

Key messages

- Sport and exercise benefit health but may also result in injury
- Many sports injuries result from true accidents but others are preventable
- Injury rates are low in child athletes and highest in young adults
- Every sport has a specific injury profile
- Preventive measures should be specific to the sport concerned and include those aimed at decreasing the number of violent contacts between athletes

the number of fractures (highest in ice hockey, judo, and karate) highlight the risk for high energy injuries.

High puck velocities, aggressive stick use, and body checking (collisions) account for most ice hockey injuries.²⁵ Catastrophic ice hockey injuries seem to be less frequent in Finland than North America,²⁶ possibly because of the larger rinks and less aggressive style in Europe. To avoid these injuries as far as possible, aggressive checking—particularly from behind the player and near the rink boards—should be minimised by game rules and strict refereeing.²⁵ Aggressive stick use may partly account for the high number of hand and wrist fractures in our study. Though facial injuries are common, they have declined with the more routine use of helmets and facemasks.²⁵ In ice hockey and many other sports mouth guards would substantially reduce dental injuries and should be designed according to the characteristics of each sport.

The injury profiles of the sports differed widely. To avoid injuries preventive measures should be specific to each sport. In general there should be greater focus on diminishing rough and violent contact between athletes.

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Does the onset of tuberculosis in AIDS predict shorter survival? Results of a cohort study in 17 European countries over 13 years

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Abstract

Objective—To assess the impact of tuberculosis on mortality in patients with AIDS.

Design—Community based cohort study.

Setting—52 centres in 17 countries (AIDS in Europe study).

Subjects—5249 patients who were alive and free of tuberculosis one month after the diagnosis of AIDS, enrolled between 1979 and 1989, and followed up until 1992.

Main outcome measures—Onset of clinically active tuberculosis or death, or both.

Results—During a mean follow up period of 15 months 201 (4%) patients developed tuberculosis and 3889 (74%) died. Patients who developed tuberculosis survived significantly longer (median 22 months) than those who did not (median 16 months). This apparent survival advantage was due to patients who survived longer having more opportunity to develop tuberculosis (or any other disease). In models that took into account the time at which tuberculosis was diagnosed, the onset of tuber-

culosis was associated with a significant increase in mortality (adjusted relative hazard of death 1.34; 95% confidence interval 1.12 to 1.60).

Conclusions—The onset of tuberculosis in patients with AIDS predicts a substantial increase in mortality. Whether this increased mortality is directly attributable to the tuberculosis remains uncertain. If the association is causal preventive chemotherapy and aggressive treatment of tuberculosis could improve survival in AIDS.

Introduction

The HIV epidemic has had a major impact on the incidence of tuberculosis and on mortality and the case fatality rate of that disease.¹⁻³ It is unclear, however, whether tuberculosis affects the course of HIV disease. In particular, we do not know whether tuberculosis shortens survival in patients with HIV infection. A recent review concluded that there was no noticeable decrease in survival attributable to tuberculosis in patients with HIV infection.¹ That conclusion rested

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on two kinds of evidence. Firstly, in patients who had died with both AIDS and tuberculosis the cause of death was almost invariably attributed to AIDS.⁴ However, the validity of a cause of death diagnosis may be limited when there are several possible causes of death. Secondly, studies from Brazil,⁵ Spain,⁶ and Europe⁷ indicate that patients with tuberculosis as the AIDS defining disease survive longer than other AIDS patients. But because clinical tuberculosis may be manifested earlier than other AIDS defining diseases in HIV infection, apparently longer survival in these patients may be due entirely to earlier diagnosis of AIDS.

We analysed data from a large European follow up study of AIDS patients (AIDS in Europe study) to assess the impact of tuberculosis on mortality in this population. To avoid using tuberculosis both to define AIDS and to predict survival after the diagnosis of AIDS we restricted analysis to patients who were free of tuberculosis at the time of their AIDS diagnosis.

Patients and methods

This non-concurrent prospective study included AIDS patients followed up at 52 centres in 17 European countries.⁷ The cohort comprised patients diagnosed as having AIDS between 1979 and 1989 and followed up until 1992. The collaborating centres, except those in Italy, enrolled all of their AIDS patients who were aged 16 or over; the Italian centres enrolled only a predefined proportion of patients. Information was collected from patients' charts on a standardised form in 1991-2 under the supervision of the coordinating centre (University of Copenhagen). Of 6655 registered patients, 6546 had complete data. Of these patients, 5249 who were alive and free of tuberculosis 31 days after their diagnosis of AIDS were included in the analysis.

Study variables—AIDS was defined according to Centers for Disease Control criteria, 1987 revision.⁸ Patient follow up started on day 32 after the diagnosis of AIDS and was terminated when the patient was last seen alive or at death. Dates of death, time the patient

was last seen alive, and diagnosis of tuberculosis (pulmonary or extrapulmonary) were based on medical charts. Eighty five per cent of tuberculosis cases (n=171) were confirmed by culture, 5% (11) were diagnosed at necropsy, and 9% (19) were diagnosed by direct smear examination, clinical assessment, and response to treatment. Potential confounders of the relation between the incidence of tuberculosis and mortality included age, sex, time of diagnosis of AIDS, region of Europe (northern, central, southern), and whether the patient took zidovudine at baseline.

Analysis—We compared patients who went on to develop active tuberculosis during follow up with those who remained free of tuberculosis. Firstly, we compared survival in these two groups (Kaplan-Meier method) ignoring the time of diagnosis of tuberculosis and adjusting for potential confounders in a proportional hazards model.⁹ To take into account that the longer a patient survives the more likely that patient is to develop a disease (including tuberculosis) we also modelled tuberculosis as a time dependent variable.⁹ In such models a patient with AIDS contributes to the estimation of the hazard of dying in the unexposed group as long as he or she is free of tuberculosis and to the estimation of the hazard of dying in the exposed group from the moment tuberculosis is diagnosed. The variable "tuberculosis" took a value of zero before the diagnosis of tuberculosis and a value of 1 thereafter. Analyses were by the SAS procedure PHREG.

Results

A total of 5249 patients were included in the study (table 1). Patients who developed tuberculosis were similar to the others in sex and main risk factors for HIV. Patients who developed tuberculosis were slightly younger than the other patients (34.2 versus 35.9 years; P=0.04), less likely to live in northern European countries (relative to central and southern countries), less likely to be taking zidovudine at the time of their AIDS diagnosis, and less likely to have developed AIDS in 1989 (relative to previous years).

During a mean follow up period of 15 months 3889 (74%) patients died and 201 (4%) developed a new episode of active tuberculosis. The tuberculosis was pulmonary in 80 cases and extrapulmonary in 107; 14 patients developed both forms. Tuberculosis was diagnosed on average 13 months after the start of follow up. Survival after the diagnosis of AIDS was significantly longer in patients who developed tuberculosis (median 22 months) than in the other patients (median 16 months; log rank test: P<0.001). The apparently lower mortality after the diagnosis of AIDS in patients who developed tuberculosis remained significant after adjustment for confounders in proportional hazards models (unadjusted relative hazard of death 0.72 (95% confidence interval 0.61 to 0.85); relative hazard of death adjusted for age, calendar year, region of Europe, and zidovudine treatment 0.69 (0.59 to 0.81)).

In analyses that allowed the risk of death to change in a given patient at the time tuberculosis was diagnosed (proportional hazards models with tuberculosis as a time dependent variable) the onset of tuberculosis appeared to increase the mortality of AIDS patients (table 2). This increase was 40% in a univariate analysis and 34% after adjustment for potential confounders. The excess risk of death was somewhat greater for pulmonary tuberculosis than for extrapulmonary tuberculosis.

The increased mortality after the onset of tuberculosis can also be expressed in terms of reduced patient survival. Under reasonable simplifying assumptions, expected survival would be divided by 1.34 (the relative hazard estimate) by the onset of

Table 1—Characteristics of 5249 patients who were free of active tuberculosis one month after diagnosis of AIDS, comparing 201 patients who developed active tuberculosis during follow up with 5048 patients who did not; AIDS in Europe study 1979-92

	Total (No (%))	No (%) who developed tuberculosis	No (%) who did not develop tuberculosis	P value
Sex:				
Men	4806 (92)	184 (92)	4622 (92)	0.90
Women	443 (8)	17 (8)	426 (8)	
Age group (years):				
≤29	1534 (29)	64 (32)	1470 (29)	0.22
30-39	2090 (40)	86 (43)	2004 (40)	
≥40	1625 (31)	51 (25)	1574 (31)	
Region of Europe*:				
Southern	1357 (26)	69 (34)	1288 (26)	<0.001
Central	1666 (32)	76 (38)	1590 (32)	
Northern	2225 (42)	56 (28)	2169 (42)	
Main risk for HIV:				
Homosexual	3456 (66)	128 (64)	3328 (66)	0.85
Intravenous drug use	1191 (23)	51 (25)	1140 (23)	
Other	449 (9)	16 (8)	433 (9)	
Unknown	153 (3)	6 (3)	147 (3)	
Treated with zidovudine:				
Yes	428 (8)	7 (3)	421 (8)	0.02
No	4821 (92)	194 (97)	4627 (92)	
Diagnosis of AIDS:				
1979-86	1314 (25)	60 (30)	1254 (25)	0.01
1987	1049 (20)	47 (23)	1002 (20)	
1988	1278 (24)	53 (26)	1225 (24)	
1989	1608 (31)	41 (20)	1567 (31)	

*Information on country of origin was missing for one patient.

Table 2—Hazard of death in AIDS patients who developed active tuberculosis, relative to those who did not, in 5249 patients enrolled in AIDS in Europe study who were alive and free of tuberculosis one month after diagnosis of AIDS, 1979-92

	Unadjusted results		Results adjusted for year of AIDS diagnosis, age, region of Europe, and use of zidovudine	
	Relative hazard	95% Confidence interval	Relative hazard	95% Confidence interval
	Pulmonary tuberculosis	1.44	1.12 to 1.86	1.43
Extrapulmonary tuberculosis	1.33	1.05 to 1.68	1.22	0.97 to 1.54
Either pulmonary or extrapulmonary tuberculosis	1.40	1.17 to 1.67	1.34	1.12 to 1.60

tuberculosis. This corresponds to a reduction of 25%. For example, an AIDS patient who might live 12 months without tuberculosis would be expected to survive only nine months after the onset of tuberculosis.

These estimations of months of life lost assume that tuberculosis increases mortality in the same way, regardless of how much time has elapsed between the diagnosis of AIDS and the onset of tuberculosis. We tested this assumption by using two separate time dependent variables for tuberculosis in proportional hazards models—one for tuberculosis occurring 365 days or less after the start of follow up and another for tuberculosis occurring after more than one year of follow up. The adjusted relative hazards of death were 1.30 (95% confidence interval 1.05 to 1.60) for tuberculosis diagnosed in the first year of follow up and 1.54 (1.12 to 2.11) for tuberculosis diagnosed thereafter.

Discussion

This study of tuberculosis and mortality based on a large population based cohort of European AIDS patients yielded a seemingly paradoxical result. Patients who developed active tuberculosis at some point during their follow up survived longer after their diagnosis of AIDS than patients who remained free of tuberculosis. On the other hand, the development of tuberculosis predicted a substantial and statistically significant increase in the risk of death. This apparent contradiction may be explained as follows. Patients who survive for a long period have a greater chance of developing tuberculosis than do patients who die early after the diagnosis of AIDS. But among patients who survive free of tuberculosis for any length of time, those who contract tuberculosis die sooner than the others.

Observing long survival in AIDS patients who develop tuberculosis may have led clinicians to underestimate the detrimental impact that tuberculosis may have on vital prognosis. Such underestimation can result from faulty heuristic interpretation of the association between long survival and tuberculosis.

Causation may be taken as flowing in one direction (tuberculosis results in long survival) instead of the other (long survival increases the chance of developing tuberculosis). Our analysis avoided this particular pitfall.

Survival was reduced by about 25% in AIDS patients who developed tuberculosis. Preliminary evidence suggests that the relative reduction in survival may be greater for pulmonary tuberculosis than for extrapulmonary tuberculosis and greater when tuberculosis occurs late rather than early after the diagnosis of AIDS. The relative hazard of death estimated in this study was weaker than the twofold increase in mortality reported in a study of 106 AIDS patients with tuberculosis compared with controls matched for CD4 cell count¹⁰; however, the confidence intervals of the two estimates overlapped.

Our study does not prove that the onset of tuberculosis increases mortality. It is possible that an unmeasured variable (such as severe immunosuppression or malnutrition) may induce both active tuberculosis and death in AIDS patients. Several arguments, however, favour a causal association. Though active tuberculosis is in principle curable, several studies point to dismal rates of compliance with antituberculous treatment in HIV positive patients.^{11,12} This problem is compounded by the increasing frequency of multidrug resistant strains of *Mycobacterium tuberculosis* in patients with HIV.¹³ Preliminary evidence also suggests that tuberculosis may accelerate the progression of HIV disease.¹⁴

There are few predictors of death among AIDS patients that may lend themselves to preventive intervention. Hence the possibility that active tuberculosis may increase by one third the mortality in AIDS patients deserves consideration. Preventive chemotherapy may reduce not only the incidence of tuberculosis¹⁵ but also mortality in HIV infected patients at high risk of mycobacterial infections. Early detection and appropriate treatment of tuberculosis may be particularly effective in HIV infected populations that now have limited access to health services. The effectiveness of such interventions cannot be inferred from this observational study but requires verification in experimental trials.

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Conflict of interest: None.

Key messages

- HIV infection increases the incidence of and mortality from tuberculosis, but whether tuberculosis affects the course of HIV infection remains uncertain
- The clinical onset of tuberculosis in AIDS patients previously free of tuberculosis predicts an increase in overall mortality of about one third
- Tuberculosis may be one of the few preventable causes of death in patients with AIDS
- Preventive chemotherapy, early detection, and supervised treatment of tuberculosis warrant further evaluation in AIDS patients

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Falling incidence of penis cancer in an uncircumcised population (Denmark 1943-90)

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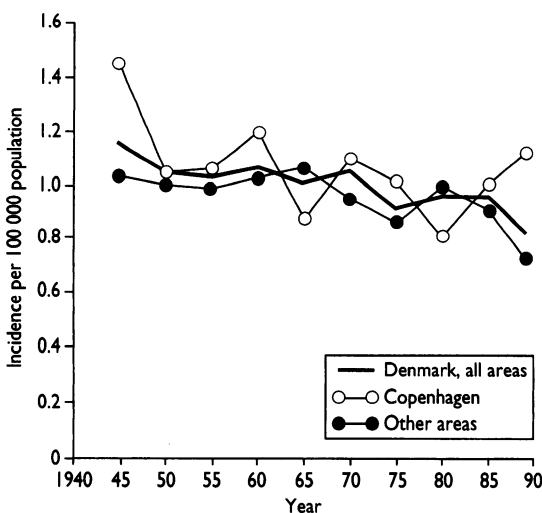
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Boys circumcised neonatally are effectively protected against penis cancer.¹ Using data from the Danish Cancer Registry we investigated the long term trends in the incidence of penis cancer in a virtually uncircumcised population.

Patients, methods, and results

Penis cancers diagnosed in Denmark during 1943-90 and notified to the cancer registry were evaluated manually. We excluded scrotal and epididymal cancers and 39 non-epidermoid penis cancers (20 basal cell carcinomas, nine melanomas, and 10 others). World standardised incidence rates were calculated and linear regression applied to evaluate the temporal changes in incidence (five year data) and age distribution. We evaluated the impact of marital status in a case control design using patients with colon and stomach cancers diagnosed in the same period as controls. The odds ratios of never having married were calculated using logistic regression.

The material comprised 1523 epidermoid penis cancers (including 207 without specified histology). Patients were 22 to 95 years old at diagnosis. Incidence rates fell 0.5% a year from 1.15 (95% confidence interval 0.94 to 1.36) in 1943-7 to 0.82 (0.65 to 0.99) per 100 000 person years in 1988-90 ($P=0.002$) (figure).



Incidence rates of penis cancer per 100 000 person years (world standardised) among men living in Copenhagen (including suburbs) and men living in other areas of Denmark, 1943-90

Of 1516 patients with information available about marital status at the time of diagnosis, 10.6% had never married. The corresponding percentages among control patients with colon and stomach cancer were 7.3% and 8.6%, respectively. The mean age at diagnosis increased among men who had ever married from 64 years in 1943-62 to 67 years in 1978-90 ($P<0.0001$). Patients with penis cancer who had never married

living in the Copenhagen area were generally younger (mean age 60 years). After adjustment for age (10 year intervals), calendar period (five year periods), and place of residence (Copenhagen and suburbs v rest of Denmark), patients with penis cancer were significantly more likely to have remained unmarried than patients with colon cancer (odds ratio=1.4; 95% confidence interval: 1.2 to 1.6). This applied in different strata of age and calendar period, and a particularly high risk was found for unmarried men in the Copenhagen area (odds ratio=1.9; 1.4 to 2.6). Compared with patients with stomach cancer, the association with unmarried marital status was not present (odds ratio=1.1; 0.97 to 1.4), except among those living in the Copenhagen area (odds ratio=1.7; 1.2 to 2.3).

Comment

Improvements in diagnostic methods can be ignored when considering factors influencing the incidence of penis cancer. Also, the proportion of undiagnosed or misclassified cases is likely to be negligible.

With phimosis and penis cancer as two central issues, neonatal circumcision has been the subject of considerable debate for more than a century.^{2,3} The virtual absence of penis cancer in populations prescribing neonatal circumcision has been a crucial argument in this discussion.¹ However, only 511 out of approximately 478 000 Danish boys aged 0-14 years were circumcised in 1986 (National Board of Health, personal communication), corresponding to a cumulative national circumcision rate of around 1.6% by the age of 15 years. Thus, the declining incidence of penis cancer in Denmark cannot reasonably be attributed to an increased practice of neonatal circumcision.

The observed association with marital status might be explained by socioeconomic and hygiene factors. The finding that patients with penis cancer and patients with stomach cancer who predominate in lower socioeconomic strata had rather similar marital status patterns supports this.⁴ Also, even though it is not established how and to what extent men who had never or ever married differ in sexual behaviour, it seems plausible that within the broad category of men who had never married, the proportion of men with lifestyles characterised by unstable partner relations and poor genital hygiene may be larger than among men who had ever married. This might particularly be so in the Copenhagen area, the only metropolitan area of Denmark. During the period under study, the proportion of Danish dwellings having a bath increased gradually from 35% in 1940 to 90% in 1990.⁵ It seems plausible that better penile hygiene resulting from this improvement in sanitary installations might have contributed to the observed trend.

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