Laryngeal cancer in Denmark: a nationwide longitudinal study based on register linkage data

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Abstract

To identify high and low risk groups for laryngeal cancer in Denmark, all individuals aged 30–74 in the 1970 census were followed up over 10 years. Census data were linked with the Central Population Register to identify persons who died or emigrated during the follow up, and with the Danish Cancer Register to identify cases of laryngeal cancer. Individuals were categorised according to sex, age, and sociodemographic characteristics as declared on the census forms. A multivariate analysis was carried out by means of multiplicative Poisson models. The study showed that the risk of laryngeal cancer was strongly related to sociodemographic factors. The risk for skilled workers living in Copenhagen (relative risk (RR) 4·76, 95% confidence interval (CI) 3·61–6·28) was estimated to be almost five times higher than the risk for men self employed in agriculture and living in rural areas. The variation in the risk of laryngeal cancer is not fully explained by known variations in tobacco and alcohol consumption, and this study highlights additional risk factors particularly related to occupation and marital state.

Tobacco and alcohol are known risk factors for laryngeal cancer.[1] Asbestos,[2–4] manmade mineral fibres,[5 6] nickel,[7–9] chromium,[7–9] wood dust,[10] and sulphuric acid[11–13] are occupational hazards suspected of increasing the risk of laryngeal cancer. The distribution of laryngeal cancer in the population may indicate whether the pattern is compatible with available knowledge on risk factors or whether additional aetiological factors seem to be present. We analysed by means of multiplicative Poisson models,[14] the distribution of laryngeal cancer in the Danish population. Individually linked data from the 1970 census and from the Danish Cancer Register provided the subjects, and enabled us to carry out a cohort study of the incidence of cancer in a population of two million.[15]

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Subjects and methods

CENSUS DATA

At the 1970 census the Central Bureau of Statistics (Danmarks Statistik) collected data on all residents in Denmark by means of self administered questionnaires. Questionnaires were checked by municipalities and coded by Danmarks Statistik. Information about individuals included sex, age, municipality, education, industry, occupation, marital state, type of dwelling, dwelling facilities, and composition of the household. Information on industry and occupation was reliable only for persons who were economically active on the census date. The classification used for industry included 245 codes, and that for occupation 218 codes.

In the present analysis the population was divided into 11 occupational groups based on a combination of these codes. The groups included those self employed in agriculture, self employed in other industries (such as shopkeepers or workers in the building industry), salaried employees with university or college education (such as school teachers), salaried employees without higher education, family workers, skilled workers, and unskilled workers. Examples of skilled workers were metal (blacksmiths, welders), wood (carpenters, furniture makers), building (plumbers, electricians), and service workers (waiters, hairdressers). Unskilled workers had not served an apprenticeship and were employed in manufacturing, construction, transport, or cleaning.

FOLLOW UP PROCEDURE

The cohort of persons aged 30–74 on the 1970 census date was followed up for deaths, emigrations, and incidence of cancer for 10 years. Deaths and emigrations were identified by linkage with the Danish Central Population Register, which holds information on all people living in Denmark since 1968. Persons belonging to the age group 30–34 in 1970 entered the cohort in 1975 only (fig 1), so that the cohort comprised at any time only those above the age of 35. Each person contributed to the total number of person-years at risk from the 1970 census date until the date of diagnosis of laryngeal cancer, death, emigration, or termination of follow up in 1980, whichever came first. Person-years at risk were divided into five year age groups, and into two five year periods of follow up (fig 1). The age categories

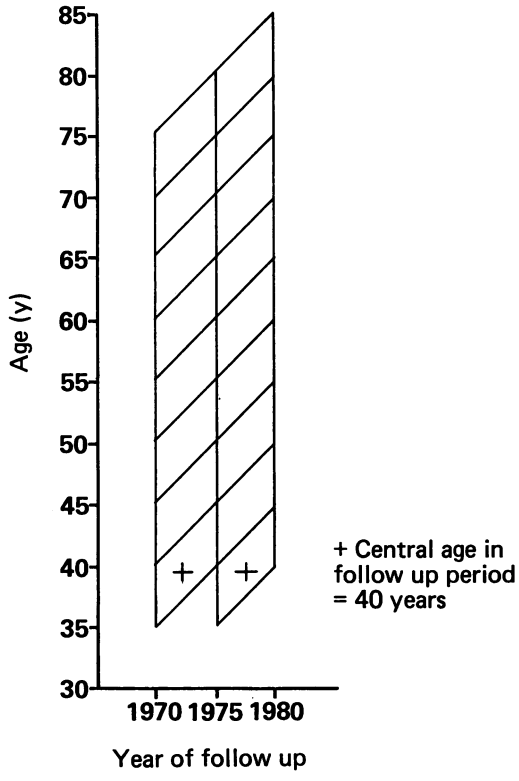

Figure 1 Definition of person-year categories used in multiplicative Poisson model analysis.

defined in this way are referred to by their central values.

All cases of laryngeal cancer (International Classification of Diseases—7 revision:161) prevalent in the census population on the 1970 census date or diagnosed during follow up were retrieved from the Danish Cancer Register, which dates back to 1943. Prevalent cases were excluded, and only the cases diagnosed during the follow up were included in the analysis. Figure 2 shows the sex and age specific incidence for laryngeal cancer.

LINKAGE PROCEDURE

The linkage between data files was made possible by the unique personal identification number that has been assigned to every resident in Denmark since 1968. The linkage was made by Danmarks Statistik and confidentiality rules were fulfilled. The linkage procedure has been described in detail.[15]

ANALYSIS

The analysis was based on multiplicative Poisson models, where the number of cases d_{ak} in subgroup ak (a = age, k = combination of other determinants)

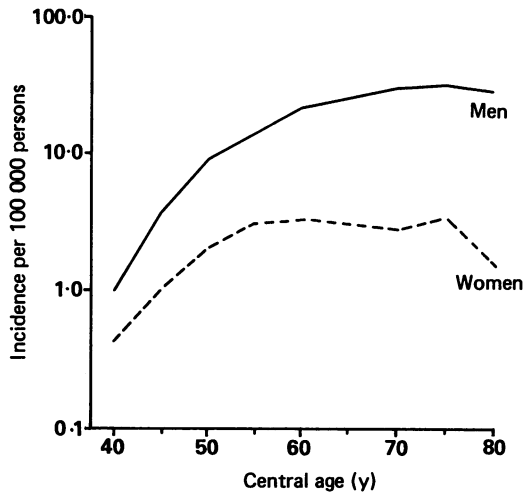

Figure 2 Age specific incidence rates for laryngeal cancer in Denmark for years 1970–80.

was assumed to be Poisson distributed. The parameter of the Poisson distribution is $\lambda_{ak}.R_{ak}$: λ_{ak} and R_{ak}, being the age specific incidence rate and the person-years at risk in subgroup ak.[16] R_{ak} is a stochastic variable but can be treated as a constant in the analyses. The general model used in this study was:

$$\log(\lambda_{ak}) = \lambda_a + \beta x_k$$

where λ_a is a parameter for age group a; x_k is a vector of indicators for the different levels of and interaction between factors; and β is a vector of parameters for the levels. This is an extension of the usual standard mortality rate analysis—namely, an internally controlled analysis in which the background incidence rates are estimated directly from the data. The estimated parameters were interpreted as relative risks (RR) with a group containing a large number of person-years at risk chosen as baseline. The models were fitted using Genstat.[17]

Age specific incidence curves (similar to fig 2) were first drawn for men and women separately at each level of the factors shown in table 1. There was no difference in incidence of laryngeal cancer according to the type of heating installation or to the source of heating, and these factors were not considered in the multivariate analysis. Final analysis included age, marital state, region of residence, occupation, type of dwelling, and first order interactions between these factors.

Models were reduced as much as possible, testing stepwise by likelihood ratio tests. Persons with missing information for one or more variables or persons belonging to small residual groups were excluded. As information about occupation was available only for a few persons above the age of 64,

Table 1 Years at risk for laryngeal cancer in Denmark (1970–80) for variables used in definition of subgroups in population aged 40–80

	% Distribution			
	Men (n = 9 946 325)	*Women (n = 10 891 151)*	*Variable used in final analysis*	*Categorisation of variables in final analysis*
Central age in follow up period:			Yes	
40	14·4	13·0		1
45	13·7	12·7		2
50	14·1	13·3		3
55	14·0	13·4		4
60	13·3	12·9		5
65	12·8	12·3		6
70	9·6	10·7		7
75	6·7	8·5		8
80	2·2	3·1		9
Marital status:			Yes	
Married	81·7	72·6		1 (used as baseline)
Single	9·8	8·6		2
Widowed/divorced	8·4	18·8		3
Heating installation:			No	
Central	81·7	82·9		
Not central	18·3	17·1		
Source of heating:			No	
Unknown	1·1	0·9		
Distant heating	22·6	25·0		
Liquid fuel	65·4	63·7		
Solid fuel	8·5	8·0		
Electricity	0·7	0·6		
Gas	1·7	1·9		
Region:			Yes	
Copenhagen	16·2	19·7		1 (used as baseline)
Greater Copenhagen/suburbs	18·6	17·4		2
Towns	24·8	25·5		3
Rural area	40·4	37·3		4
Occupation:*			Yes	Men Women
Self employed, agriculture	11·5	0·4		2 2
Self employed, other industries	11·8	1·8		3 3
Family worker, agriculture	0·013	3·8		E 2
Family worker, other industries	0·051	3·7		E 4
Salaried employee, higher education	11·9	4·1		4 5
Salaried employee, no higher education	17·0	16·1		1 1 (used as baseline)
Skilled worker	12·8	0·3		5 6
Unskilled worker	26·5	16·2		6 6
Worker not otherwise specified	0·7	0·2		E E
Housewife	0·015	49·1		E E
Pensioner	6·7	17·3		E E
Type of dwelling:†			Yes	
Single family house	67·1	61·3		1 (used as baseline)
Apartment house	31·5	37·7		2
Other	1·4	1·0		E

*Occupation available for those aged 40–70 only (data set 1).
†Type of dwelling included in data set 2 only (age category 40–80).
E = Excluded from the analysis.

Table 2 Number of person-years at risk and incidence of laryngeal cancer in Denmark for years 1970–80

	Age 40–70		*Age 40–80*	
	Total	*Included in data set 1*	*Total*	*Included in data set 2*
Men:				
Person-years	9 063 015	8 288 676	9 946 325	9 810 924
Cases	1226	1057	1489	1470
Women:				
Person-years	9 632 440	4 400 649	10 891 151	10 782 274
Cases	209	88	244	243

Table 3 Accepted models in multiplicative Poisson analysis for economically active men and women aged 40–70 in follow up period (data set 1) and for all men and women aged 40–80 (data set 2)

Data set 1	Data set 2
$\lambda_{ijkl} = \alpha_i + \beta_j + \gamma_k + \delta_l$	$\lambda_{ijkm} = \alpha_i + \beta_j + \gamma_k + \eta_m$

i = Five year age groups (40–70 or 40–80). j = Marital state, three groups. k = Region of residence, four groups. l = Occupation, six groups (different for men and women). m = Type of dwelling, two groups.

the models were fitted firstly for the subgroup of men and women aged 30–64 at census (data set 1), and secondly for the whole cohort of men and women aged 30–74 years at census (data set 2) with occupation excluded from the analysis. Table 2 shows person-years at risk and numbers of incident cases of laryngeal cancer in each of these data sets.

Results

Table 3 shows the final models for data sets 1 and 2. The same variables remained in the final models for men and women. In data set 1, with information on occupation and for persons aged 30–64 at census, type of dwelling was non-significant and was not included in the final models. In data set 2 type of dwelling remained as a significant variable. Interactions between the variables were not included in the models as they were non-significant, or close to the 5% level.

Table 4 shows the goodness of fit of the final models and likelihood ratio tests for excluding factors from the models. For men the data were adequately fitted by the model for data set 1 ($p = 0.97$) but less adequately fitted for data set 2 ($p = 0.04$). Non-significant p values of goodness of fit were obtained for women in both data sets. In data set 1 the tests for excluding variables from the final models showed highly significant p values for marital state, region of residence, and occupation for men and women. In data set 2 the significant effect of type of dwelling was probably present as a consequence of not including occupation.

Table 5 shows the estimated RRs and the 95% CIs for each level of the variables included in the final models. Residence in a rural area was the baseline for calculating RRs for region. All other areas showed higher risks of laryngeal cancer (RR > 1) with the highest risk for persons living in Copenhagen (RR = 1·62 for men and 3·06 for women, dataset 1; 1·66 for men and 1·83 for women; data set 2).

Relative risks for unmarried men and women (baseline, married persons) were less than unity (RR = 0·76 for men and 0·45 for women, data set 1; 0·80 for men and 0·53 for women, data set 2) in both data sets. Conversely, the RRs for widowed or divorced people were significantly above unity (RR = 1·43 for men and 2·22 for women, data set 1; 1·42 for men and 1·70 for women, data set 2).

For occupation (data set 1 only) salaried employees without higher education constituted the baseline category. Among men, occupation was a strong risk indicator; RRs ranged from 0·46 for those self employed in agriculture (11·5% of the male workforce) to 1·36 for skilled workers (11·8%), indicating a difference of about threefold in the incidence of laryngeal cancer between these categories. Among women, self employed persons and family workers in agriculture (4·2% of the female workforce) were also the category with lowest risk (RR = 0·26). Skilled and unskilled workers pooled together (16·5% of the population) showed the highest risk (RR = 1·57).

Type of dwelling was a risk factor in data set 2 only; the RR for living in an apartment house relative to living in a single family house was 1·43 for men and 1·88 for women.

Table 4 Likelihood ratio test for goodness of fit and for excluding factors from the final model in multiplicative Poisson models for association between demographic factors and laryngeal cancer

	Data set 1 Economically active aged 40–70			Data set 2 All persons aged 40–80		
	Test value	Degrees of freedom	p	Test value	Degrees of freedom	p
			Men			
Goodness of fit	427·6	487	0·97	237·2	201	0·04
Test for exclusion of:						
Marital state	18·9	2	<0·0005	27·4	2	<0·0005
Region	31·7	3	<0·0005	38·7	3	<0·0005
Type of dwelling	—			30·0	1	<0·0005
Occupation	75·4	5	<0·0005	—		
			Women			
Goodness of fit	179·6	481	0·99	167·3	201	0·96
Test for exclusion of:						
Marital state	18·5	2	<0·0005	22·9	2	<0·0005
Region	12·4	3	0·005–0·01	15·0	3	0·002
Type of dwelling	—			10·7	1	<0·0005
Occupation	12·7	5	0·025	—		

Table 5 RRs and 95% CIs associated with demographic factors for economically active men and women aged 40–70 and for all men and women aged 40–80 in follow up period

	Data set 1 Economically active aged 40–70		*Data set 2 All persons aged 40–80*	
	RR	*(95% CI)*	*RR*	*(95% CI)*
		Men		
Marital state:				
Married	1·00		1·00	
Unmarried	0·76	(0·58–0·99)	0·80	(0·64–0·99)
Widow/divorced	1·43	(1·18–1·72)	1·42	(1·23–1·64)
Region of residence:				
Copenhagen	1·62	(1·37–1·93)	1·66	(1·41–1·97)
Greater Copenhagen/suburbs	1·19	(0·99–1·44)	1·31	(1·11–1·55)
Provincial towns	1·33	(1·13–1·57)	1·42	(1·23–1·64)
Rural area	1·00		1·00	
Type of dwelling:	NS			
Single family house			1·00	
Apartment house			1·43	(1·26–1·62)
Occupation:			Not included	
Self employed, agriculture	0·46	(0·34–0·63)		
Self employed, other	1·17	(0·95–1·45)		
Salaried employee, higher education	0·76	(0·59–0·98)		
Salaried employee, no higher education	1·00			
Skilled worker	1·36	(1·11–1·66)		
Unskilled worker	1·16	(0·97–1·39)		
		Women		
Marital state:				
Married	1·00		1·00	
Unmarried	0·45	(0·16–1·25)	0·53	(0·28–0·97)
Widow/divorced	2·22	(1·41–3·49)	1·70	(1·28–2·26)
Region of residence:				
Copenhagen	3·06	(1·52–6·16)	1·83	(1·21–2·78)
Greater Copenhagen/suburbs	1·79	(0·81–3·84)	1·67	(1·10–2·54)
Provincial towns	2·44	(1·19–4·99)	1·26	(0·84–1·88)
Rural area	1·00		1·00	
Type of dwelling:	NS			
Single family house			1·00	
Apartment house			1·88	(1·36–2·60)
Occupation:			Not included	
Self employed, agriculture	0·26	(0·04–1·75)		
Self employed, other	0·83	(0·25–2·75)		
Family worker, other	0·62	(0·19–2·06)		
Salaried employee, higher education	0·50	(0·15–1·64)		
Salaried employee, no higher education	1·00			
Worker	1·57	(0·99–2·49)		

Discussion

Laryngeal cancer is not as common in Denmark as it is in certain other areas of the world—for instance, southern Europe—but the incidence has increased steadily.[18 19] Among men, the age adjusted incidence per 100 000 (world standard population) was 1·5 for years 1943–7 and 5·5 for years 1983–6. This cancer is much less frequent in women, with the corresponding incidences being 0·4 and 1·1. The present study showed that demographic factors are strongly related to the occurrence of this cancer. For example, the risk of laryngeal cancer for skilled male workers living in Copenhagen (RR 4·76; 95% CI 3·61–6·28) was estimated to be almost five times higher than the risk for men self employed in agriculture and living in rural areas.

Alcohol and tobacco are well known causes of laryngeal cancer.[1] The demographic variables may appear as risk factors because they are associated with alcohol and tobacco consumption, and we examined these associations. The tobacco consumption in Denmark is known from annual marketing surveys of 20 000 persons.[20] As in other countries, region is associated with tobacco consumption; the percentage of smokers in 1970 ranged from 64% in rural areas to 74% in Copenhagen among men, and from 35% to 58% among women. The percentage of heavy cigarette smokers ranged from 6% in rural areas to 19% in Copenhagen for men, and from 2% to 13% for women. Danes' habits with regard to alcohol consumption were investigated, in 1978, in a survey of 2596 persons.[21] Fifty nine per cent of men in

Table 6 High risk occupational groups among men for incidence of laryngeal cancer in Denmark (1970–80)

Occupation	*Observed*	*Expected*	*RR*
Restaurants and breweries:			
Waiter	19	2·99	6·36
Brewery worker	13	4·29	3·03
Restaurant owner	10	4·50	2·22
Catering officer	3	0·49	6·15
Shipyard:			
Shipyard worker	8	3·94	2·03
Smith in shipyard	6	3·78	1·59
Mechanic in shipyard	5	1·56	3·21
Boatbuilder	4	0·86	4·63
Building:			
Bricklayer	19	8·85	2·15
Carpenter in carpenter's shop	10	5·50	1·82
Construction enterprise owner	7	2·75	2·54
Plumber	4	2·38	1·68
Smith in plumber's shop	3	1·01	2·97
Chemical industry:			
Chemical industry worker	13	6·37	2·04
Stone, clay, or glass industry worker	10	7·09	1·41
Rubber industry worker	3	1·40	2·14
Butchers and bakers:			
Slaughterhouse worker	14	6·10	2·29
Bakery shop owner	6	3·73	1·61
Butcher in slaughterhouse	5	2·64	1·89
Baker	5	3·46	1·45
Butcher in butcher's shop	3	1·14	2·63
Seamen:			
Self employed fisher	11	5·56	1·98
Stoker	6	3·15	1·91
Sea captain, pilot	5	2·66	1·88
Metal industry:			
Mechanic in engineering work	10	6·86	1·46
Car and motorcycle repair, shop owner	7	3·50	2·00
Fitter in metal industry	6	2·33	2·57
Iron and steel industry worker	6	4·00	1·50
Foreman in engineering work	6	3·30	1·82
Owner of engineering workshop	6	4·01	1·50
Smith in metal industry	6	2·45	2·45
Foreman in radio/TV production	5	1·68	2·97
Smith in engineering work	5	2·65	1·89
Smith in engineering work	4	2·16	1·85
Drivers and chauffeurs:			
Driver in various retail sales	11	7·44	1·48
Self employed taxi driver	8	4·51	1·77
Driver in food industry	7	3·45	2·03
Bus driver	5	2·09	2·39
Driver in various industries	5	3·41	1·47
Crane driver in building	5	2·78	1·80
Self employed contractor	5	2·96	1·69
Driver, not otherwise specified	4	2·25	1·78
Bus driver as public servant	4	2·19	1·82
Self employed in various forms of transport	3	1·47	2·04
Shop assistant:			
Senior shop staff in various industries	10	6·89	1·45
Senior shop staff in wholesale trade	8	5·33	1·50
Shop assistant in department stores	3	0·55	5·48
Mixed:			
Shop owner, household utensils	12	7·36	1·63
Porter in real estate administration	8	4·10	1·95
Porter in other industry	8	3·57	2·24
Self employed in cleaning	4	2·37	1·69
Fireman	4	0·73	5·45
Draughtsman	4	1·76	2·27
Typographer for newspaper	4	2·09	1·91
Hospital porter	4	2·25	1·78
Actor	2	0·45	4·49
Non-informative occupations:			
Worker in manufacturing, not otherwise specified	20	11·70	1·71
Unknown trade	13	7·89	1·65

Copenhagen, 50% in provincial towns, and 45% in rural areas declared that they had consumed alcohol during the preceding weekdays; the corresponding numbers for women were 36%, 32%, and 27%. The same differences, though at higher levels, were observed between proportions of drinkers during the weekend. The regional variations in alcohol and tobacco consumption are, therefore, in the same direction as the variations in the risks for laryngeal cancer.

In 1970 the percentage of smokers according to occupation among men ranged only from 73% for salaried employees with higher education to 75% for unskilled workers. The range was between 55% and 61% for women.[20] In 1978 there was a slightly higher percentage of regular drinkers among salaried employees and skilled workers (about 60% of regular male drinkers on weekdays) than among self employed and unskilled workers (53%).[21] Thus there is no clear relation between the consumption of tobacco and alcohol and RRs for laryngeal cancer in the different occupational categories. This observation is supported by the findings of a Danish case referent study on laryngeal cancer and occupation, in which the RRs of 1·3 for skilled workers and of 1·9 for semiskilled or unskilled workers were hardly changed after adjustment for alcohol or tobacco consumption.[7]

Marital state was also a risk indicator for laryngeal cancer with an excess risk for widowed or divorced and married persons compared with unmarried persons. Widowed and divorced persons normally have an excess risk of mortality and morbidity compared with married persons.[22] This is generally also true for unmarried people compared with those who are married. The excess risk of laryngeal cancer found for married persons in this study differs from this pattern. Nevertheless, the analysis of mortality data in Denmark 1970–80 supports the results of the present study, as the cumulative death rate for all respiratory cancers was 4·1% for married men and only 3·4% for unmarried men[23] (and O Andersen, personal communication). This unusual trend was not observed for women or for other causes of death in men.

The analysis suggested occupational group as being an independent risk factor for laryngeal cancer. In men the highest risk was found for skilled workers

(RR = 2·95 95% CI 2·17–4·00), a threefold excess risk compared with men self employed in agriculture. To pinpoint the specific occupations at high risk we tabulated the incidence of laryngeal cancer for men for 492 specific occupational groups defined by the detailed codes for occupation and industry in the census data. Expected numbers were calculated from the age specific incidence rates for all economically active men.

The observed number of cases of laryngeal cancer exceeded the expected number plus one in 58 out of the 492 groups. These groups are listed in table 6. For some the occupational titles indicate exposure to known risk factors for laryngeal cancer. Workers in restaurants and breweries may be expected to have an excess alcohol consumption. Workers in shipyards and buildings may be exposed to asbestos and man made mineral fibres. Not all the excess risks shown in table 6, however, seem to be associated with known risk factors. Examples are the excess risk of laryngeal cancer among butchers, bakers, and drivers and among the metal workers in engineering, which include smiths, mechanics, foremen, and shop owners. Welding as a risk factor for laryngeal cancer has been studied in a case-control study in Denmark. The study included 271 cases, and showed a moderately increased risk (RR = 1·3) when alcohol and tobacco were controlled for.[24] It also identified drivers as a high risk group for laryngeal cancer.[7]

Observational studies serve to generate hypotheses about aetiology. This multivariate analysis of sociodemographic factors showed an almost fivefold variation in the risk of laryngeal cancer within the relatively small population of Danish men. Tobacco smoking and alcohol drinking alone do not explain this variation, and groups such as butchers, bakers, drivers, and engineering workers seem to be exposed to occupational risk factors that should be scrutinised.

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