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Trends in Lung Cancer Mortality in Three Broad Italian Geographical Areas Between 1969 and 1987

Riccardo Capocaccia, Eva Negri, Carlo La Vecchia and Adriano Decarli

Trends in death certification rates from lung cancer in broad Italian geographical areas (north/centre/south) were analysed over the period 1969–1987. In northern Italy, lung cancer rates in young and middle-aged males reached a peak between the mid and late 1970s, and tended to decline afterwards; only above age 60 was mortality still rising in the 1980s. A similar pattern of age-specific rates was observed in central areas, while in the South rates tended to level off in the early 1980s only below age 55, but were still upwards in subsequent age groups. Consequently, the north/south ratio for the overall age-standard rate increased slightly between the late 1960s and mid 1970s, from 1.68 (corresponding to a world standardised rate of 47.1/100 000 in the north vs. 28.1 in the south) to 1.73, but declined to 1.55 between 1985 and 1987 (for a rate of 69.1/100 000 males in the north vs. 44.6 in south). In the younger age groups a diverging pattern was observed: at ages of 25–34 rates in 1985 and 1987 were apparently higher in the south (1.0 vs. 0.9/100 000 in the north), and in the 35–44 age group the north/south ratio decreased from 1.7 to 1.2 (with rates of 12.9 and 10.7, respectively, in 1985 and 1987). Among females, lung cancer rates increased in all geographical areas and age groups except the youngest (25–34 years). Under the age of 50, the rises were proportionally similar in various geographical areas, thus widening the north/south difference in absolute terms. Above the age of 50, the north/south difference tended to be wider in relative terms too, reaching a factor of 2 in the 65–74 age group. The overall age-standardised north/south ratio for females increased from 1.51 in 1969–1974 (5.6 vs. 3.7/100 000) to 1.87 in 1985–1987 (8.4 vs. 4.5/100 000). These trends reflect changes in smoking habits in subsequent generations of Italian males and females from different areas of the country, and confirm the central role of cigarette smoking in lung cancer rates in various populations, although this does not exclude some influence by other, mainly occupational, lung carcinogens on the substantial differences in lung cancer rates in various Italian geographical areas.
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INTRODUCTION

There are substantial differences in mortality from lung cancer in various Italian geographical areas, with a clear north/south gradient. In the early 1970s, overall age-standardised lung cancer rates for males were 67% higher in the north than in the south of the country, and 55% higher in females, with central areas showing generally intermediate rates [1]. In the mid 1970s geographical differences in overall lung cancer rates tended to rise to 79% higher in the north for males and 83% for females [2, 3]. This was essentially attributed to the pattern of change in

Table 1. Trends in lung cancer mortality in males from selected Italian geographical areas, 1969–1987

Age group	Geographical area	Age-standardised* rates (ratios) in selected calendar periods 1969–1974	1975–1979	1980–1984	1985–1987
25–34	North	1.4 (1)†	1.4 (1)	1.1 (1)	0.9 (1)
	Centre	1.6 (1.2)	1.6 (1.2)	1.6 (1.4)	1.5 (1.6)
	South	1.0 (0.72)	1.2 (0.86)	1.2 (1.2)	1.0 (1.1)
35–44	North	15.7 (1)	15.6 (1)	13.9 (1)	12. 9 (1)
	Centre	10.7 (0.68)	12.7 (0.82)	12.4 (0.89)	11.4 (0.88)
	South	9.3 (0.59)	10.2 (0.66)	10.2 (0.74)	10.7 (0.83)
45–54	North	74.6 (1)	91.9 (1)	95.2 (1)	80.0 (1)
	Centre	53.9 (0.72)	65.5 (0.71)	68.3 (0.72)	59.9 (0.75)
	South	41.7 (0.56)	50.1 (0.55)	55.5 (0.58)	52.1 (0.65)
55–64	North	197.6 (1)	244.6 (1)	281.9 (1)	294.7 (1)
	Centre	151.1 (0.76)	181.4 (0.74)	214.5 (0.70)	228.0 (0.78)
	South	112.5 (0.57)	137.4 (0.56)	169.4 (0.60)	181.3 (0.61)
65–74	North	329.6 (1)	409.9 (1)	455.3 (1)	475.5 (1)
	Centre	273.1 (0.83)	333.7 (0.81)	367.1 (0.81)	384.5 (0.81)
	South	202.7 (0.61)	239.6 (0.58)	283.8 (0.63)	316.3 (0.67)
75–84	North	225.3 (1)	383.5 (1)	521.0 (1)	560.8 (1)
	Centre	204.9 (0.91)	327.3 (0.83)	424.1 (0.81)	464.6 (0.83)
	South	155.7 (0.69)	234.4 (0.61)	315.1 (0.60)	356.2 (0.64)
0–84	North	47.1 (1)	60.0 (1)	68.1 (1)	69.1 (1)
	Centre	37.4 (0.79)	46.6 (0.78)	53.3 (0.78)	55.0 (0.79)
	South	28.1 (0.60)	34.7 (0.58)	41.6 (0.61)	44.6 (0.65)
35–64	North	83.5 (1)	101.8 (1)	111.9 (1)	109.4 (1)
	Centre	62.3 (0.75)	75.0 (0.74)	84.4 (0.75)	84.5 (0.78)
	South	47.4 (0.57)	57.2 (0.56)	67.3 (0.60)	69.4 (0.63)

*On the World Standard Population. †Reference category.

smoking habits during previous decades, since the rise in cigarette smoking occurred earlier and to a greater extent in northern areas of the country [2, 4].

However, no detailed analysis of trends in age-specific lung cancer rates in various Italian geographical areas has been published. Examination of age-specific rates allows important inferences on the impact of smoking in each subsequent generation, according to their specific pattern of smoking [5, 6]. In this article, therefore, we present trends in age-specific and age-standardised death certification rates from lung cancer in three broad Italian geographical areas (north/centre/south) between 1969 and 1987.

MATERIALS AND METHODS

Lung cancer death certification numbers were abstracted from computer tapes provided by the Central Institute of Statistics with extract of all death records for the period 1969–1987, including the following information: year of death, age at death, sex, province of residence, and cause of death, classified according to the International Classification of Diseases (ICD, eighth revision for 1969–1978 and ninth revision for 1979–1987).

Estimates of the resident population for each geographical area, calendar year, sex and age group were developed and partially published by the National Institute of Health (Istituto Superiore di Sanità) [7].

On the basis of these data, lung cancer death certification rates for four calendar periods and each decade of age from 25–34 to 75–84, as well as overall rates and truncated 35 to 64 years were computed for each broad geographical area by direct standardisation on the world standard population.

Further, log-linear age, period and cohort (APC) models have been applied to fit single-year period- and age-specific mortality rates. In order to compare the mortality experience of the cohorts between different geographical areas or between different sexes, age and cohort effects estimated from the model have been combined to give the theoretical 0–84 cumulative mortality rates of the different birth-cohorts.

It is known that APC models are affected by an identifiability problem due to the linear relationship between age, period, and cohort factors [8]. This problem has been overcome by constraining the linear part of the period effect to nil. Thus, the linear component of the time trend is entirely attributed to the

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Table 2. Trends in lung cancer mortality in females from selected Italian geographical areas 1969–1987

Age group	Geographical area	Age-standardised* rates (ratios) in selected calendar periods			
		1969–1974	1975–1979	1980–1984	1985–1987
25–34	North	0.6 (1)	0.6 (1)	0.4 (1)	0.3 (1)
	Centre	0.5 (0.86)	0.5 (0.93)	0.2 (0.66)	0.9 (3.61)
	South	0.4 (0.68)	0.3 (0.62)	0.5 (1.23)	0.5 (2.04)
35–44	North	2.5 (1)	2.7 (1)	2.4 (1)	2.8 (1)
	Centre	2.3 (0.92)	2.2 (0.82)	2.4 (0.98)	2.6 (0.92)
	South	2.2 (0.88)	1.9 (0.71)	2.0 (0.82)	2.2 (0.79)
45–54	North	8.4 (1)	9.7 (1)	10.0 (1)	9.8 (1)
	Centre	8.1 (0.97)	8.0 (0.83)	9.2 (0.92)	8.7 (0.88)
	South	5.7 (0.68)	5.5 (0.57)	5.4 (0.54)	5.3 (0.54)
55–64	North	19.7 (1)	24.5 (1)	27.3 (1)	31.5 (1)
	Centre	16.7 (0.85)	19.1 (0.78)	23.3 (0.85)	25.2 (0.80)
	South	12.3 (0.63)	14.5 (0.59)	15.2 (0.56)	15.7 (0.50)
65–74	North	34.0 (1)	43.1 (1)	49.2 (1)	57.4 (1)
	Centre	30.3 (0.89)	32.9 (0.76)	40.0 (0.81)	47.3 (0.83)
	South	22.4 (0.66)	24.5 (0.57)	28.2 (0.57)	29.2 (0.51)
75–84	North	48.3 (1)	61.5 (1)	71.7 (1)	77.0 (1)
	Centre	41.0 (0.85)	54.1 (0.88)	56.3 (0.79)	63.8 (0.83)
	South	27.5 (0.57)	34.4 (0.56)	40.3 (0.56)	41.6 (0.54)
0–84	North	5.6 (1)	6.9 (1)	7.5 (1)	8.4 (1)
	Centre	4.9 (0.88)	5.5 (0.80)	6.3 (0.84)	7.1 (0.84)
	South	3.7 (0.65)	4.0 (0.58)	4.4 (0.58)	4.5 (0.53)
35–64	North	9.0 (1)	10.8 (1)	11.5 (1)	12.7 (1)
	Centre	8.1 (0.89)	8.6 (0.80)	10.2 (0.88)	10.6 (0.83)
	South	6.0 (0.67)	6.4 (0.60)	6.6 (0.57)	6.8 (0.53)

*On the World Standard Population; †Reference category.

cohort factor. From a descriptive point of view this is correct, since successive cohorts do actually live in successive periods of time. Age effects describe then the age mortality trend of the cohorts while ageing. Both age and cohort effect are adjusted for non-linear period effects. More details on this approach are reported elsewhere [8].

The solution of the APC model can be expressed as:

$$\text{logit}\,(r_{ijk}) = A_i + C_k + P_j{}^* + \text{constant}$$

where r_{ijk} are the estimated mortality rates at age i and year j for the birth-cohort k, and A_i, C_k, $P_j{}^*$ are, respectively, the estimated age, cohort, and non-linear period effects [8]. The theoretical cumulative rates of the different cohorts, adjusted for higher-order period effects, have then been computed by the expression:

$$R\text{cum}_k = 1 + \exp\left\{\Sigma_i\,[1 - \exp - (A_i + C_k + \text{constant})]^{-1}\right\}$$

This measure can be interpreted as the cumulative rate of the cohort with a mortality pattern given by the common age trend (constant + A_i) and an age-independent odds ratio (C_k). The advantage of this indicator consists in the possibility of comparing in absolute terms the cohort mortality trends estimated from different datasets. This is not allowed by simple cohort effects C_k, giving odds ratio vs. a dataset-specific reference.

RESULTS

Table 1 gives the age-standardised death certification rates from lung cancer in males in four separate calendar periods (1969–1974; 1975–1979; 1980–1984; 1985–1987) for each subsequent age group from 25–34 to 75–84, plus truncated 35–64 and overall rates, together with the ratios between north, centre and south. In northern Italy, lung cancer rates in young and middle age males reached a peak between the mid and late 1970s, and tended to decline afterwards. Only above the age of 60 was mortality still rising in the 1980s. A similar pattern of age-specific rates was observed in central Italy, while in the south rates tended to level off in the early 1980s only below the age of 55, but were still upwards in subsequent age groups.

Consequently, the north/south ratio for the overall rate increased slightly between the late 1960s and the mid 1970s, from 1.68 (corresponding to a world-standardised rate of 47.1/100 000 males in the north vs. 28.1 in the south) to 1.73, but declined to 1.55 (69.1 vs. 44.6/100 000) in the most recent years. A similar pattern was observed in middle age (35–64 years). Only in the younger age groups was a different pattern of rates observed: at ages 25 to 34 lung cancer mortality in the 1980s was indeed apparently higher in the south (although no inference is possible on statistical significance, since there were only about a dozen deaths per year per area), and in the subsequent 35 to 44 age group the north/south ratio decreased from 1.7 to 1.2 A general tendency towards levelling of differences is also evident in any of the subsequent age groups, although this was somewhat discontinuous for the superimposed period and cohort effects, for instance due to cigarette shortages during and after the Second World War [4]. To illustrate this different pattern across age groups, mortality trends at all ages (0–84), in middle age (from 35 to 64 years) and in the young (from 35 to 44) are presented in Fig. 1.

Lung cancer death rates among females increased in all geographical areas and age groups except the youngest (25–34 years). Some diverging cohort effect was evident, too. For instance, the rises were smaller in the 45 to 54 age group, possibly again in relation to some post-war tobacco shortage. Under the age of 55, mortality in central Italy approached that in the north. In proportional terms, the rises were similar in the north and south of the country under age 50, thus widening absolute differences. Above the age of 50, the north/south difference tended to widen in relative terms, reaching a factor of 2 in the 65–74 age group. The north/south ratio increased from 1.51 to 1.87 at all ages, and from 1.50 to 1.87 for the truncated 35 to 64 rates (Table 2). Trends in rates for overall, truncated and young female adults for each broad geographical area are presented in Fig. 2.

These data suggest that a levelling-off, or perhaps also reversal, of the mortality differences among males between geographical areas is occurring in more recent years. The results of the log-linear model give a further insight on this phenomenon. The theoretical cumulative mortality rates for the ages 0–84 of the different birth cohorts for various parts of the country are plotted in Fig. 3. Cumulative rates are very low (about 3%) and similar for the earliest cohorts. The rates are then progressively increasing for each successive cohort. In the north, cumulative rates attained the maximum value (18%) for the 1930 cohort, slowly

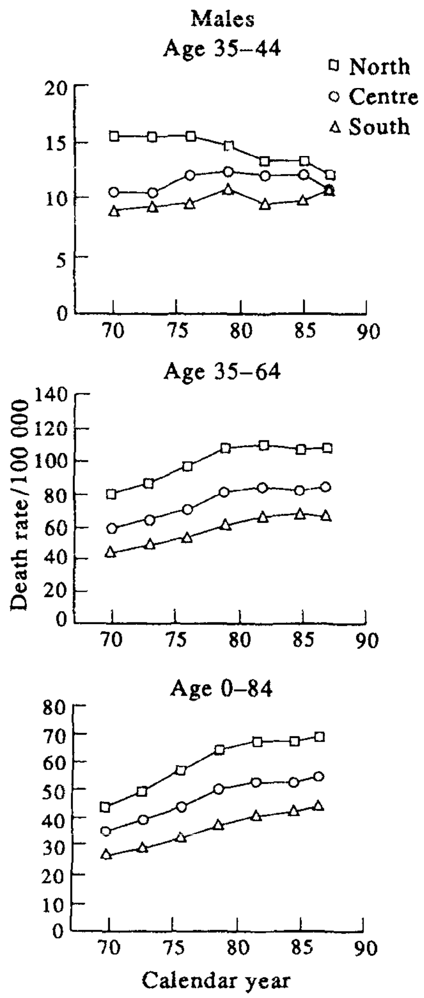

Fig. 1. Trends in lung cancer mortality in males in various Italian geographical areas, 1969–1987.

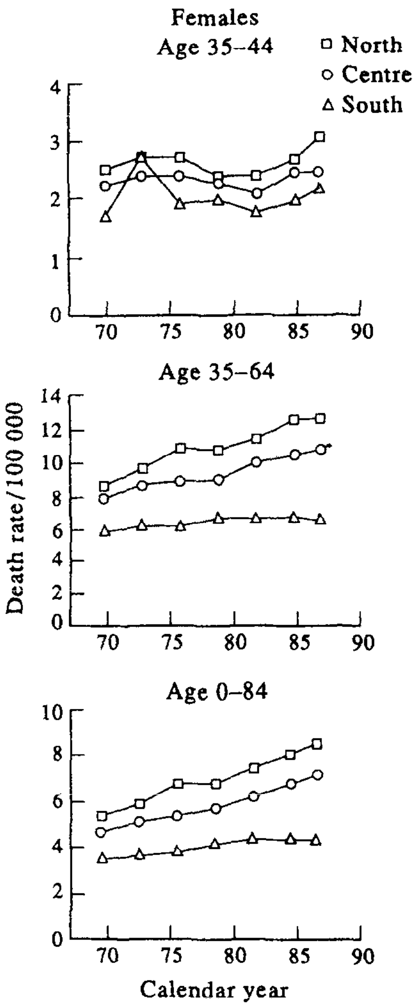

Fig. 2. Trends in lung cancer mortality in females in various Italian geographical areas, 1969–1987.

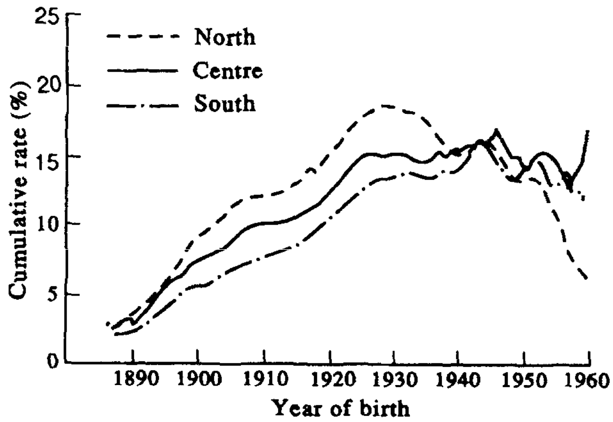

Fig. 3. Lung cancer cumulative mortality rates for subsequent cohorts of males in various Italian geographical areas.

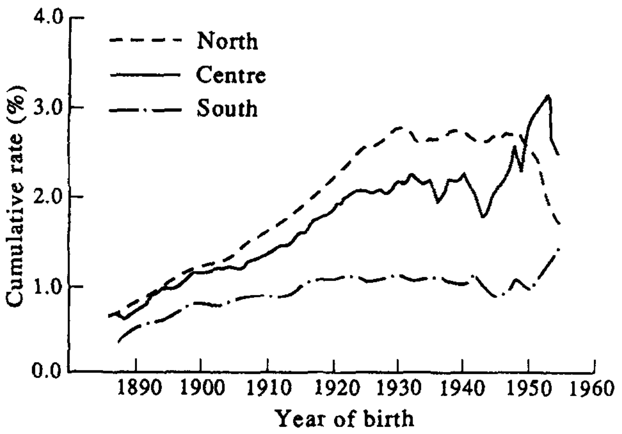

Fig. 4. Lung cancer cumulative mortality rates for subsequent cohorts of females in various Italian geographical areas.

decreased for generations 1930–1950, and steeply decreased for the most recent cohorts. Conversely, in the southern regions the maximum value (16%) was reached by the 1943 cohort, and a moderate decrease was estimated for the following cohorts. As a consequence, the cumulative rates were higher in the north for the cohorts 1896–1940, similar for the two region for the cohorts 1940–1950, and higher in the south for the most recent ones.

Corresponding figures for females are shown in Fig. 4. Very low rates are estimated for the earliest cohorts (0.7% in the north, and 0.3% in the south). In each subsequent cohort, the values increased, until a maximum (about 2.7%) in the north for generations 1930–1950, and approximately a plateau (at about 1%) in the south for the years 1920–1950. For the most recent cohorts, contrasting trends are estimated: increasing in the south, and steeply decreasing in the north.

Male-to-female rate ratio in each of the three areas are further considered in Table 3 for three different age groups (0 to 84, 35 to 64 and 35 to 44). In the north, both the overall and the truncated sex ratio increased up to the late 1970s (from 8.4 to 9.8 and from 9.3 to 9.7, respectively), and decreased thereafter to below the late 1960s values (8.2 and 8.6, respectively). Again in the north, the sex ratio of 6.2 at ages 35–44 in the late 1960s or early 1970s decreased to 4.6 in the mid to late 1980s. In central and northern areas the male to female ratio remained approximately constant, around a factor of 8 for the overall and truncated rates, and of 5 at ages 35–44. In the south, the sex ratios tended to increase for overall (from 7.7 to 9.9) and truncated rates (from 7.8 to 10.2), but remained approximately stable around a factor of five in early middle age (35 to 44 years) from the late 1970s onwards.

DISCUSSION

The major interest of these data lies in the fact that they first present an analysis of trends in cancer mortality over the past two decades in three different areas within Italy, characterised by substantial heterogeneity in cancer rates. Since cigarette smoking is a major identified cause of lung cancer, trends can be related to the changing patterns of smoking in various areas of Italy over previous decades.

Southern Italy, in fact, had a later economic development and, largely in consequence of it, the spread of smoking was delayed among males and, even more, among females, for questions of custom, too [4,9]. Since the cost of cigarettes had in the past major importance, a lower number of cigarettes consumed per smoker, together with a later age at starting regular smoking in the south may have been more important than the prevalence of smokers *per se* [4].

In more recent decades this pattern has been totally reversed, and in the early 1980s smoking prevalence among males was substantially higher in southern than in northern areas [9]. This is well reflected in the widening of the north/south difference between the late 1960s and the mid 1970s, followed by a levelling off over more recent calendar years.

In a sense, the information given by inspection of mortality rates in the younger age groups is even more important. Although absolute numbers are extremely low, lung cancer mortality is between 25 and 34 years now higher in the south than in the north, and in the subsequent 35–44 age groups rates are now comparable. Besides *a posteriori* reflecting the pattern of tendencies observed in smoking prevalence, trends in the young offer useful indications on the most likely future patterns of trends in lung cancer [10].

Among females, smoking is a recent habit in Italy, particularly in the south where only very recently an appreciable proportion of young women started to smoke (i.e. 26% in the age group 20–29 in 1986–1987 [9]). Not surprisingly, therefore, the north/south differences have been widening considerably in most of the birth cohorts and only in the south have females lung cancer rates increased in the generations born after 1950, when the impact of smoking is relatively limited compared to the much longer exposure to other environmental carcinogens [11].

Most of this discussion of trends in lung cancer has been related to patterns of cigarette smoking in various Italian areas, since tobacco smoking nowadays accounts for over 85% of lung

Table 3. Summary trends in age standardised sex ratios (males to females) for lung cancer in selected Italian geographical areas*, 1969–1987

Calendar period	North, age group 0–84	North 35–64	North 35–44	Centre, age group 0–84	Centre 35–64	Centre 35–44	South, age group 0–84	South 35–64	South 35–44
1969–1974	8.4	9.3	6.2	7.6	7.7	4.6	7.7	7.8	4.2
1975–1979	9.8	9.4	5.8	8.5	8.7	5.8	8.6	8.9	5.4
1980–1984	9.0	9.7	5.7	8.4	8.3	5.2	9.5	10.2	5.1
1985–1987	8.2	8.6	4.6	7.8	8.0	4.4	9.9	10.2	4.8

*On the World Standard Population.

cancer deaths in males and approximately 50% in females [12]. The observation that shifts in smoking habits well explain the different patterns of trends in lung cancer mortality in various Italian geographical areas does not exclude some influence by other, mainly occupational, lung carcinogens. It nevertheless provides further confirmation of the central role of cigarette smoking on lung cancer rates in various populations and geographical areas.

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Evidence for Bimodal Distribution of Breast Carcinoma ER and PgR Values Quantitated by Enzyme Immunoassay

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Breast carcinoma oestrogen receptor (ER) and progesterone receptor (PgR) values obtained by radioligand binding assays have commonly been observed to have approximate log-normal distributions. We examined the distribution of log-transformed receptor values obtained by enzyme immunoassay for 5468 primary breast carcinomas in five Ontario laboratories. In each laboratory, it was found that the frequency histograms for the log transformed receptor values were not unimodal, and generally were suggestive of bimodality. This was not affected by stratification by age or inferred menopausal status (≤ 49, ≥ 50 years), and could not be explained by kit characteristics. However, the low point in the distribution varied from 5 to 63 fmol/mg cytosol protein, depending on the receptor, patient age and laboratory. The tendency towards biomodality was more distinct for ER than for PgR. It remains to be determined whether the low points on the frequency histograms have clinical relevance for discriminating between hormone-sensitive and hormone-insensitive tumours.
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INTRODUCTION

QUANTITATION OF the oestrogen and progesterone receptor (ER and PgR) content of breast carcinomas is well recognised as an aid in the management of breast cancer patients. Until recently, measurement of steroid receptor concentration has relied on the use of radioligand binding methods (RBA), in which the radiolabelled steroid is bound to the steroid binding site of the receptor protein. It has been observed that the distribution of receptor values in large populations of tumours assayed by this method is markedly skewed. This asymmetry may be reduced with a logarithmic transformation ([1, 2] and our own unpublished data).

Recently, receptor assays using monoclonal antibodies to epitopes on the receptor protein other than the steroid binding site have been developed. These have a number of technical advantages over radioligand binding methods [3, 4]. Many