Information Services) that were concerned with any of the following eight prognostic factors in relation to breast cancer: tumour grade, oestrogen (ER), progesterone receptor (PR) status, thymidine labelling index (TLI), DNA ploidy (DNA index), S-phase fraction (SpF), epidermal growth factor receptor (EGFr) expression and c-*erb*B-2 gene amplification (or overexpression). The articles obtained from this search were scrutinised and those that investigated a possible relationship between two or more of these biological prognostic factors, or between any of these biological factors and lymph node status and/or tumour size, were considered for inclusion in this analysis. Relevant articles published up to December 1989 were included. A reported correlation was considered to be significant only if it achieved the conventional level of 5% ($P < 0.05$).

Criteria for exclusion were publication in a language other than English; articles dealing with prognostic factors but which did not investigate a correlation between them; articles that reported the same series of patients more than once (in such situations the publication that described the results in greater detail was selected for inclusion).

Since the vast majority of articles had defined lymph node status as being positive or negative while reporting a correlation with other prognostic factors, this classification was maintained in this review in order to ensure uniformity. Further subdivisions within the lymph node positive group reported by some workers were not considered. For example, Tandon *et al.* [9] found no correlation between lymph node metastasis and c-*erb*B-2 overexpression when the former was classified as being positive or negative; but upon sub-dividing the lymph node positive patients into those with 1–3 nodes and 3+ nodes positive subgroups, a weak positive correlation between the extent of lymph node involvement and oncogene overexpression was found. In this situation c-*erb*B-2 was considered not to have any association with node status. In a few older articles clinical stage (rather than lymph node status and tumour size) had been mentioned; in such cases stage of tumour was taken to indicate tumour size for the purpose of this review. In most reports axillary node status and tumour size represented those reported by the pathologist. In most articles histological grade of the tumour was reported, but in a few, nuclear grade had been taken into account; both these have been used interchangeably to indicate tumour grade.

This overview is essentially a meta-analysis, in that it is an exercise in combining the results of independent studies which have addressed similar questions. Because of diversity of the presentation of results in the various publications surveyed, one of the simplest forms of meta-analyses was employed, namely the counting method as has been described by Brozek and Tiede [10], Jones and Fiske [11], Wilkinson [12] and Rosenthal [13]. In this form of meta-analysis, the number of studies achieving statistical significance (at $P < 0.05$) and not achieving statistical significance were counted. If a number of studies have been carried out to look at a particular possible correlation for which the null hypothesis (of zero correlation) is true, it would be expected that by chance in the long run only 5% of the studies would manifest a statistically significant correlation. For each possible correlation examined, the proportion of studies showing a statistically significant correlation was calculated and an exact binomial 99% confidence interval was determined for that proportion (from tables published in Documenta Geigy[14]). If the 99% confidence interval included 5%, it was taken as failing to exclude the null hypothesis of a zero correlation, whilst if the entire interval was greater than 5% it was taken as rejecting the null hypothesis of a zero correlation.

RESULTS

The literature review is summarised in Tables 1 and 2. The numbers in small print in each cell refer to the various articles reviewed with respect to a correlation between a set of two prognostic factors. The numbers in the numerator are references to those articles that have confirmed the presence of a statistically significant correlation whilst those in the denominator refer to articles that have failed to confirm a significant correlation between two factors. By adding up the number of articles referred to in the numerator and denominator (total numbers

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Table 1. Review of correlations between biological prognostic factors

	Tumour grade	ER	PR	TLI	Ploidy (DNA index)
ER	29 33 37 38 39 40 41 42 43 46 55 57 63 64 66 67 68 71 72 75 / 25 26 27 30 48 50 73 74 99 = **20/9**				
PR	40 41 55 57 66 67 68 75 / 63 = **8/1**	32 41 53 54 60 61 63 66 76 78 131 / = **11/0**			
TLI	81 82 87 89 93 / = **5/0**	81 83 85 88 90 92 93 / = **7/0**	81 90 93 / = **0/3**		
Ploidy (DNA-index)	91 98 99 100 102 105 107 108 110 112 115 116 117 119 120 121 / 95 = **16/1**	94 96 98 99 100 103 107 108 109 110 111 113 114 115 116 117 118 120 121 122 123 / 90 91 95 101 105 106 112 = **21/7**	96 110 111 115 116 118 120 121 122 / 91 = **9/1**	90 / = **1/0**	
S-phase fraction	91 97 105 108 110 115 120 / 95 = **7/1**	90 91 95 96 97 108 110 118 120 123 / 115 = **10/1**	91 96 110 118 120 / 90 115 = **5/2**	90 91 / = **2/0**	90 91 96 101 103 105 110 118 120 123 / 95 = **10/1**
EGF receptor	129 132 / 133 = **2/1**	125 127 128 129 130 131 132 / 124 126 = **7/2**	130 131 132 / = **3/0**	/ = **0/0**	/ = **0/0**
C-*erb*B-2 oncogene	141 143 147 148 149 150 151 152 / 136 138 140 145 = **8/4**	9 135 143 147 148 150 152 / 134 136 138 140 141 142 = **7/6**	9 135 144 150 / 141 = **4/1**	/ = **0/0**	/ 151 = **0/1**

The numbers in small print in each cell are references to the various articles reviewed; those in the numerator are references to articles that have reported the presence of a statistically significant correlation between two prognostic factors while those in the denominator are references to articles that have reported the absence of a statistically significant correlation. Numbers in bold print denote the total numbers of references in these two categories. ER = oestrogen receptor; PR = progesterone receptor; TLI = tumour labelling index.

Table 2. Review of correlations between clinical and biological prognostic factors

	Nodal status	Tumour size
Tumour grade	15 16 20 22 23 24 **72** = **7/2** 17 19	15 21 23 24 **72** = **5/2** 18 20
ER	32 73 131 = **3/37** 26 27 28 29 30 31 34 35 36 37 39 41 43 44 45 47 50 51 52 54 55 56 57 58 59 61 62 63 65 67 68 72 74 75 77 78 90	36 59 74 131 = **4/31** 25 26 27 28 31 32 34 37 41 43 45 47 49 50 51 55 56 61 62 63 65 66 67 68 69 70 72 73 75 77 78
PR	= **0/16** 32 41 54 55 56 57 59 61 63 65 66 67 68 75 78 90	59 65 = **2/11** 41 55 56 61 66 67 68 69 70 75 78
TLI	80 = **1/7** 79 81 82 85 86 87 89	84 90 92 = **3/7** 80 81 82 86 87 89 93
DNA-index (ploidy)	106 107 114 115 116 118 121 123 = **8/12** 91 95 96 100 101 108 109 110 117 119 120 122	104 112 114 119 = **4/16** 90 91 95 100 101 105 107 110 113 115 116 117 120 121 122 123
S-phase fraction	118 = **1/8** 91 95 96 108 110 115 120 123	90 123 = **2/6** 91 95 97 110 115 120
EGF receptor	131 = **1/2** 129 133	129 = **1/1** 133
C-*erb*B-2 oncogene	135 = **1/16** 9 136 137 138 139 140 141 142 143 144 145 146 147 148 150 152	145 = **1/9** 9 135 136 138 146 147 150 151 152

depicted in bold print), a numerical assessment of the extent of agreement or disagreement on the presence of a correlation between two factors is obtained.

Meta-analyses of data in Table 1 and in Table 2 are given in Table 3 and Table 4, respectively. In each cell of Tables 3 and 4 the proportion of studies which have reported a statistically significant correlation (A) and the lower limit of the 99% confidence interval for the proportion with a statistically significant correlation (B) is given.

An examination of Table 1 reveals that the number of reports that supported the presence of a correlation between the various biological prognostic factors was consistently greater than the number that did not. For example, 20 articles found a correlation between ER and tumour grade whilst nine did not; seven articles observed a correlation between TLI and ER and no article contradicted this; 10 articles reported a correlation between S-phase fraction and DNA index while only one failed to do so, and so on. The meta-analysis of this data (given in Table 3) shows that of the 20 correlations for which the lower 99% confidence limit could be determined, 18 had a lower 99% confidence limit greater than 5%, thus rejecting the null hypothesis (of zero correlation). The only situations where the null hypothesis could not be excluded were the relationships between tumour grade and EGF receptor (this might well be due to the small number of studies available for analysis), and that between PR and TLI (where none of the three studies reported a statistically significant correlation). The latter finding of a lack of correlation between PR and TLI was unexpected, since a strong correlation was demonstrable between ER and TLI. In summary, a broad correlation appeared to exist between the various biological prognostic factors examined. The presence of such an interrelationship may indicate that these factors reflect, directly or indirectly, some common properties—such as growth rate and/or metastatic potential—of breast cancer.

A review and a meta-analysis of correlations between the two clinical and the eight biological prognostic factors is given in Tables 2 and 4, respectively. The review in Table 2 is conspicuous by a general lack of agreement among published reports

Table 3. Meta-analysis of correlations between biological prognostic factors in breast cancer

	Tumour grade		ER		PR		TLI		Ploidy	
	A	B								
ER	69.0%	43.5%	A	B						
PR	88.9%	41.5%	100.0%	61.8%	A	B				
TLI	100.0%	34.7%	100.0%	46.9%	0.0%	0.0%*	A	B	Ploidy	
DNA-index ploidy	94.1%	63.7%	75.0%	49.2%	90.0%	45.6%	100.0%	—	A	B
S-phase fraction	87.5%	36.9%	90.9%	49.1%	71.5%	20.3%	100.0%	7.1%	90.9%	49.1%
EGF receptor	66.7%	4.1%*	77.8%	30.7%	100.0%	17.1%	0	—	0	—
C-*erb*B-2 oncogene	66.7%	27.3%	53.9%	18.9%	80.0%	18.5%	0	—	0	—

A = proportion of studies reporting a statistically significant correlation. B = lower limit of the 99% confidence interval for the proportion of studies with a statistically significant correlation.
* Lower 99% confidence limit is less than 5%.

Table 4. Meta-analysis of correlations between clinical and biological prognostic factors in breast cancer

	Nodal status		Tumour size	
	A	B	A	B
Tumour grade	77.8%	30.7%*	71.4%	20.3%*
ER	7.5%	0.9%	11.4%	2.0%
PR	0%	0%	15.4%	0.8%
TLI	12.5%	0.1%	30.0%	3.7%
DNA-index (ploidy)	40.0%	14.6%*	20.0%	3.6%
S-phase fraction	11.1%	0.1%	25.0%	1.4%
EGF receptor	33.3%	0.2%	50.0%	0.3%
C-*erb*B-2 oncogene	5.9%	0.03%	10.0%	0.1%

* Lower 99% confidence limit is greater than 5%.

with respect to an association between lymph node status and tumour size on the one hand and the biological prognostic factors on the other. In virtually every case (except those relating to tumour grade; see later for possible explanation), the number of articles referred to in the denominator is greater than that in the numerator, suggesting a general lack of association between clinical and biological prognostic factors. The meta-analysis shown in Table 4 demonstrates that out of the 16 correlations examined, in only three of them was the lower 99% confidence limit greater than 5% in which the null hypothesis of a zero correlation could be rejected. In one of these, the relationship between nodal status and DNA index, the correlation was nevertheless in the anticipated direction (Table 2).

The striking exceptions to the general lack of correlation between clinical and biological prognostic factors observed in Tables 2 and 4 are the suggestion of an association between lymph node status and tumour grade and tumour size and tumour grade where the null hypothesis could be rejected. This finding was surprising because tumour grade is well correlated with the other biological prognostic factors examined (Tables 1 and 3), which in their own turn do not correlate with the clinical factors (Tables 2 and 4). It should also be noted that of all the biological parameters included in this overview, tumour grade is the only one that is determined subjectively. It is possible that prior knowledge of the presence of lymph node involvement might bias the pathologist while (subjectively) grading a tumour.

DISCUSSION

A review such as this suffers from many potential deficiencies. These include: (1) publication bias, i.e. bias on part of journals to favour publication of positive results; (2) the possible subconscious bias of authors in analysing and interpreting their data in order to obtain a positive correlation; (3) lack of statistical power in some studies due to relatively small sample size; (4) variability in criteria (or cut-off levels) used to classify patients, ER positive vs. ER negative, diploid vs. aneuploid, high vs. low SpF etc.; (5) variability in assay techniques; (6) variability in types of patients included in different studies; (7) intercorrelations among some of the variables considered in the studies reviewed (such as that between ER and PR), so that all the analyses will not be tests of independent hypotheses; (8) differing study designs, and many others. Perhaps one way to minimise such difficulties would have been to include only large studies or weighting them more heavily than smaller ones. But a large study may have been poorly conducted in terms of assay techniques, and defining what is large and what is small is a subjective decision which could introduce a further bias. No

selection criteria was likely to have been perfect and none would have been better than any other. For all these reasons a meta-analysis, from which no relevant published report has been excluded, is the only process that allows one to draw meaningful conclusions from a review such as this.

Of course, the ideal way to address some of the difficulties listed above (especially points 2, 4 and 7) would have been to have had access to the raw data of every study, both for those which have been published and for those which have not been published. To obtain the raw data from so many studies would probably not be possible, and availability of the raw data from only some of the studies would produce a biased meta-analysis. However, although what we have attempted to do from published sources does have major obvious limitations, it is, at least, a statistically sound method for performing a rigorous and systematic overview of this subject.

The statistical overview conducted here suggests two broad conclusions namely that there exists a general interrelationship between the various biological prognostic factors themselves, whilst there exists a relative lack of correlation between the clinical or anatomical prognostic factors on the one hand and the biological prognostic factors on the other. In the case of the former, 18/20 correlations had the lower 99% confidence limit that was greater than 5% (thus excluding the null hypothesis of a zero correlation) whilst in case the latter 13/16 correlations had the lower 99% confidence limit that was less than 5% (thus supporting the null hypothesis of a zero correlation). It should, however, be pointed out that, since the likely direction of the bias of authors as well as of publishers would be to tend to overstate the possibility of the existence of a correlation, it is possible that Table 1 has a bias in favour of reporting a positive correlation. By the same token, however, such a bias makes the relative lack of correlation between clinical and biological prognostic factors (in Table 2) even more convincing.

The size of a breast tumour may be considered a product of its biological aggressiveness and its chronological age, divided by the degree of host resistance to growth. The presence (and extent) of axillary node involvement may be considered the product of biological potential for metastasis (which may differ from biological aggressiveness) and chronological time, divided by host resistance to metastasis. Since host resistance is neither currently well understood nor quantifiable, for practical purposes prognosis of breast cancer might be considered as being determined by the product of biological aggressiveness and/or metastatic potential on the one hand and chronological age of breast cancer on the other.

It is well recognized that axillary lymph node status is the most important independent determinant of disease-free and overall survival in breast cancer [1,4,153,154]. One aspect of the prognostic influence of lymph node status and tumour size appears, however, not to have been fully recognized. This is the observation made by some investigators that once the disease recurs after ostensibly curative local therapy, lymph node status (or tumour size or stage) ceases to have any prognostic influence; and that postrelapse survival of node-positive and node-negative patients become identical [6,7,8,156–158]. On the other hand, at least two of the biological prognostic factors, namely ER status and TLI, have been shown to continue to be predictive even after relapse; with ER-positive patients and those with low TLI surviving longer after relapse than those who are ER-negative or have high TLI [6,155,157–164]. This finding has been interpreted as suggesting that lymph node status is not an indicator of intrinsic aggressiveness of breast cancer or of its metastatic potential, but rather is an indicator of chronological age from the time of inception. Oestrogen receptor status and TLI, on the other hand, are true indicators of the biological behaviour of breast cancer and exert their influence throughout the course of the disease [6,7,8,165,166].

The review conducted here indicates that there is, in general, a lack of correlation between lymph node status and tumour size and the various biological prognostic factors in breast cancer. This implies that node-positive (or large size) tumours are biologically no different from those that are node-negative (or small in size); and that the former have the same chance as the latter of being ER-positive or negative, being diploid or aneuploid, having high or low TLI, having single or multiple copies of the oncogene c-*erb*B-2, and so on. This suggests that the apparent influence of axillary node status and tumour size on prognosis cannot be explained by an analysis of the biology of breast cancer, and that clinical and biological prognostic factors might influence prognosis through different mechanisms. This would be compatible with the contention that axillary node status and tumour size are of prognostic significance only in as much as they reflect the relative chronological age of breast cancer [6–8].

However, an alternative interpretation of this overview might be that lymph node status and tumour size mediate their prognostic influence through a biological property of breast cancer that is yet to be identified.

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Recombinant Interleukin-2 in Metastatic Renal Cell Carcinoma—A European Multicentre Phase II Study

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This multinational, multicentre study represents the introduction of recombinant interleukin-2 (rIL-2) in Europe. From December 1987 to June 1989, 57 eligible patients with metastatic renal cell cancer were treated with rIL-2 administered as continuous intravenous infusion. 8 out of 51 evaluable patients responded (16%), 2 complete remission (CR) and 6 partial remission (PR). 10 patients had no change (20%). The response duration for CR was 209 and 394+ days. The median response duration for PR was 371 (range 140–506+) days. Dose-limiting grade 3–4 toxicities were hypotension in 52% of the patients, arrhythmia (4%), dyspnoea (8%), creatinine rise (4%), peripheral neurotoxicity (10%) and central neurotoxicity (10%). Toxicities most often recovered solely on interrupted therapy. 2 patients died due to catheter-related septicaemia and one patient died of rIL-2 induced renal failure. The study confirmed the antitumour efficacy of rIL-2 in renal cell cancer. Toxicities were numerous, but manageable by close observation in a normal oncology ward without routine use of an intensive care unit.
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INTRODUCTION

RECOMBINANT INTERLEUKIN-2 (rIL-2) alone or in combination with lymphokine-activated killer (LAK) cells has shown antitumour efficacy in several animal tumour models [1–3]. Since the initial reports from Rosenberg *et al.* [4], a number of clinical trials have confirmed that rIL-2-based immunotherapy can result in durable responses in tumours refractory to conventional therapeutic approaches [5–10]. The contribution of LAK cells to the therapeutic efficacy has still not been clarified. There seems to be no increase in the total number of responding patients although it has been claimed that there may be more complete responses when rIL-2 is combined with LAK cells [11].

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West *et al.* have developed a schedule for continuous rIL-2 infusion obviating the use of an intensive care unit while maintaining antitumour efficacy [10]. Based on this regimen, a European multinational, multicentre, non-randomised phase II trial using rIL-2 alone in metastatic renal cell carcinoma was initiated. The present paper deals with the results from this study representing the introduction of rIL-2 based immunotherapy in Europe. A preliminary report has been presented [8].

PATIENTS AND METHODS

Patients

From December 1987 to June 1989, 61 patients with histologically proven metastatic renal cell carcinoma entered the protocol. The distribution of patients according to the participating institutions is given in Table 1. The protocol entry criteria are summarised in Table 2. All patients had progressive disease, defined as at least 25% increase of the area of any tumour lesion before entering the study. The response status of all patients was reviewed in a blinded fashion by a central review committee consisting of 3 physicians and 2 radiologists. 4 patients were judged to be ineligible and were excluded from all further analysis. The reasons for excluding these 4 patients were as follows: performance status < 80 in 2 cases, lung infection and severe tachycardia in 1 case, and prior chemotherapy in 1 case.