ation of cytosolic sulfotransferase activities in MCF-7 human breast carcinoma cells. *J Steroid Biochem Molec Biol* 1993, **46**, 481–487.
18. Tormey DC, Lippman ME, Edwards BK, Cassidy JG. Evaluation of tamoxifen doses with and without fluoxymesterone in advanced breast cancer. *Ann Int Med* 1983, **98**, 139–144.
19. Bamforth KJ, Dalgliesh K, Coughtrie MWH. Inhibition of human liver steroid sulfotransferase activities by drugs: a novel mechanism of drug toxicity? *Eur J Pharmacol* 1992, **228**, 15–21.
20. Hochberg RB, Ladany S, Welch M, Lieberman S. Cholesterol and cholesterol sulfate as substrates for the adrenal side-chain cleavage enzyme. *Biochemistry* 1974, **13**, 1938–1945.
21. Askoy IA, Otterness DM, Weinshilboum RM. Cholesterol sulfation in human liver. Catalysis by dehydroepiandrosterone sulfotransferase. *Drug Metab Dispos* 1993, **21**, 268–276.

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# Estimating Completeness of Cancer Registration in Saarland/Germany With Capture–Recapture Methods

**H. Brenner, C. Stegmaier and H. Ziegler**

**Completeness of population-based cancer registration has been most commonly quantified by indirect measures, such as the death certificate only index or the mortality/incidence ratio. A major disadvantage of these measures is their strong dependence on the case fatality rate. Capture–recapture methodology offers an approach to estimate completeness directly which does not share this limitation. In this paper, a three-sources modelling approach is employed to derive estimates of completeness for the population-based cancer registry of Saarland. Overall, completeness is found to be high: estimates for all types of cancer range from 95.5 to 96.9% for calendar years 1970, 1975, 1980 and 1985. There is some variation with age (consistently high levels above age 30 years, a minimum of 87.7% in age group 15–29 years) and between cancer sites. Among the most common cancer sites, estimates of completeness are highest for gastrointestinal cancers (97.2%) and breast cancer (97.1%), while lower estimates of completeness are derived for cancers of the female genital organs (92.5%), the urinary tract (91.8%) and the prostate (91.0%). Although capture–recapture estimates are sensitive to the underlying assumptions about dependence between sources, careful application is encouraged to supplement traditional methods for evaluating completeness of cancer registration.**

**Key words: cancer registries, capture–recapture methods, completeness, epidemiological methods**
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## INTRODUCTION

THE COMPLETENESS of case ascertainment by population-based cancer registries is most commonly measured by the death certificate only index (DCO index) or by the mortality/incidence ratio (M/I ratio) [1]. For example, these measures are routinely employed as indicators of completeness in *Cancer Incidence in Five Continents*, a widely used series of volumes providing compilations of cancer incidence data from population-based cancer registries all over the world [2–5]. The DCO index quantifies the proportion of cases which are identified exclusively on the basis of the death certificate. It is an indirect measure of completeness which strongly depends, among other things, on the case fatality rate of cancers. The same limitation obviously applies to the M/I ratio. Nevertheless, these measures can be useful for comparing completeness of registration for cancers with similar case fatality rates.

However, it may often be preferable to obtain direct estimates of completeness of cancer registration which do not depend on case fatality rates. Such estimates are straightforward in situations in which there is an independent source of case

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ascertainment [6]. In such situations, completeness can be estimated by the proportion of cases also identified by the cancer registry among cases ascertained by the independent source. Although this method has repeatedly been employed (e.g. [8–11]), it can rarely be used for standard comparisons between registries, since such independent sources are often unavailable. Even if such sources exist, they are often incomplete themselves and not representative of all cases.

Recently, capture–recapture methods have gained increasing popularity in epidemiology as a tool to derive direct estimates of completeness of disease registration [7–19]. Capture–recapture methodology is a widely used tool in wildlife sciences for estimating the size of free-living animal populations [20]. In short, the principle is as follows: sequential independent samples of animals are captured and tagged, and the size of the animal population is estimated from the numbers of animals captured and recaptured in overlapping samples. An analogous approach may be employed to estimate the total number of cases in epidemiological monitoring of disease in that cases notified by various incomplete sources are regarded as overlapping samples from the entire "population" of cases.

In this paper, we present estimates of completeness of the population-based cancer registry of Saarland/Germany using capture-recapture methodology. The DCO index is presented for comparison, and use and limitations of various approaches to estimate completeness are discussed.

## MATERIALS AND METHODS

The cancer registry of Saarland, which has been operating since 1966, covers incident cases of cancer in Saarland, a small, highly industrialised state in southwest Germany with a population of about 1.05 million people. The cancer registry of Saarland is the only population-based cancer registry within the western part of Germany that met the inclusion criteria for all of the latest three volumes of *Cancer Incidence in Five Continents* [3–5]. There are multiple sources of notification including clinicians, general practitioners and pathologists. In addition, all death certificates of residents of Saarland are linked with the cancer registry to enable follow-up of cancer patients and to supplement the database by cancer cases not previously notified to the registry.

This analysis is based on incident cases of malignant neoplasms (ICD-9 positions 140-208), excluding non-melanoma skin cancer (ICD-9 position 173), diagnosed in 1970, 1975, 1980, 1985 and 1990. Exclusion of non-melanoma skin cancer is common practice in reports of cancer incidence due to the notorious under-reporting of this type of cancer. All cases were categorised according to notification by one or several of the following main sources of notifications: (1) clinicians, (2) pathologists, and (3) death certificates. Notifications by general practitioners were combined with notifications by clinicians in the first category, since their numbers were relatively small compared to the notifications by other sources. Each notified case can either be included or not in each of the individual categories, but registration is incomplete with regard to cases missed by all three sources. Therefore, there are $2^3 - 1 = 7$ possible combinations of sources of notification for which the case numbers are known, whereas there is an unknown number of cases missed by all three sources.

The analysis followed a procedure outlined by Bishop and colleagues [21] in which log-linear models are fit to the known case numbers for the former seven combinations (which are assumed to arise from Poisson distributions), with dichotomous indicators for presence or absence in each source as independent variables. The parameter estimates are then used to estimate the number of unregistered cases which provides the basis for estimating completeness of registration. The analyses started from a saturated model that contains an intercept term, the three indicators and all possible interaction terms between pairs of these indicators. Two-factor interaction terms were iteratively excluded from the model in a backward elimination strategy based on likelihood ratio tests ($\alpha = 0.05$) to derive more precise estimates of completeness, if possible. Separate models were fit for individual calendar years, age categories, cancer sites (grouped into broad categories to minimise problems of diagnostic misclassification) and administrative districts. The analyses were carried out using the software package GLIM [22]. The capture–recapture estimates of completeness were compared with the DCO index as a commonly used indicator of incompleteness. The DCO index was calculated as the proportion of patients notified by death certificates only among all patients notified by clinicians, pathologists or death certificates.

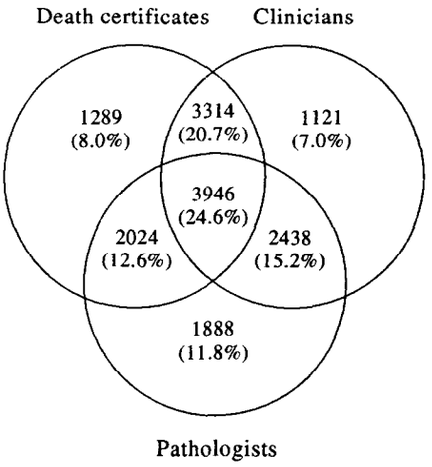


**Figure 1. Cancer cases reported to the cancer registry of Saarland in 1970, 1975, 1980 and 1985 by clinicians, pathologists and death certificates.**

## RESULTS

Figure 1 depicts the numbers of cancer cases registered in Saarland in 1970, 1975, 1980 and 1985 by death certificates, clinicians and pathologists. While the majority of cases is reported by more than one of these sources, it is evident that each individual source contributes a substantial number of cases that would not be reported by the other two sources. For example, 1289 cases were reported by the death certificate only, which corresponds to a DCO index of 8.0% among these patients.

Table 1 shows the capture–recapture estimates of complete-

*Table 1. Capture–recapture estimates of completeness of the Saarland cancer registry by calendar year*

| Calendar year | No.* | Completeness (95% CI) | DCO index (%) |
|---|---|---|---|
| 1970 | 3505 | 0.955 (0.945–0.963) | 9.1 |
| 1975 | 3980 | 0.969 (0.961–0.976) | 6.3 |
| 1980 | 4120 | 0.957 (0.949–0.964) | 9.9 |
| 1985 | 4478 | 0.963 (0.953–0.970) | 7.0 |
| 1990 | 4658 | 0.881 (0.852–0.906) | 8.5 |

*Total number of registered cases. DCO, death certificate only.

*Table 2. Capture–recapture estimates of completeness of the Saarland cancer registry by age for calendar years* 1970, 1975, 1980 *and* 1985

| Age (years) | No.* | Completeness (95%CI) | DCO index (%) |
|---|---|---|---|
| 0–14 | 90 | 0.937 (0.885–0.966) | 5.6 |
| 15–29 | 236 | 0.877 (0.827–0.914) | 2.1 |
| 30–44 | 1007 | 0.943 (0.930–0.954) | 3.1 |
| 45–59 | 3529 | 0.964 (0.955–0.971) | 3.3 |
| 60–74 | 7221 | 0.970 (0.964–0.975) | 7.3 |
| ≥75 | 3999 | 0.958 (0.947–0.967) | 15.1 |

*Total number of registered cases. DCO, death certificate only.

ness for all sites of cancer by calendar year. Completeness is estimated to be in a narrow range between 95.5 and 96.9% for 1970, 1975, 1980 and 1985. For 1990, the estimate is considerably lower: 88.1% (95% confidence interval, 85.2–90.6%). Since there is often a long latency period between tumour diagnosis and eventual inclusion in the registry data base, this low value most likely reflects delay of reporting rather than underreporting (only notifications included in the database by early 1993 contributed to this investigation). For this reason, the year 1990 was excluded from all other analyses. The DCO index ranged from 6.3% in 1975 to 9.9% in 1980.

Stratification by age yielded consistently high estimates of completeness around 95% for patients above the age of 30 (Table 2). Lower estimates were obtained for the age groups 0–14 and 15–29, but these estimates are rather imprecise due to the small numbers of cases in these age groups. The DCO index was lowest for 15–29 year olds (2.1%). It strongly increased with age and reached a maximum of 15.1% in the population above age 75.

There was also some variation in estimated completeness between the most common diagnostic groups (Table 3). Notification of gastrointestinal cancers and of breast cancer was estimated to be 97% complete, while lower levels between 90 and 95% were estimated for cancer of the female genital tract, the prostate and the urinary tract. Even slightly lower values were estimated for some of the less common cancers not included in Table 3, such as cancer of the nervous system (85.8%) or cancer of the lymphatic or haematopoietic tissue (89.2%). An analogous analysis for non-melanoma skin cancer (ICD-9 position 173), which was excluded from all other analyses, yielded an estimate of completeness of only 27.2% (95% confidence interval, 9.8–56.3%). The DCO index for the most common cancers included in Table 3 varied between 2.7% for breast cancer and 11.2% for cancers of the lower respiratory tract.

Additional analyses, in which separate capture–recapture estimates of completeness were derived for the seven administrative districts of Saarland, did not reveal any major regional variation of completeness. Estimates ranged from 97.2% for the capital Saarbrücken to 93.2% for the Saar-Pfalz-Kreis, a more rural administrative district in southeast Saarland.

## DISCUSSION

Our analyses confirm the conclusion based on traditional measures of completeness of a high standard of cancer registration in Saarland: overall completeness is estimated to be around 96%, with some variation with age and between cancer sites, but very little variation over time and between different regions. This temporal and regional stability is reassuring with respect to the use of the cancer registry for monitoring cancer incidence in Saarland.

Despite high levels of overall completeness, completeness was estimated to be less satisfactory in some subgroups of patients. The low estimate of completeness (87.7%) in age group 15–29 years may seem surprising at first. An explanation could be a better prognosis of cancers in this age group, so that only a minority of cases missed by other sources is notified by death certificates. In addition, the imprecision of this estimate of completeness, which is due to the small number of cases in this age group, has to be taken into account (95% confidence interval, 82.7–91.4%). The differences in estimates between various cancer sites are not easily explained. They could reflect differences in participation in cancer registration between physicians of various specialities. The extremely low estimate of completeness of non-melanoma skin cancer adds further justification for the exclusion of this type of cancer from routine reports of cancer incidence as well as from other analyses in this study.

Our results also emphasise the value of multiple sources of notification to achieve high levels of completeness: for example, without access to death certificates or reports from pathologists, completeness would have been about 8 or 12% lower, respectively. This has important implications for the planning of new cancer registries in which such access is hindered by overly restrictive confidentiality rules in many instances.

In the interpretation of our results, a major limitation of capture–recapture methodology has to be taken into account:

*Table 3. Capture–recepture estimates of completeness of the Saarland cancer registry by cancer site for calendar years* 1970, 1975, 1980 *and* 1985

| Cancer site | ICD-9 | No.* | Completeness (95% CI) | DCO index (%) |
|---|---|---|---|---|
| Gastrointestinal tract | 150–154 | 3867 | 0.972 (0.964–0.978) | 8.0 |
| Trachea, bronchus, lung, pleura | 162, 163, 165 | 2265 | 0.963 (0.949–0.973) | 11.2 |
| Breast | 174–175 | 1999 | 0.971 (0.964–0.977) | 2.7 |
| Female genital organs | 179–184 | 1624 | 0.925 (0.888–0.951) | 3.6 |
| Prostate | 185 | 882 | 0.910 (0.880–0.933) | 7.6 |
| Urinary tract | 188–189 | 973 | 0.918 (0.891–0.939) | 5.8 |
| All sites† | 140–208† | 16083 | 0.961 (0.956–0.965) | 8.0 |

*Total number of registered cases. †Excluding non-melanoma skin cancer (ICD-9 position 173). DCO, death certificates only.

the estimate of the number of unregistered cases is based on extrapolation from models that are fit to the observed numbers of registered cases. Such extrapolation always carries some dangers. More formally, an implicit assumption in the models used in this paper is the assumption of absence of any three-source interaction between sources of notification. There is no way to check this assumption, since a three-source interaction cannot be included in the models which are saturated when all two-source interaction terms are included. Therefore, mechanisms that might simultaneously preclude cases from registration by all three sources could remain undetected and potentially lead to overoptimistic estimates of registry completeness. This problem is of particular concern among older patients, who are often not referred for comprehensive diagnostic or therapeutic measures by clinicians, and, as a consequence, are also less likely to have cancer diagnoses verified histologically and to have cancer certified as the underlying cause of death on death certificates. This may partly explain the surprisingly high estimates of completeness among the elderly in our analysis. Similarly, in the cancer registry of Saarland, one source of dependence of notifications is introduced by the fact that arrival of a death certificate for a previously unregistered case initiates efforts to obtain an additional notification from the clinician who filled out the death certificate. This may also have lead to some overestimation of completeness in our analysis.

Nevertheless, the three-sources method used in this paper is less sensitive to dependence of ascertainment between sources than the capture–recapture approach based on two sources of notification only, because two-source interactions can be taken into account in the analysis. With the two-sources capture–recapture method, which has been more commonly employed in the context of disease monitoring in the past, one has to make the stronger assumption of independence of notification between those two sources.

An additional limitation of the site-specific capture–recapture estimates of completeness which is shared with other site-specific indices of completeness of cancer registration arises from the well-known inaccuracies of diagnoses on death certificates [23–26]. In our analysis, this problem was minimised by combining types of cancer into common groups between which misclassification has been shown to be frequent, such as colon and rectal cancer, or cervical and endometrial cancer.

Our analyses also point to a further limitation of the capture–recapture approach based on death certificates as one source of notifications. Since many patients die years after their diagnosis, registration of cases remains incomplete for recent years whenever a sizeable proportion of patients is notified by death certificates only. This reduces the use of the capture–recapture approach for timely monitoring of completeness of cancer registration.

Despite these limitations, the capture–recapture approach has some important advantages over traditional, indirect indices of completeness, such as the DCO index or the M/I ratio. Unlike these measures, the capture–recapture approach estimates completeness independently from the case fatality rate, which allows comparisons of completeness of registration even for cancers with different prognosis. This is an important feature for regional and temporal monitoring of cancer incidence, since the case fatality rates strongly vary between types of cancer, between populations, between age groups and over time. For example, variation of the DCO index between cancer sites, which ranged from 2.7% for breast cancer to 11.2% for cancers of the lower respiratory tract in this study, primarily reflects differences in prognosis. Similarly, the high DCO rate in the population above the age of 75 may, at least partly, be due to high case fatality rates in this age group.

Therefore, despite its limitations, we encourage more frequent albeit careful use of the capture–recapture approach in estimating completeness of cancer registration. Implementation is straightforward in many instances since this approach is using data routinely collected by many registries, without the need for a special survey. Nevertheless, the underlying assumptions and possible mechanisms that might lead to their eventual violation require critical discussion. Furthermore, the performance of capture–recapture methods and other indicators of completeness should be checked against enumeration of cases by alternative, independent sources whenever such sources are available. Such investigations may help to obtain a clearer picture of the validity of the capture–recapture approach.


1. Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG eds. *Cancer Registration: Principles and Methods* (IARC Scientific Publications No. 95). Lyon, International Agency for Research on Cancer, 1991.
2. Waterhouse JAH, Muir C, Correa P, Powell J. *Cancer Incidence in Five Continents*, Vol. III (IARC Scientific Publications No. 15). Lyon, International Agency for Research on Cancer, 1976.
3. Waterhouse J, Muir C, Shanmugaratnam K, Powell J. *Cancer Incidence in Five Continents*, Vol. IV (IARC Scientific Publications No. 42). Lyon, International Agency for Research on Cancer, 1982.
4. Muir C, Waterhouse J, Mack T, Powell J, Whelan S. *Cancer Incidence in Five Continents*, Vol. V (IARC Scientific Publications No. 88). Lyon, International Agency for Research on Cancer, 1988.
5. Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J. *Cancer Incidence in Five Continents*, Vol. VI (IARC Scientific Publications No. 120). Lyon, International Agency for Research on Cancer, 1992.
6. Goldberg J, Gelfand HM, Levy PS. Registry evaluation methods: a review and a case study. *Epidemiol Rev* 1980, **2**, 210–220.
7. Wittes J, Sidel VW. A generalization of the simple capture–recapture model with applications to epidemiological research. *J Chron Dis* 1968, **21**, 287–301.
8. Wittes JT, Colton T, Sidel VW. Capture–recapture methods for assessing the completeness of case ascertainment when using multiple information sources. *J Chron Dis* 1974, **27**, 25–36.
9. Hook EB, Albright SG, Cross PK. Use of Bernoulli census and log-linear methods for estimating the prevalence of spina bifida in livebirths and the completeness of vital records reports in New York State. *Am J Epidemiol* 1980, **112**, 750–758.
10. Hook EB, Regal RR. Validity of Bernoulli census, log-linear, and truncated binomial models for correcting for underestimates in prevalence studies. *Am J Epidemiol* 1982, **116**, 168–176.
11. Neugebauer R. Application of a capture-recapture method (the Bernoulli census) to historical epidemiology. *Am J Epidemiol* 1984, **120**, 626–634.
12. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture–recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988, **41**, 495–501.
13. Cochi SL, Edmonds LE, Dyer K, *et al.* Congenital rubella syndrome in the United States, 1970–1985. *Am J Epidemiol* 1989, **129**, 349–361.
14. Frischer M, Bloor M, Finlay A, *et al.* A new method of estimating prevalence of injecting drug use in an urban population: results from a Scottish city. *Int J Epidemiol* 1991, **20**, 997–1000.
15. Hilsenbeck SG, Kurucz C, Duncan RC. Estimation of completeness and adjustment of age-specific and age-standardized incidence rates. *Biometrics* 1992, **48**, 1249–1262.
16. Laporte RE, Tull ES, McCarty D. Monitoring the incidence of myocardial infarctions: applications of capture–mark–recapture technology. *Int J Epidemiol* 1992, **21**, 258–263.
17. Hook EB, Regal RR. The value of capture–recapture methods even for apparent exhaustive surveys. The need for adjustment for source of ascertainment intersection in attempted complete prevalence studies. *Am J Epidemiol* 1992, **135**, 1060–1067.

18. McCarty DJ, Tull ES, Moy CS, Kwoh CK, LaPorte RE. Ascertainment corrected rates: applications of capture–recepture methods. *Int J Epidemiol* 1993, **22**, 559–565.
19. Frischer M, Leyland A, Cormack R, *et al.* Estimating the population prevalence of injection drug use and infection with human immunodeficiency virus among injection drug users in Glasgow, Scotland. *Am J Epidemiol* 1993, **138**, 170–181.
20. Cormack RM. The statistics of capture–recapture methods. *Oceanogr Mar Biol Ann Rev* 1968, **6**, 455–506.
21. Bishop YMM, Fienberg SE, Holland PW. *Discrete Multivariate Analysis: Theory and Practice*. Cambridge, Massachussetts, MIT Press, 1975.
22. Payne CD, ed. *The GLIM Systems Release* 3.77. *Generalized Linear Interactive Modelling Manual*. Oxford, Numerical Algorithms Group, 1986.
23. Barclay THC, Phillips AJ. The accuracy of cancer diagnosis on death certificates. *Cancer* 1962, **15**, 5–9.
24. De Faire U, Friberg L, Lorich U, Lundman T. A validation of cause-of-death certification in 1156 deaths. *Acta Med Scand* 1976, **200**, 223–228.
25. Percy C, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981, **71**, 242–250.
26. Reynolds DL, Nguyen VC, Clarke EA. Reliability of cancer mortality statistics in Ontario: a comparison of incident and death diagnoses, 1979–1983. *Can J Publ Health* 1991, **82**, 120–126.

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# Modulation of Bcl-2 and Ki-67 Expression in Oestrogen Receptor-positive Human Breast Cancer by Tamoxifen

**S.R.D. Johnston, K.A. MacLennan, N.P.M. Sacks, J. Salter, I.E. Smith and M. Dowsett**

**The expression of the *bcl*-2 proto-oncogene, which is associated with prolonged cell survival and prevention of programmed cell death, was investigated in human primary breast carcinomas prior to and following endocrine therapy with the anti-oestrogen, tamoxifen. Using the BCL-2-100 antibody, a 26-kD protein was detected by western immunoblot in the cytosols of oestrogen receptor (ER)+ve human breast cancers. In a cross-sectional study, the immunohistochemical expression of Bcl-2 was observed in 32% of invasive breast cancers, but in 65% of tumours treated with tamoxifen ($P = 0.009$). There was a significant association of Bcl-2 with ER status, with 64% of untreated and 88% of tamoxifen-treated Bcl-2-positive tumours being ER+ve. A significantly lower Ki-67 score was found in tamoxifen-treated tumours which were Bcl-2-positive compared with Bcl-2-negative (9.3 versus 24.6%, $P = 0.01$). In a separate series of sequential Trucut biopsies from 18 patients, the frequency of Bcl-2 expression was increased in ER+ve tumours from 3/12 to 8/11 following tamoxifen ($P = 0.04$). This was also associated with a significant reduction in mean Ki-67 score from 32 to 12% ($P = 0.0004$). The observations from this study clearly indicate that Bcl-2 in human breast cancer is associated with ER status, and that expression is enhanced in ER+ve tumours following tamoxifen, in association with reduced cell proliferation.**

**Key words: Bcl-2, breast cancer, tamoxifen, oestrogen receptor, Ki-67**
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## INTRODUCTION

THE *bcl*-2 proto-oncogene encodes a 26-kD protein localised at the inner mitochondrial membrane [1, 2] whose expression appears to block programmed cell death (apoptosis) in certain haemopoietic cell lines [3]. Subsequent immunohistochemical studies have shown the Bcl-2 protein to be expressed in a high percentage of follicular lymphomas which are associated with a t(14;18) reciprocal chromosomal translocation [4, 5]. In a number of non-lymphoid tissues, which are all characterised by cell turnover involving apoptosis, Bcl-2 expression can be demonstrated in cells at particular stages of differentiation [6]. These tissues include complex differentiated epithelia, such as the skin and gastrointestinal tract, in addition to hormonally-regulated glandular epithelia, such as thyroid, prostate and breast. During the normal ovulatory cycle, the breast epithelium undergoes hyperplasia and involution which involves apoptosis [7], and Bcl-2 expression has been observed within premenopausal ductal epithelial cells [6].

In view of the relationship between Bcl-2 expression and prolonged cell survival, together with the evidence for its