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Non-AIDS defining malignancies (NADM) in the D:A:D study: Time trends and predictors of survival

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Background

- HIV appears to play a role in some non-AIDS-defining malignancies (NADM), which is of particular concern given the aging HIV-positive population
- It is important to monitor trends in incidence rates of NADMs and survival after a diagnosis of NADM
- We aimed to study these issues in the D:A:D Study

Methods:

- Information was collected from 8 of 11 cohorts participating in D:A:D
- New NADM from 1/1/2004-1/2/2010 were centrally validated; information captured included cancer type/site and histology report
- Incidence rates (IR) were calculated for NADMs overall and for lung, anal and Hodgkin's lymphomas (HL) separately
- Using Kaplan-Meier methods, survival times were calculated as the time from NADM diagnosis until the earliest of the patient's death, 1st February 2010 or 6 months after their last clinic visit

Methods:

- Incidence of NADM compared over time using Poisson regression analysis
- Factors associated with mortality following NADM diagnosis identified using Cox regression
- Primary analysis considered the following factors at time of NADM diagnosis (fixed-covariate analysis):

  Gender; mode of infection; race; smoking status; hepatitis B/C status; age; calendar year; nadir/latest CD4; latest HIV RNA; any prior AIDS-defining or non-AIDS defining malignancy.
- Subsequent analyses additionally incorporated CD4 counts and HIV RNA levels after NADM diagnosis (time-updated analysis)

Characteristics at time of NADM diagnosis

Over 176,775 person-years, 880 patients developed a new NADM
Incidence: 4.98/1000 PY, 95% CI [4.65, 5.31]

		N	% / IQR
Total number		880	100
Gender, n (%)	Male	708	80.5
Age (years)	Median (IQR)	50	44 - 49
Mode of infection, n (%)	MSM	408	46.4
	IDU	153	17.4
	Heterosexual	256	29.1
Ethnicity, n (%)	White	479	54.4
	Black	27	3.1
	Unknown	363	41.3
BMI (kg/m^2), n (%)	<18	319	36.3
	>30	79	9.0

Characteristics at time of NADM diagnosis

Over 176,775 person-years, 880 patients developed a new NADM
Incidence: 4.98/1000 PY, 95% CI [4.65, 5.31]

		N	% / IQR
Any use of ARV		813	92.4
CD4 count (cells/mm^3)	Median (IQR)	392	245 -580
Nadir CD4 count (cells/m^3)	Median (IQR)	127	49 - 245
HIV RNA (log_{10} copies/ml)	Median (IQR)	1.7	1.7 - 2.4
Prior NADM, n (%)		48	5.5
Prior ADM, n (%)		91	10.3
HCV positive, n (%)		75	8.5
HBV positive, n (%)		55	6.3
Current smoker, n (%)		303	34.4

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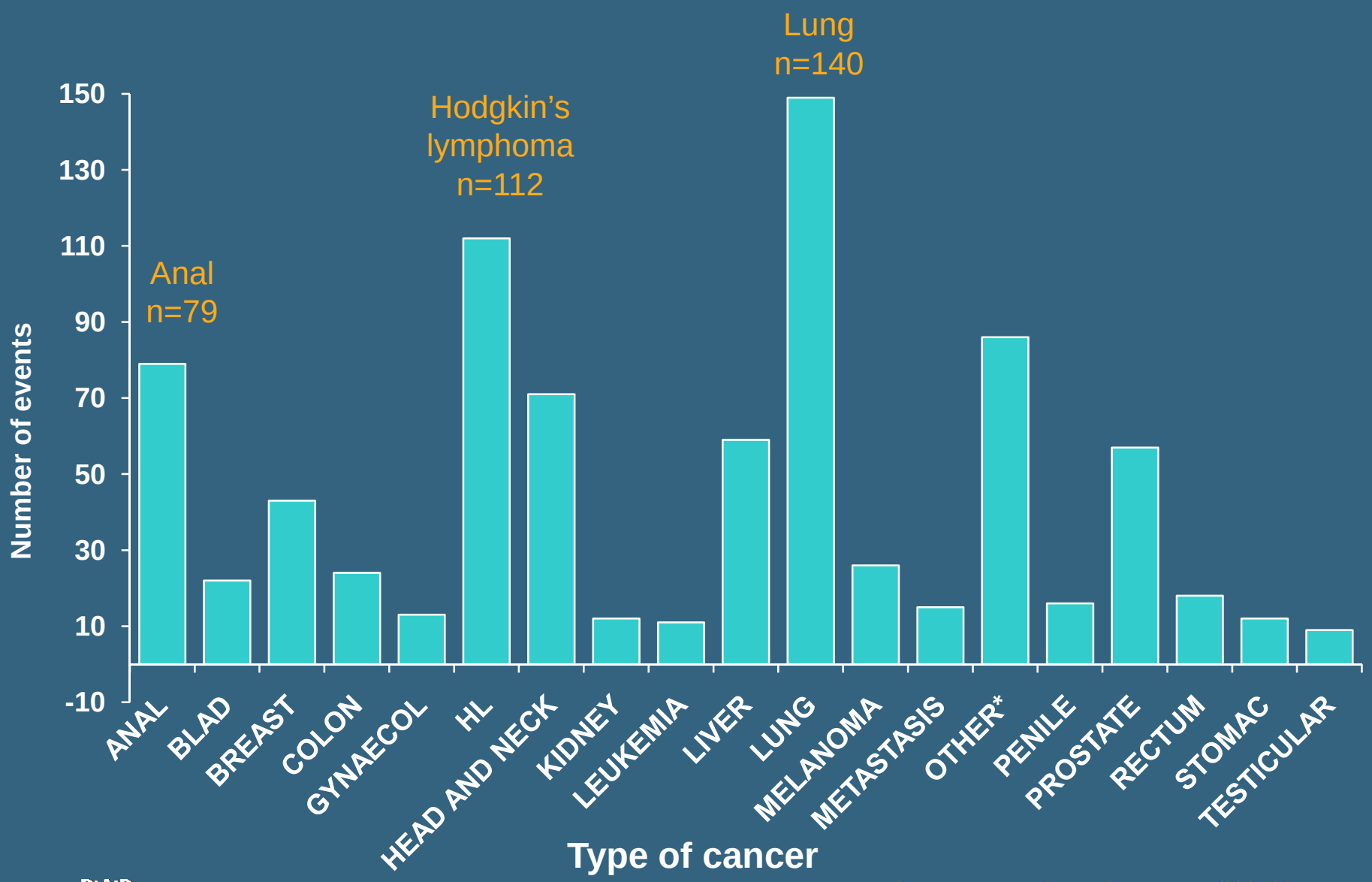
Types of NADMs



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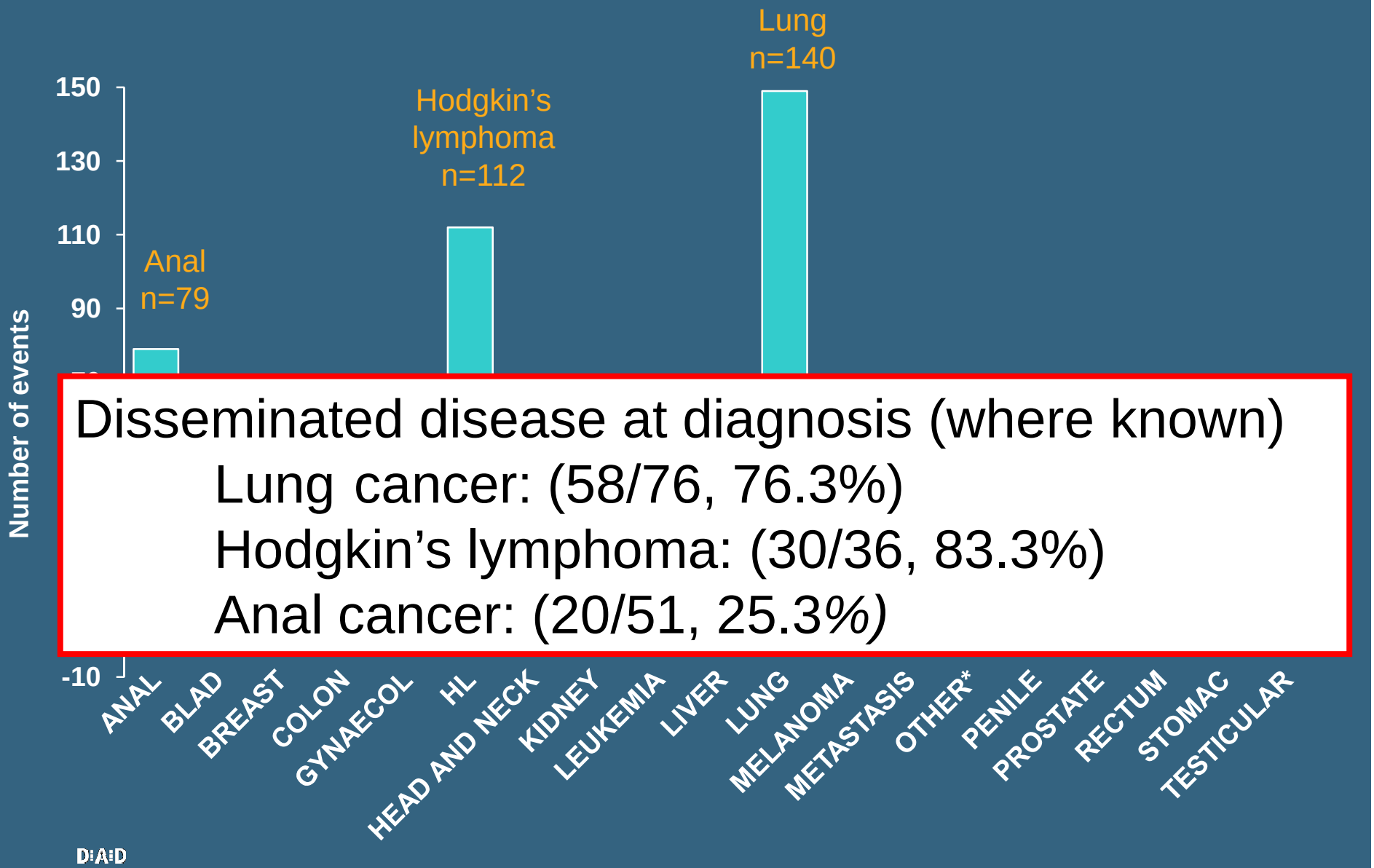
* Pancreatic cancer, esophageal cancer, gall bladder cancer

Types of NADMs



Disseminated disease at diagnosis (where known)

Lung cancer: (58/76, 76.3%)

Hodgkin's lymphoma: (30/36, 83.3%)

Anal cancer: (20/51, 25.3%)

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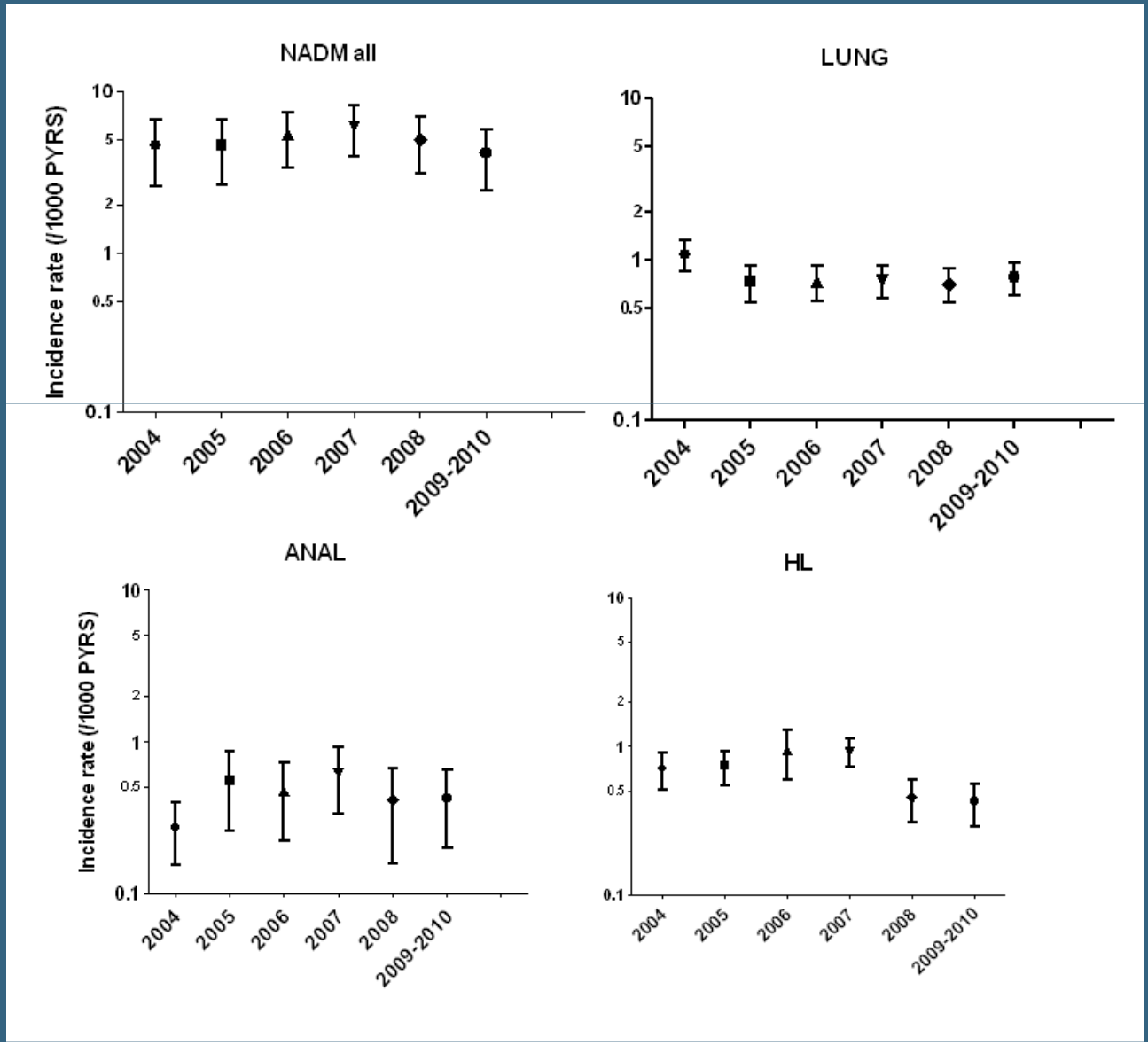
Incidence rate (with 95% CI) of NADM stratified by calendar year



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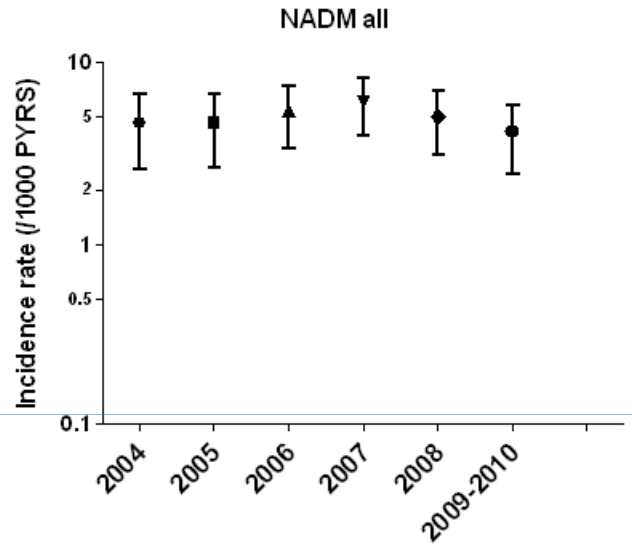
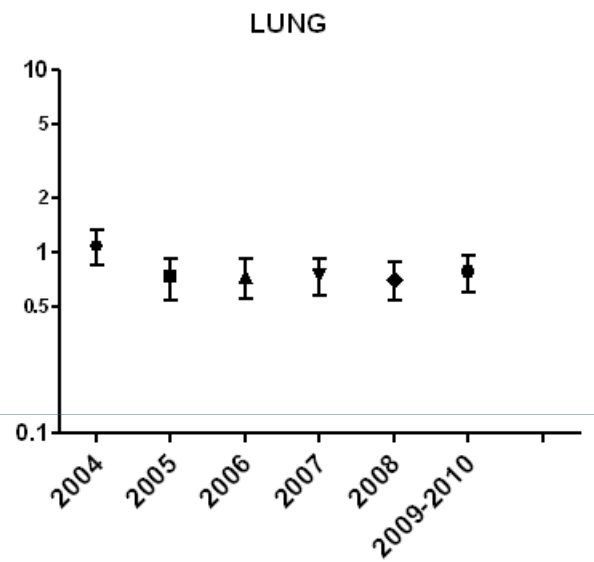
Incidence rate (with 95% CI) of NADM stratified by calendar year

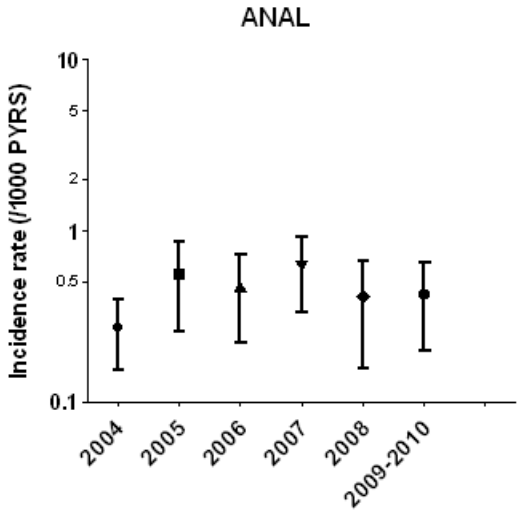
Age adjusted P for trend= 0.81

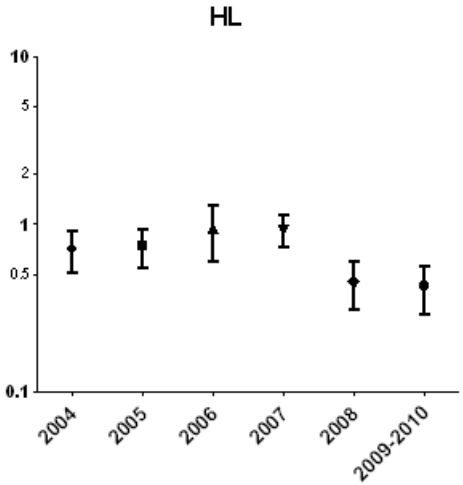




Age adjusted P for trend= 0.43

Age adjusted P for trend= 0.71





Age adjusted P for trend= 0.001

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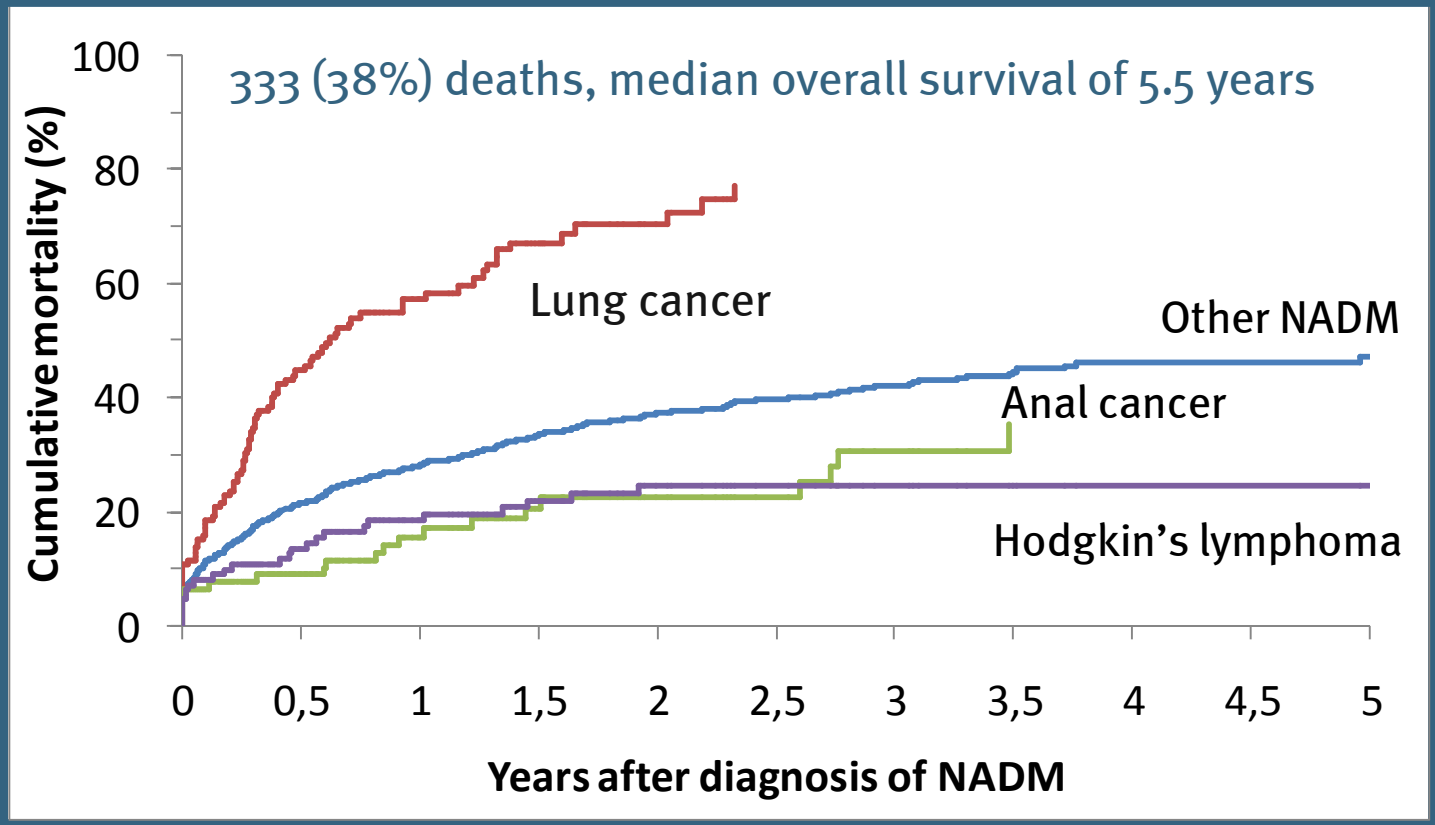
Kaplan-Meier plot showing mortality following NADM diagnosis, stratified by type of NADM



Number at risk

Lung cancer	140	69	35	24	14	10					
Other NADM	549	416	327	269	211	175	121	83	58	39	29
Anal Cancer	79	69	56	45	38	30	21	13			
Hodgkin's lymphoma	112	90	75	65	55	47	38	28	19	12	9

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Causes of death

- For 289 (88.4%) deaths the underlying cause was the NADM itself

Underlying cause of death	Lung cancer	Anal cancer	Hodgkin's Lymphoma
NADM	84 (94%)	17 (85%)	16 (64%)
Non-malignant cause	1 (1%)	2 (10%)	1 (4%)
ADM	-	-	1 (4%)
Unknown	4 (4.5%)	1 (5.0%)	7 (28.0%)

Factors (at diagnosis) associated with mortality

Factor		Unadjusted RH (95%CI)	Adjusted RH (95% CI)
Age	(/5 years older)	1.13 (1.02, 1.25)	1.11 (0.99, 1.25)
Male (vs. Female)		1.54 (1.14, 2.08)	**1.52** (1.10,2.09)
Mode of infection	MSM (vs. Heterosexual) IDU (vs. Heterosexual)	1.03 0.80,1.34) 1.41 (1.03, 1.93)	- **1.59** (1.18,21.14)
HCV	HCV positive	1.39(0.99, 1.96)	1.28 (0.97, 1.90)
Smoking	Never smoker Current Ex-smoker	1 1.67 (1.15, 2.42) 2.24 (1.53, 3.27)	1 1.28 (0.87, 1.90) **1.66** (1.12, 2.46)
HBV	HBV positive (vs. Neg)	1.54 (1.05, 2.27)	-
Year of diagnosis	(/later year)	0.91 (0.84, 0.97)	**0.91** (0.85,0.98)
CD4	(/50 cells/mm^3 higher)	0.95 (0.93, 0.97)	**0.95** (0.93, 0.98)
HIV RNA	(/log_{10} copies/ml higher)	1.05 (0.96, 1.15)	-

Factors associated with mortality

- Significantly *higher* risk, compared to other NADMs, in those with
  - Lung cancer: RH 2.29 [1.76, 2.99]
- Significantly *lower* risk, compared to other NADMs, in those with
  - Anal cancer: RH 0.56 [0.35, 0.89]
  - HL: RH 0.48 [0.32, 0.73]
- Higher risk associated with disseminated disease at diagnosis
  - Lung: RH 5.22 [1.85, 14.76]
  - Anal: RH 3.30 [0.85, 12.90]
  - HL: not done
- In adjusted time-dependent model, higher mortality in those with lowest latest CD4 (RH 0.89 [0.86, 0.93] /50 cells higher)

Limitations and strengths

- No information on performance status or alcohol consumption
- Limited data on use of chemo- and/or radio-therapy, or on dissemination/stage of disease
- No collection of socioeconomic status

- Centrally validated NADMs
- Detailed information on cause of deaths
- Detailed data collection on several important and specific HIV-related risk factors

Conclusions

- The incidence of NADM overall, and of the three most commonly occurring NADM, has remained relatively stable from 2004-2010
- The prognosis after diagnosis of NADM, in particular lung cancer and disseminated cancer, is poor but has improved somewhat over time
- A higher CD4 count, either at diagnosis or over follow-up, was associated with improved survival;
    - Maintenance of a high CD4 count through use of ART is important

Conclusions

- Smoking and IVDU were associated with poorer outcomes;

  Focussed attempts to reduce the prevalence of these lifestyle factors may lead to further improvements in survival in the future

- Earlier diagnosis of both HIV and NADMs, and research into better management of NADMs is warranted

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