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Dysplasia and the Natural History of Cervical Cancer: Early Results of the Toronto Cohort Study

Steven A. Narod, D.W. Thompson, M. Jain, Claus Wall, Lois M. Green and Anthony B. Miller

A sample of 176 808 Pap smears, taken from 70 236 women, was constructed from the records of a large cytopathology laboratory between 1962 and 1981. The prevalence of cervical dysplasia, based on the distribution of initial smear results, rose from 42.7 to 94.9 per 1000 during the study period. The relative risks (RR) for the manifestation of a malignancy (carcinoma *in situ* or worse) in a subsequent cervical smear were 1.48, 3.42, 20.9 and 71.5 for women with minimal, mild, moderate and severe dysplasia, respectively, compared with the entire cohort. The initial degree of dysplasia for women developing a malignancy was much more likely to be interpreted as moderate (RR = 5.0) or severe (RR = 42.3) than were those for controls. These results are strongly supportive of the hypothesis that the degree of dysplasia is related to the risk of development of cancer of the cervix.
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INTRODUCTION

SCREENING FOR cancer of the cervix is based on the premise that there is a natural progression from a normal cervical epithelium through dysplasia to carcinoma *in situ* to invasive cancer of the cervix, and that if individuals could be identified and treated early in this process, progression to invasive disease could be prevented. A successful community-based screening program should ultimately lead to a decrease in the incidence of cervical cancer and reduced mortality from the disease. The Canadian Task Force on Cervical Cancer Screening [1] supported cytological screening programs for women who have had sexual intercourse, and recommended that annual screens be performed between the ages of 18 and 35 years, and every 5 years thereafter until age 60, providing the results of satisfactory smears are negative. Consensus regarding the ideal screening interval has not been achieved, possibly because the natural history of carcinoma of the cervix at different ages is not entirely clarified.

Several studies have demonstrated that the cumulative incidence of preneoplastic lesions exceeds the expected incidence of invasive disease [2–5], and spontaneous regression of some early lesions has been demonstrated [5]. The optimum screening interval would be ideally estimated from data generated by a controlled trial, but as such a study is unlikely to occur, results from non-experimental designs must suffice.

An unusual opportunity for review of preneoplastic abnormalities of cervical epithelium was available through the experience of a large laboratory in Toronto during the period 1962 to 1981. Pap smears had been performed on a large part of the

female population in metropolitan Toronto, processed in a uniform manner and supervised by cytopathologists associated with university affiliated hospitals. A detailed diagnostic system was uniformly applied, which classified dysplasia into minimal, mild, moderate and severe degrees. The period 1962–1981 coincided with the decline in the use of cervical conisation procedures and was largely prior to the widespread acceptance of diagnostic colposcopy, cryotherapy and laser techniques for very localised or for lesser degrees of epithelial abnormality. In the interval under assessment, there was a rapid build-up of the proportion of women previously screened, and of the proportion in the younger age groups. This coincided with an increasing proportion of cases with lesser degrees of abnormality. These cases were generally monitored cytologically by repeat assessment until progression to more significant abnormality had been demonstrated. It is this monitored group that is the main subject of this report. In an attempt to clarify the natural history of cervical dysplasia, and to investigate the relationship between degree of dysplasia and the subsequent risk of progression, we have analysed a large sample of the Pap smear results generated by this single large Toronto laboratory between the years 1962 and 1981.

PATIENTS AND METHODS

The population base for the study consisted of all Toronto area women for whom Pap smears were submitted to Cytopathology Associates laboratory between 1962 and 1981. This service was established in 1962 and has since recorded over 2 000 000 cervical smears, representing approximately 35% of all smears originating in the Toronto area. Information was provided by the referring physician on the date of the smear, data of birth, address, the clinical diagnosis (if not part of a routine screen), and the recent use of oral contraceptives. Physicians were asked to indicate if the woman had been previously screened.

Information regarding sexual activity or smoking was not supplied. Specimens were interpreted and reported in a uniform manner by 1 of 20 cytopathologists associated with the laboratory. Abnormalities were classified as benign (non-dysplastic) atypia, dysplasia (minimal, mild, moderate or severe) or malignant (carcinoma *in situ*, adenocarcinoma, squamous carcinoma or malignant, unspecified) in accordance with the subsequent recommendations of the Canadian Task Force on Screening for Cervical Cancer [1]. For the purposes of this study, histological reports of carcinoma *in situ*, squamous carcinoma and malignancy, unspecified were combined to form a single category (carcinoma *in situ* or worse) indicating the presence of malignant cells. The diagnosis of carcinoma *in situ* used in the analysis was based on the physician's report on a smear subsequent to a biopsy or the follow-up carried out by the laboratory staff.

If the woman had been screened before, the laboratory staff attempted to link the current result with those for smears previously submitted. A patient record was thus created which consisted of all of the cytology reports belonging to a woman during the period. The number of smears comprising such a record in this study ranged between 1 and 25 per person, with a mean of 2.52.

The study population was composed of two overlapping groups. Initially, a random sample of all records was constructed, based on the terminal two digits of the unique laboratory identification number or on the terminal two digits of the Ontario health insurance number for specimens submitted after 1972. This probability sample consisted of approximately 3% of all eligible laboratory records. In addition, all records in which one or more component smears was interpreted as minimal dysplasia or worse were retained. There were 75 585 records in the total sample. A computerised record linkage was then performed on the combined sample in order to uncover any duplicate records not identified by the laboratory. This linkage, based on the Ontario health insurance number, reduced the total number of study subjects to 70 236. Of these, 20 461 women had been selected at random, and a further 49 775 women added because of a cytological diagnosis of dysplasia.

This sampling strategy was chosen in order to address two types of questions. The random sample was useful in estimating both the prevalence and incidence of cervical dysplasia in the general (screened) population, and the sample of abnormal tests was created in order to accurately estimate the risk of progression from dysplasia to cervical malignancy. Because of the rarity of cervical cancer, an accurate estimate of its incidence was not possible using the probability sample alone. As discussed above, this study population provides a unique experience to assess the probability of progression to carcinoma *in situ* or worse, uninfluenced by any procedure other than repeat smear examinations. Towards the end of the time period, follow-up colposcopy and early therapeutic intervention was more generally available for those with cytologically detected dysplasia.

Prospective study

The prevalence of cervical dysplasia was estimated by tabulating the distribution of initial smears for women in the probability sample. Incidence rates were calculated using the life-table method, both for persons with normal smears and for persons with cervical dysplasia. For the estimation of rates of dysplasia and invasive cancer among initially normal women, the probability sample was used, but to estimate the risk of progression from dysplasia to more advanced disease, results from the entire cohort were considered. Person-years were accumulated from the date of the initial smear or from the date when a more advanced stage was first documented, depending on the condition under consideration. After a report of an abnormal smear, a woman was no longer eligible to re-enter the cohort of normal women. Person-years at risk for women with dysplasia were accumulated from the date of the first dysplastic smear, including those for women whose first documented smear was reported as dysplastic. A woman was considered at risk until either the date of the last recorded smear, or until the endpoint of interest (or a more advanced stage) was reached. Although it is recognised that the actual development of dysplasia occurred at some time during the interval between the diagnostic and the preceding smear, for simplicity, the date of the abnormal smear was used. The endpoint of malignancy was ascertained either by the cytological interpretation or through the physician report. The distinction between carcinoma *in situ* and invasive carcinoma was based in the analysis upon clinical information supplied by the physician. Because the diagnosis of carcinoma *in situ* is generally made by colposcopy or biopsy subsequent to an

Correspondence to A.B. Miller.
S.A. Narod is at the McGill Centre for Human Genetics, Montreal General Hospital, 1650 Cedar Avenue, Montreal H3G 1A4; D.W. Thompson is at the Department of Pathology and Department of Obstetrics and Gynecology, Toronto General Hospital; M. Jain, C. Wall and L.M. Green are at the National Cancer Institute of Canada, Epidemiology Unit; and A.B. Miller is at the Department of Preventive Medicine and Biostatistics, McMurrich Building, University of Toronto, Toronto, Ontario, M5S 1A8, Canada.
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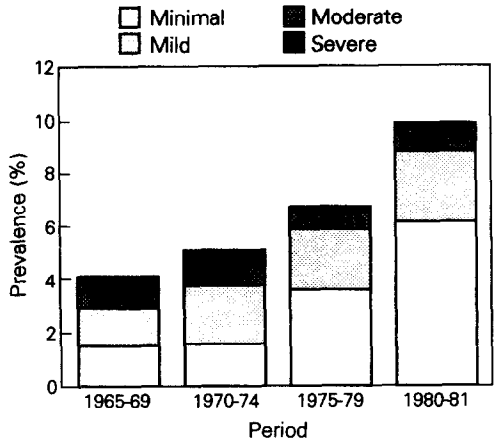

Fig. 1. Prevalence of cervical dysplasia (all types) in cohort by calendar period.

abnormal cervical smear, and the histological report of carcinoma *in situ* in general reflected the cytology of the previous smear, the date of diagnosis for carcinoma *in situ* was taken as the date of the previous smear. An incident case was defined as a malignant smear occuring at some time in a woman whose initial smear was in a category less severe than carcinoma *in situ*.

To assess whether or not a proportion of the incident cases were in fact prevalent cases, with the initial smear falsely interpreted as negative, risk estimates were recalculated using different lead-in times, i.e. person-years of exposure were not accumulated until after the subject had remained in the cohort for a specified period, either 3 or 10 months.

Case-control study

Study subjects could be divided into four groups on the basis of the observed abnormalities during the interval under assessment: (1) women who experienced only normal smears during the period of observation; (2) women who were diagnosed as having a dysplastic abnormality, but did not progress to malignancy (carcinoma *in situ* or worse); (3) women who were diagnosed as having a dysplastic abnormality and subsequently progressed to malignancy; and (4) women who had only a normal smear prior to progression to malignancy.

The general strategy of the retrospective study was to compare the screening histories of women in groups (2) and (3), prior to the discovery of cervical dysplasia. Four subgroups were constructed from women who had initially normal smears and screening patterns were compared: (1) those members of the probability samples who developed cervical dysplasia. Because only 1 woman in this group subsequently developed malignancy, this group was felt to be representative of non-cancer cases; (2) all women with a clinical diagnosis of carcinoma *in situ*; (3) all women with a histological diagnosis of malignant cells on at least one smear; (4) all women with severe dysplasia.

It was possible for women to belong to more than one group.

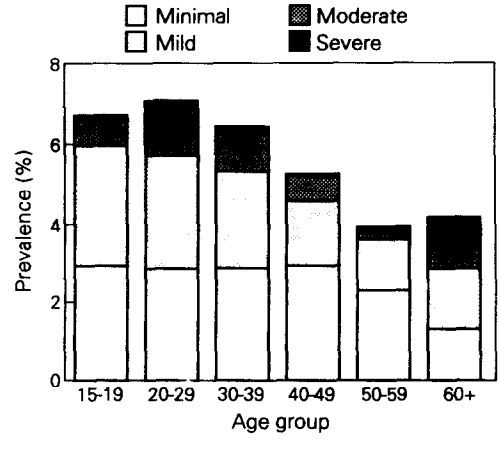

Fig. 2. Prevalence of cervical dysplasia at entry into cohort.

Table 1. Incidence of cervical dysplasia among women with normal smears, 1962–1981

Age group	Cases observed	Person-years at risk	Rate (per 1000/year)
15–19	11	341	32.3
20–29	242	4418	54.8
30–39	181	3738	48.8
40–49	145	3471	41.8
50–59	71	2689	26.4
60–69	29	1016	28.5
70+	10	280	35.7
Total	689	16053	42.9

RESULTS

The prevalence of lesions on first smear increased throughout the study period (see Fig. 1). Most of this increase could be accounted for by an increase in the diagnosis of minimal dysplasia. The increase was seen in all age groups, but was most dramatic for younger women. The proportion of women with abnormalities seen at first smear in women aged 20–29 rose from 2.7% (7/258) to 16.3% (49/229) between 1965 and 1980. Excluding minimal dysplasia, this proportion rose from 2.3% to 8.1% during the period.

The prevalence of milder forms of dysplasia was highest among women aged 15–39 (Fig. 2) but more advanced dysplasia was more common with increased age. Incidence rates for dysplasia peaked in women aged 20–29 (Table 1). The risk of progression from a dysplastic to a malignant smear did not vary substantially between the ages of 30 and 70 (Table 2) but increased dramatically with the grade of dysplasia reported (Table 3), indicating that the current classification was meaningful in predicting outcome. The relative risks for progression to malignancy (compared to the incidence in the control group)

Table 2. Incidence of cervical cancer among women with dysplasia (all types) by age group

Age group	No. of cases	Person-years at risk	Rate (per 100 000/year)
20–29	17	14957	113.7
30–34	36	15743	228.7
40–49	24	13315	180.2
50–59	14	7650	183.0
60–69	6	2204	272.2
70+	5	660	757.5
Total	102	54529	187.1

Table 3. Incidence of cervical cancer among women at different stages of neoplastic progression

Type of smear	No. of cases	Person-years at risk	Rate (per 100 000 per year)	Relative risk (95% CI)
All controls	5	20 976	23.6	1.0
Minimal dysplasia				
Lead in 0 months	8	22 753	35.1	1.48 (0.48, 4.51)
Lead in 3 months	8	20 742	38.5	1.62 (0.53, 4.95)
Lead in 10 months	8	16 590	48.2	2.02 (0.66, 6.18)
Mild dysplasia				
Lead in 0 months	19	23 231	81.5	3.42 (1.28, 9.15)
Lead in 3 months	18	21 396	84.1	3.53 (1.31, 9.51)
Lead in 10 months	17	175 802	96.7	4.06 (1.50, 11.0)
Moderate dysplasia				
Lead in 0 months	56	11 264	497.6	20.9 (8.37, 52.0)
Lead in 3 months	47	10 165	462.3	19.4 (7.73, 48.7)
Lead in 10 months	29	8386	346.6	14.5 (5.62, 37.5)
Severe dysplasia				
Lead in 0 months	46	2697	1706	71.5 (28.4, 179)
Lead in 3 months	32	2460	1301	54.6 (21.3, 140)
Lead in 10 months	23	2059	1117	46.9 (17.8, 123)

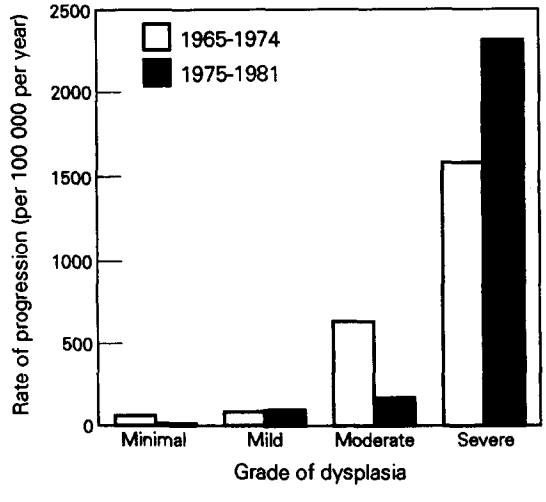

Fig. 3. Incidence of cervical malignancy among women with dysplasia by degree and calendar period.

were 1.48, 3.42, 21.1 and 72.3 for minimal, mild, moderate and severe dysplasia, respectively. These risks were modified somewhat when a lead-in time of 10 months was introduced, the effect being most pronounced for severe dysplasia. This is as expected, because a smear reported as other than cancer (in cases reported on subsequent smears as cancer) is most likely to have been reported as severe dysplasia. 5 cases of cervical cancer were observed in the control group, similar to the 4.85 cases expected when population incidence rates provided by the Ontario Cancer Registry were applied [6].

The probability of progression was greater when dysplasia (all degrees combined) was diagnosed prior to 1975. As shown in Fig. 3, this was largely a result of a markedly reduced risk of progression for women diagnosed with moderate dysplasia.

The screening histories of women who developed cervical malignancy (either a smear showing malignant cells or a subsequent clinical diagnosis of carcinoma *in situ*) were compared with the histories of the entire group. Because of the high risk associated with severe dysplasia seen in the prospective study, women with this finding were also examined. There was little difference in the length of the average screening interval prior to the first abnormality for women who eventually developed malignancy and controls (1.53 years for malignancy vs. 1.43 years for controls, $P = 0.41$). The interval between the last normal smear and the first detected abnormality was in fact longer for control women than for women who developed malignancy ($P < 0.01$). Of the 30 women in the study who were observed to progress after a smear reported as normal, 77% had a normal Pap smear recorded in the 5 years prior to the malignant smear. An intervening smear showing dysplasia was recorded in 15 of these cases. For women who progressed from "normal" to dysplasia to malignancy, the average interval between reported normal smear and malignancy was 5.39 years, whereas the same progression was only 2.59 years in women without a previously reported smear showing dysplasia ($P < 0.01$). The degree of dysplasia initially detected was a strong predictor of progression to malignancy. The odds ratios for the development of malignancy during the period of the study were 5.0 and 42.3 when the first detected abnormalities were moderate and severe dysplasia, respectively, compared to an initial presentation of mild dysplasia. These ratios were consistent with the large risk estimates associated with severity of dysplasia in the life-table analysis.

DISCUSSION

In this study, a data base was created by drawing upon the records of a large laboratory facility. There are several drawbacks to such an approach in the study of the natural history of cervical cancer. The women in our study have all participated in a screening program and are not necessarily typical of the target unscreened population. The average interval between screens in our study was 1.34 years, whereas only 56% of 1060 Toronto women reported previously [7] indicated that they had been screened in the 5-year interval 1973–1976. There is little or no information in this study regarding the treatment received by women with identified lesions and consequently, the natural history of the condition cannot be determined from these records alone. Information on sexual history, smoking and socioeconomic status is not available. The accuracy of the test employed has been shown to be imperfect, false negative tests resulting from poor sampling technique or failure in interpretation [8]. Nevertheless, we feel a laboratory database is valuable when information is provided on a large number of women followed in a uniform manner for a considerable period of time.

The age distribution of dysplasia on entry was similar to the distribution of incidence, and an accumulation of pre-invasive disease with aging was not seen. The prevalence of dysplasia at study entry was much lower than would be expected if our incidence rates are applied to the cohort and an entirely progressive natural history of dysplasia is postulated. This discrepancy is explainable by regression of disease, by prior treatment of dysplasia detected before the study, or by a marked increase in risk profile upon entering the study. The risk for invasive cancer increased greatly with moderate and severe dysplasia, even when the possible effects of false negative smears were limited by a 10 month lead-in time. The IARC Working Group on Cervical Cancer [9] has adopted a more stringent definition of a positive test than ours, as they require confirmation of suspected lesions by a repeat smear. Although we accepted the cytology report on face value, the effect of cytological degree of dysplasia upon outcome was evident.

The IARC Working Group On Cervical Cancer [9, 10] has suggested that by measuring the duration of protection following a negative smear, the optimum screening interval can be obtained. However, the demonstration of a reduced risk of disease following a negative test is not in itself evidence of any benefit attributable to the procedure. Merely identifying a person as not being in a preclinical phase of a disease indicates that such a person has a decreased likelihood of developing invasive disease in the near future, compared to an unscreened individual. This does not depend on the availability of any effective treatment; a normal chest X-ray is predictive of a reduced empiric risk of developing symptomatic lung cancer below that of the general population, some of whom will be harboring detectable preclinical lesions. The size of the apparent protective effect will diminish with time since the most recent screen. This phenomenon has been named by Morrison as the "healthy screenee" effect [11]. Furthermore, it is unclear how the knowledge of the duration of protection following a negative screen is to be used in estimating the ideal screening interval. For example, in the study by MacGregor *et al.* [12], no case of invasive cervical cancer had a negative screen recorded in the year prior to diagnosis. If a minimum of 1 year is required for the progression from cervical dysplasia to invasive cancer, this result is to be expected. It is optimistic to suppose, all factors considered, that annual screening would eliminate the disease. A better approach would be to estimate the risk of invasive cancer following any Pap smear, particularly in circumstances with adequate quality control of sampling and interpretation, according to the presence or absence, and if present, degree of cytological abnormality. Our results suggest that it may be prudent to advise screening often enough to ensure that the first abnormal smear shows minimal change.

In the present study we examined the screening pattern prior to the first dysplastic smear. The small difference in frequency of screening prior to first abnormality could be explained by age alone, older women being less frequently screened (Table 4). Although women who subsequently developed malignancy were much more likely to have an advanced stage of dysplasia detected initially, this was not because a long interval had followed their last screen.

Despite increasing prevalence of preneoplastic disease, the incidence of cervical cancer in Ontario has fallen markedly during the period of study, from 23.81 per 100 000 in 1965 to 12.01 per 100 000 in 1981 [6]. This trend is apparent in all age groups.

Initially, the benefit of cervical screening may have been achieved largely through the detection and treatment of carcinoma *in situ* and microinvasive stages of cancer. However, this study focuses on the earlier phases of cervical epithelial abnormality for which currently detection and therapeutic intervention largely occurs. Our data suggest that the continuing decline may be due in part to an interruption in the rate of progression of severe dysplasia, once established, possibly by the introduction of more effective therapy.

Because this study population was part of an "unorganised" programme of cervical screening (i.e. there is no system in place in Ontario to ensure that identified women return regularly for repeat examination, as recommended by Hakama *et al.* [13], a number of women were precluded from observation. We therefore propose to link this study cohort to the Ontario Cancer Registry to identify recently diagnosed cases of *in situ* and invasive cancer of the cervix. This expanded data file will enable us to further explore some of the issues raised by this analysis.

In conclusion, data from this cohort of women support the belief that cervical dysplasia is a risk factor for subsequent malignancy, and that severe dysplasia confers the greatest risk.

Table 4. Comparison of screening histories of women with initially normal smears developing different stages of neoplasia

	Study group			
	Controls	Severe dysplasia	Carcinoma *in situ*	Malignant cells
No.	942	392	178	30
Age at first screen (years)	36.0	33.3	32.7	42.6
Age at first abnormal smear (years)	37.3	36.0	35.3	45.9
Proportion of women whose first detected abnormality was				
Mild dysplasia	0.90	*	0.36	0.53
Moderate dysplasia	0.09	*	0.46	0.27
Severe dysplasia	0.008	*	0.18	0.20
Average screening interval prior to the first abnormality (years)				
All ages	1.43	1.35	1.43	1.53
Ages 20–30	1.2	1.3	1.4	1.3
30–40	1.5	1.4	1.5	1.5
40–50	1.5	1.5	1.5	1.3
50+	1.5	2.0	1.3	2.3
Average time elapsed between last reported normal smear and first dysplastic smear (years)	1.77	1.65	1.51	1.56

*These figures are not provided because the method of ascertainment would cause women presenting with severe dysplasia to be over-represented.

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HIV-Associated Lymphoma: Histopathology and Association with Epstein–Barr Virus Genome Related to Clinical, Immunological and Prognostic Features

Court Pedersen, Jan Gerstoft, Jens D. Lundgren, Peter Skinhøj, Jette Bøttzauw, Christian Geisler, Stephen J. Hamilton-Dutoit, Søren Thorsen, Ida Lisse, Elisabeth Ralfkiær and Gorm Pallesen

All 51 cases of HIV-related malignant lymphoma in Denmark diagnosed from 1983 to 1989 were reviewed. There were 12 Burkitt-type lymphomas, 30 immunoblast-rich lymphomas and 9 other lymphomas. Patients with immunoblast-rich lymphomas had significantly lower CD4 cell counts (median 60 vs. 188 × 10^6/l, $P < 0.05$), and more often a history of previous AIDS-defining illnesses (50% vs. 0%, $P < 0.005$), compared with patients with Burkitt-type lymphomas. Epstein–Barr virus (EBV) DNA was demonstrated in 14 of 19 immunoblast-rich tumours, and in 2 of 7 Burkitt-type lymphomas ($P = 0.10$). Compared with EBV DNA-negative tumours EBV DNA-positive tumours were associated with lower CD4 cell counts (median 39 vs. 188 × 10^6/l, $P = 0.01$). It is concluded that two main types of HIV-related malignant lymphoma exist. One is associated with severe immunosuppression, is often of immunoblast-rich morphology, and may be linked to EBV, whereas the other may occur in the absence of immunosuppression, is often of Burkitt-type morphology, and is probably not linked to EBV. In addition to these two main types, other non-Hodgkin lymphomas and Hodgkin's disease do occur.
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INTRODUCTION

LIKE PATIENTS with genetically determined immune deficiency and patients with iatrogenic immunosuppression after organ transplantation [1–2], patients infected with human immunodeficiency virus (HIV) are at greatly increased risk for developing non-Hodgkin B-cell lymphomas [3–5], and in 1985 the Centers for Disease Control included non-Hodgkin lymphoma as an AIDS-defining illness [6]. In the USA non-Hodgkin lymphoma has been reported to be present in 2.9% of notified AIDS cases [7]. Among Danish AIDS patients reported in or before 1987, malignant lymphoma comprised approximately 5% of primary AIDS diagnoses, and in this population the cumulative risk for developing lymphoma within 18 months of the AIDS diagnosis was estimated to be 10% [8]. In a small group of patients on long-term antiretroviral therapy, Pluda *et al.* [9] estimated the probability of developing malignant lymphoma to be approximately 30% by 30 months of therapy and 45% by 36 months of therapy. As the AIDS epidemic progresses and as the