- enteropathogens on the growth of children in rural Bangladesh. *Pediatrics* 1984;73:799-805.
- 5 Martorell R, Habicht JP, Yarbrough C, Lechtig A, Klein RE, Western KA. Acute morbidity and physical growth in rural Guatemalan children. *Am J Dis Child* 1975;129:1296-301.
 - 6 Black RE, Merson MH, Taylor PR, et al. Glucose vs sucrose in oral rehydration solutions for infants and young children with rotavirus-associated diarrhea. *Pediatrics* 1981;67:79-83.
 - 7 Kielmann AA, McCord C. Weight-for-age as an index of risk of death in children. *Lancet* 1978;i:1247-50.
 - 8 Chen LC, Chowdhury AKMA, Huffman SA. Anthropometric assessment of energy-protein malnutrition and subsequent risk of mortality among preschool aged children. *Am J Clin Nutr* 1980;33:1836-45.
 - 9 Trowbridge FL, Newton LH. Seasonal changes in malnutrition and diarrheal disease among preschool children in El Salvador. *Am J Trop Med Hyg* 1979;28:135-41.
 - 10 Trowbridge FL, Newton LH, Campbell CC. Nutritional status and the severity of diarrhoea. *Lancet* 1981;i:1375.
 - 11 Gordon JE, Guzman MA, Ascoli W, Scrimshaw NS. Acute diarrheal disease in less developed countries. 2. Patterns of epidemiological behavior in rural Guatemalan villages. *Bull WHO* 1964;31:9-20.
 - 12 Tomkins A. Nutritional status and severity of diarrhoea among preschool children in rural Nigeria. *Lancet* 1981;i:860-2.
 - 13 Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh 1-3. *Am J Clin Nutr* 1984;39:87-94.
 - 14 Gomez F, Galvan RR, Cravioto J, Frenk S. Malnutrition in infancy and childhood, with special reference to kwashiorkor. In: Levine SZ, ed. *Advance in pediatrics*. Vol 7. Chicago: Year Book Publishers, 1955:131-69.
 - 15 Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. *Statistical package for the social sciences*. New York: McGraw Hill, 1975.
 - 16 Breslow NE, Day NE. *Statistical methods in cancer research*. Vol 1. *The analysis of case-control studies*. Lyons: International Association for Research on Cancer, 1980:142-3. (Scientific publication No 32.)
 - 17 Rothman KJ, Boice JD. *Epidemiologic analysis with a programmable calculator*. Boston: Epidemiology Resources, 1982:5-7.
 - 18 Miettinen OS. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976;103:226-35.
 - 19 Schlesselman J. *Case control studies. Design, conduct, analysis*. New York: Oxford University Press, 1982:227-90.
 - 20 Munson D, Franco D, Arbeter A, Velez H, Vitale JJ. Serum levels of immunoglobulins, cell-mediated immunity and phagocytosis in protein-calories malnutrition. *Am J Clin Nutr* 1974;27:625-8.
 - 21 Schlesinger D, Stokel A. Impaired cellular immunity in marasmic infants. *Am J Clin Nutr* 1974;27:615-20.
 - 22 Purtilo DT, Riggs RS, Evans R, Neafe RC. Humoral immunity of parasitized, malnourished children. *Am J Trop Med Hyg* 1976;25:229-32.
 - 23 Koster F, Gaffar A, Jackson TM. Recovery of cellular immune competence during treatment of protein-calorie malnutrition. *Am J Clin Nutr* 1981;34:887-91.
 - 24 Chandra RK. Reduced secretory antibody response to live attenuated measles and poliovirus vaccine in malnourished children. *Br Med J* 1975;ii:583-5.
 - 25 Sirisinha S, Suskind R, Edelman R, Asvapaka C, Olson RE. Secretory and serum IgA in children with protein-calorie malnutrition. *Pediatrics* 1975;55:166-70.
 - 26 Green F, Heyworth B. Immunoglobulin-containing cells in jejunal mucosa of children with protein energy malnutrition and gastroenteritis. *Arch Dis Child* 1980;55:380-3.
 - 27 Kielmann AA, Uderoi IS, Chandra RK, et al. The effect of nutritional status on immune capacity and immune responses in preschool children in a rural community in India. *Bull WHO* 1976;54:477-83.
 - 28 Brunser O, Reid A, Monckeberg F, Maccioni A, Contreras I. Jejunal mucosa in infant malnutrition. *Am J Clin Nutr* 1968;21:976-83.
 - 29 Hirschhorn N, Molla A, Molla AM. Reversible jejunal disaccharidase deficiency in cholera and other acute diarrheal diseases. *Johns Hopkins Medical Journal* 1969;125:291-300.
 - 30 Coello-Ramirez P, Lifshitz F, Zuniga V. Enteric microflora and carbohydrate intolerance in infants with diarrhea. *Pediatrics* 1972;49:233-42.
 - 31 Gribbin M, Walker-Smith J, Wood C. Delayed recovery following acute gastroenteritis. *Acta Paediatrica Belgica* 1976;29:167-76.

(Accepted 17 February 1989)

Smoking and leanness: evidence for change in Finland

Bernard Marti, Jaakko Tuomilehto, Heikki J Korhonen, Leena Kartovaara, Erkki Vartiainen, Pirjo Pietinen, Pekka Puska

Abstract

Many studies have shown smokers to weigh less than non-smokers, which is plausible given the metabolic effects of cigarette smoke. The interrelation between smoking and relative body weight and its change over time were analysed by using data from Finnish population based surveys from 1982 and 1987. Among both men and women the inverse association between smoking and body mass index was clearly weakened between 1982 and 1987. In 1987 among men aged 25-44 smoking was positively related to body mass index. Moreover, the relation between smoking and waist to hip girth ratio was positive in both sexes at all ages. Years of smoking was nevertheless confirmed as a significant inverse predictor of relative weight. A cluster of unfavourable health habits, including high consumption of alcohol and saturated fats, especially emerged among younger smokers. This may have been due to different selection of smokers in Finland, where smoking increasingly seems to be a form of deviant or risk taking behaviour.

It is concluded that at a population level the metabolic effects of smoking seem to be increasingly overridden by several other unfavourable health behaviours of smokers.

Introduction

Numerous epidemiological studies have compared the body weights of smokers and non-smokers, and nearly all have found that smokers as a group weigh less than people who have never smoked.¹⁻¹¹ Among men the inverse association between smoking and body weight is strongest in older smokers and weakest in younger smokers, which may be due to the duration of smoking.^{3,4,7} For example, metabolic studies have shown that smokers have an increased resting energy

expenditure.¹² Behavioural, environmental, and cognitive factors, however, are also active determinants of diet, exercise, and body weight.⁴ Indeed, smoking has shown a U shaped relation with relative weight in several studies, smokers of 5-20 cigarettes a day being the leanest.^{2,5,7,8,13}

Though paradoxical given the metabolic effects of smoking, possibly heavier smokers may weigh more because they have other unhealthy habits such as heavy drinking and little exercise.^{14,15}

This paper examines the association between smoking and body mass index among the Finnish population in 1982 and 1987. The study used population based data collected as part of the World Health Organisation's multinational project of monitoring trends and determinants in cardiovascular diseases (MONICA).¹⁶

Subjects and methods

In 1982 and 1987 cross sectional surveys of risk factors were carried out in four areas in Finland.¹⁶ Independent random samples were drawn from these four populations covering the age range 25-64 years. Response rates in the surveys were 80-94%.^{16,17} This analysis is based on data from 4508 men and 4648 women in 1982 and 2913 men and 3212 women in 1987. The surveys included a self administered questionnaire checked by an interviewer and physical measurements. Weight, height, and girth of waist and hips were measured in light clothing by trained personnel. The body mass index (weight (kg) divided by height (m) squared) was used as a measure of relative body weight.

Information on smoking was obtained by seven standardised questions in the questionnaire. Those subjects who reported that they had smoked regularly for at least a year and at least once a day on average

National Public Health Institute, Mannerheimintie 166, SF-00300 Helsinki, Finland

Bernard Marti, MD, research fellow

Jaakko Tuomilehto, MD, professor

Heikki J Korhonen, MD, research fellow

Leena Kartovaara, MPOLSC, systems analyst

Erkki Vartiainen, MD, assistant professor

Pirjo Pietinen, DSC, assistant professor

Pekka Puska, MD, professor

Correspondence to: Dr Tuomilehto.

Br Med J 1989;298:1287-90

during the past month were classified as current smokers. All others were classified as current non-smokers. The participants reported the number of years of regular smoking and current smokers the number of cigarettes, pipefuls, or cigars smoked daily. In 1987 only 56 (1.9%) of the men and 3 (0.1%) of the women reported smoking pipe or cigars, and these forms of smoking accounted for less than 3% of the overall number of episodes of daily smoking in men and practically none in women.

Alcohol consumption was assessed by questions on the amount of beer, mild alcoholic beverages, strong alcoholic beverages, and wine consumed in the previous seven days. Alcohol consumption in g/week was estimated by applying the average alcoholic content and sizes of bottles or portions in Finland.¹⁸ An overall index of saturated fat intake was calculated on the basis of answers to questions related to consumption of milk fat and amount and type of fat spread used on bread.¹⁹ Leisure time physical activity was assessed on a four point scale by means of a multiple choice question characterising the amount and type of usual exercise.²⁰

Associations of smoking state with the body mass index and their change over time (period effect) were analysed for men and women separately by two way analysis of variance, age being entered as a covariate. Mean values of body mass index among subgroups stratified by different numbers of years of smoking were adjusted for age and the number of cigarettes smoked daily with general linear models, and determinants of body mass index among smokers were also analysed by multiple least squares linear regression. Standard statistical software packages were used for analyses.^{21 22}

TABLE I—Age adjusted means and analysis of variance of body mass index (kg/m²) among Finnish men and women stratified by smoking state and period (1982 and 1987)

	1982		1987	
	Body mass index	No studied	Body mass index	No studied
Men:				
Non-smokers	26.65	2779	26.97	1911
Current smokers	25.82	1729	26.45	1002
Total	26.32	4508	26.79	2913
Difference between non-smokers and smokers	0.83		0.52	
Women:				
Non-smokers	26.19	3852	26.51	2691
Current smokers	24.43	796	25.09	521
Total	25.88	4648	26.27	3212
Difference between non-smokers and smokers	1.76		1.42	

Main effects: period (subjects heavier in 1987 than in 1982), men $p < 0.001$, women $p < 0.001$; smoking state (non-smokers heavier than smokers), men $p < 0.001$, women $p < 0.001$.

Two-way interaction: period by smoking state (five year increase in body mass index greater in smokers than non-smokers), men $p = 0.036$, women $p = 0.118$.

TABLE II—Linear correlation coefficients of smoking with body mass index (kg/m²) among Finnish men and women aged 25-64 in 1982 and 1987 and linear correlation coefficients of smoking with waist to hip girth ratio in subjects of same age ranges in 1987

		1982			1987		
		Age 25-44	Age 45-64	Total	Age 25-44	Age 45-64	Total
Smoking* with body mass index	Men	0.03 (2300)	-0.13 (2208)	-0.06 (4508)	0.06 (1364)	-0.06 (1549)	-0.02 (2913)
	Women	-0.03 (2227)	-0.12 (2421)	-0.15 (4648)	0.00 (1528)	-0.08 (1684)	-0.11 (3212)
Smoking* with waist to hip girth ratio	Men				0.11 (1364)	0.04 (1549)	0.05 (2913)
	Women				0.08 (1528)	0.04 (1684)	0.01 (3212)

*Seven point scale: never smoked = 1; ex-smoker for ≥ 6 months = 2; ex-smoker for < 6 months = 3; irregular smoker = 4; current smoker of 1-14 cigarettes a day = 5; current smoker of 15-24 cigarettes a day = 6; current smoker of ≥ 25 cigarettes a day = 7.

TABLE III—Mean values of body mass index (kg/m²) adjusted for age and number of cigarettes smoked daily stratified by duration of smoking history among 990 male current smokers in 1987*

	Years of smoking				
	1-10 (n=200)	11-20 (n=372)	21-30 (n=253)	31-40 (n=126)	≥ 41 (n=39)
Body mass index (SE)	26.95 (0.30)	26.90 (0.22)	26.19 (0.26)	25.63 (0.37)	24.06 (0.69)

*Remaining 12 male current smokers in 1987 excluded from analysis because of lack of data.

Results

Table I presents the mean values of body mass index in men and women in 1982 and 1987 stratified by smoking state. Overall there was a significant increase in weight in both sexes from 1982 to 1987. The increase among men was significantly greater in smokers than non-smokers ($p = 0.036$ for interaction), and a similar trend was observed among women.

Age emerged as an important modifying factor of the association between smoking and weight (table II); in both sexes the inverse relation tended to be stronger in older (age 45-64) than younger subjects (25-44). The correlations were of low order, indicating that smoking was not a main determinant of relative weight. From 1982 to 1987, however, all correlation coefficients showed a remarkably consistent shift (by 0.03 to 0.07) in the positive direction. Thus in 1987 a significant positive association between smoking and weight was observed in all younger men, and in the older men the inverse association substantially decreased from 1982 to 1987. In addition, in 1987 both younger men and women showed a positive association between smoking and the waist to hip girth ratio.

To elucidate the reasons for the apparent reduction in weight difference between smokers and non-smokers between the two survey years determinants of body weight among current smokers were first analysed cross sectionally. In the 1987 data age was a strong predictor of body weight among the younger smokers, but among the older smokers duration of smoking was the strongest. The number of cigarettes smoked a day was a significant positive predictor of body weight in younger but not older men (data not shown). When the analysis was repeated for the 1982 data the findings were practically identical. This showed that among the smokers smoking related predictors of body weight had not changed.

To estimate the importance of years of smoking as a predictor of body weight in men mean values of body mass index adjusted for age and number of cigarettes smoked daily were computed for men with histories of 1-10, 11-20, 21-30, 31-40, and ≥ 41 years of smoking (table III). There was a consistent inverse gradient between years of smoking and relative weight that was especially pronounced after more than 20 years of smoking.

Among men smokers drank more alcohol, ate more saturated fats, exercised less, were less well educated, and had higher resting heart rates than non-smokers

TABLE IV—Mean values (SD in parentheses) of selected characteristics of male current non-smokers and smokers in 1982 and 1987

	1982			1987		
	Non-smokers (n=2779; 61.6%)	Smokers (n=1729; 38.4%)	All (n=4508; 100.0%)	Non-smokers (n=1911; 65.6%)	Smokers (n=1002; 34.4%)	All (n=2913; 100.0%)
Alcohol consumption* (g/week)	46.0 (76.0)	95.3 (141.5)	65.3 (109.2)	45.5 (71.1)	95.8 (150.1)	63.4 (108)
Saturated fat intake† (g/day)	28.2 (21.3)	32.8 (23.1)	30.0 (22.2)	24.0 (19.8)	30.9 (23.2)	26.4 (21.3)
Leisure time exercise‡	2.01 (0.77)	1.75 (0.70)	1.91 (0.75)	2.00 (0.74)	1.78 (0.70)	1.93 (0.73)
Years of education	9.1 (3.8)	8.8 (3.2)	9.0 (3.6)	9.8 (3.8)	9.4 (3.4)	9.7 (3.7)
Resting heart rate (beats/min)	69.0 (12.5)	74.8 (12.9)	71.2 (12.9)	70.0 (12.4)	75.9 (13.1)	72.0 (13.0)
Age (years)	45.2 (11.0)	42.9 (11.2)	44.3 (11.1)	46.1 (11.3)	43.3 (10.9)	45.1 (11.3)
Cigarettes smoked daily	—	18.2 (9.3)	—	—	18.3 (9.8)	—

*Self reported alcohol consumption during week preceding surveys.

†Saturated fat from milk and fat used on bread only (see text for results of analysis of variance).

‡Four point scale from sedentary to training for competitive endurance sports.

(table IV). With the exception of consumption of saturated fats these differences remained remarkably stable between 1982 and 1987. With respect to saturated fat consumption, however, the downward trend was significantly steeper in non-smokers (-4.2 g/day) than smokers (-1.9 g/day) ($p=0.025$ for age adjusted interaction for period by smoking state). Among women smokers had a lower mean age than non-smokers. Saturated fat intake also decreased in women between 1982 and 1987—in non-smokers by 3.1 g/day but in smokers by only 1.3 g/day ($p=0.021$ for age adjusted interaction for period by smoking state).

A further analysis of variance of body mass index in current male smokers in 1987 examined the interaction effect of alcohol consumption and age. Among the 25-44 year olds the highest average body mass index was found in those who were both heavy smokers and heavy drinkers, whereas in the older age group (45-64) men with high cigarette and alcohol consumption had the lowest body mass index. Owing to the comparatively small numbers of current smokers who reported some alcohol consumption during the week before the survey the three way interaction term failed to reach significance ($p=0.10$). The finding nevertheless illustrated the opposed character of the smoking-alcohol-weight interrelation between younger men (synergistic) and older men (antagonistic) and indicated that the clustering of unhealthy habits tended to be more pronounced in younger than older middle aged men. Similar associations with body weight, alcohol consumption, and age were not seen in women smokers.

Discussion

Years of smoking have been shown to be the main determinant of lung cancer. Recently years of smoking has been recognised as the most informative measure of smoking for the risk of cardiovascular disease.²³ It is also a predictor of body weight,⁷ and our cross sectional data accord with other observations of an inverse association between the duration of smoking and relative weight for men. Metabolic studies have shown an increased resting energy expenditure in smokers,¹² so it is not surprising that the cumulative negative effect of smoking on body weight should be most clearly seen after several years of smoking. An increased metabolic rate among smokers might also explain why smokers weigh less than non-smokers despite their sometimes higher energy intake and often lower levels of leisure activity.^{3,4,24} On the other hand, the daily amount of smoking was a positive rather than negative predictor of body weight in younger smokers. Similar findings have been reported from The Netherlands.⁵

Our main finding was that the usually observed inverse association of smoking with body weight¹⁻¹¹ disappeared in Finnish men and became substantially attenuated in Finnish women during 1982-7. More-

over, in as short a time as five years a substantial increase in weight had occurred both in smokers and in non-smokers. Interestingly, recently published figures from the United States also show that in two large population based surveys smokers were leaner than non-smokers in 1976-80 but no longer so in 1981-3.¹⁰

We have little doubt that our observation was real. Weight and height of all subjects were measured by trained personnel under standardised conditions. Self reported smoking habits have been validated by measurement of serum thiocyanate concentration and shown to be reliable.¹⁷ Alcohol consumption during the week before the survey was validated by measurement of serum γ -glutamyltransferase activity,¹⁸ and the appropriateness of the saturated fat intake variable, based on milk, butter, and margarine consumption, was tested with three day food consumption records.²⁵

What might be the reasons for a diminishing difference in body weight between smokers and non-smokers in Finland? Other workers have also noted an intriguing modifying effect of age on the association between smoking history and body weight in cross sectional analyses.^{3,7} In a large representative sample of men and women from the United States current smokers aged up to 34 and with a history of smoking for 1-20 years were not leaner than age matched non-smokers, whereas smokers aged 50 or over and with a history of smoking for less than 11 years were significantly leaner than non-smokers.⁷ Even though biological effects of cigarette smoke on humans require a long incubation period, the observation that younger smokers show a smaller effect of an equal number of years of smoking on body mass index than older smokers suggests that factors other than smoking are responsible, possibly related to health habits.

Individual health behaviour with an increased clustering of unfavourable health habits especially among younger men might be the most likely explanation for our results. From our data male and female Finnish smokers showed a significant departure from the population wide trend towards a lower saturated fat intake from 1982 to 1987. This suggests that smokers may have been more resistant to adopting healthier dietary habits than non-smokers, which may reflect current smokers' lack of interest in health promotion in general. This seemed to be particularly true for the younger male smokers, as the combination of high alcohol and high cigarette consumption was associated with higher relative weight in younger men but not in older men or in women. This agrees with an observation from the United States that alcohol consumption tended to mitigate the inverse smoking-body mass index relation in men but not in women.¹⁰ Secondly, smoking was significantly and positively related to the waist to hip girth ratio in younger men.²⁶ Interestingly the waist to hip girth ratio has been suggested as a better predictor of coronary risk than body mass index.⁶ Waist to hip girth ratio reflects the distribution of body fat and may be more closely related to health habits and lifestyle than the body mass

index, which is also modified by differences in body build and muscularity.²⁷ In general our results accord with observations from the United States of a clustering of negative health habits among smokers, which may have become more pronounced in recent years.⁸

We can only speculate why the characteristics of smokers in Finland seem to be changing. In the past smoking was considered to be a "normal" habit; but with the Finnish antismoking legislation from 1977, increased antismoking education, and changing public attitudes smoking is being regarded more as a deviant behaviour. Thus today smokers may be personalities more prone to risk taking and unhealthy behaviours than earlier. It may be hypothesised that the hard core of current smokers, who hitherto have resisted anti-smoking campaigns, consist of an increasing selection of people with unfavourable health behaviour. In another Finnish study²⁸ persistence in smoking was associated with greater use of alcohol and coffee, possibly due to a common pathophysiology of dependence.²⁹ On the other hand, the average number of cigarettes smoked daily by current smokers did not increase from 1982 to 1987 as one would expect for the hypothesis of an increasing cluster of negative health habits.

In conclusion our population based data from large samples of middle aged Finnish men and women suggest that the metabolic effects of smoking are apparently increasingly overridden by the present behavioural characteristics of smokers such as high alcohol and saturated fat consumption and little exercise. The earlier generally accepted notion that smokers weigh less than non-smokers¹¹ may thus soon turn out to be anachronistic. It also seems plain that antismoking health education aimed at young and middle aged men should place more emphasis on correcting an unhealthy lifestyle as a whole.

BM was supported by grant No 3.763-0.87 from the Swiss National Science Foundation.

- Gordon T, Kannel WB, Dawber TR, McGee D. Changes associated with quitting cigarette smoking: the Framingham study. *Am Heart J* 1975;90:322-8.
- Noppa H, Bengtsson C. Obesity in relation to smoking: a population study of women in Göteborg, Sweden. *Prev Med* 1980;9:534-43.
- Jacobs DR, Gothenborg S. Smoking and weight: the Minnesota Lipid Research Clinic. *Am J Public Health* 1981;71:391-6.
- Wack JT, Rodin J. Smoking and its effects on body weight and the systems of caloric regulation. *Am J Clin Nutr* 1982;35:366-80.
- Baecke JA, Burema J, Frijters JE, Hautvast JG, Wiel-Wetzel WA. Obesity in

- young Dutch adults (II): daily life-style and body mass index. *Int J Obes* 1983;7:13-24.
- Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow-up of participants in the study of men born in 1913. *Br Med J* 1984;288:1401-4.
- Albanes D, Jones Y, Micozzi MS, Mattson M. Associations between smoking and body weight in the US population: analysis of NHANES II. *Am J Public Health* 1987;77:439-44.
- National Center for Health Statistics, Schoenborn CA, Benson V. *Relationships between smoking and other unhealthy habits: United States, 1985*. Hyattsville, Md: United States Department of Health and Human Services, 1988. (*Advance Data from Vital and Health Statistics*, No 154.)
- Lund-Larsen PG, Tretli S. Changes in smoking habits and body weight after a three-year period—the cardiovascular disease study in Finnmark. *J Chronic Dis* 1982;35:773-80.
- Williamson DF, Forman MR, Binkin NJ, Gentry EM, Remington PL, Trowbridge FL. Alcohol and body weight in United States adults. *Am J Public Health* 1987;77:1324-30.
- Kromhout D, Saris WH, Horst CH. Energy intake, energy expenditure, and smoking in relation to body fatness: the Zutphen study. *Am J Clin Nutr* 1988;47:668-74.
- Hofstetter A, Schutz Y, Jequier E, Wahren J. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med* 1986;314:79-82.
- Killen JD, Fortmann SP, Telch MJ, Newman B. Are heavy smokers different from light smokers? *JAMA* 1988;260:1581-5.
- Marti B, Salonen JT, Tuomilehto J, Puska P. 10-Year trends in physical activity in the eastern Finnish adult population: relationship to socio-economic and lifestyle characteristics. *Acta Med Scand* 1988;224:195-203.
- Salonen JT, Puska P, Kottke TE, Heinonen OP. Coronary risk factor clustering patterns in eastern Finland. *Int J Epidemiol* 1981;10:203-10.
- Puska P, Salonen JT, Nissinen A, et al. Change in risk factors for coronary heart disease during 10 years of a community programme (North Karelia project). *Br Med J* 1983;287:1840-4.
- Puska P, Tuomilehto J, Salonen JT, et al. *The North Karelia project: a comprehensive community programme for control of cardiovascular diseases in North Karelia, Finland 1972-1977*. Copenhagen: WHO/EURO, 1981.
- Salonen JT, Happonen P, Salonen R, et al. Interdependence of associations of physical activity, smoking, and alcohol and coffee consumption with serum high-density lipoprotein and non-high-density lipoprotein cholesterol—a population study in eastern Finland. *Prev Med* 1987;16:647-58.
- Pietinen P, Nissinen A, Vartiainen E, et al. Dietary changes in the North Karelia project (1972-1982). *Prev Med* 1988;17:183-93.
- Tuomilehto J, Marti B, Salonen JT, Virtala E, Lahti T, Puska P. Leisure-time physical activity is inversely related to risk factors for coronary heart disease in middle-aged Finnish men. *Eur Heart J* 1987;8:1047-55.
- SPSS. *Statistical package for the social sciences. SPSSX advanced statistics guide*. Chicago, Illinois: SPSS, 1985.
- SAS Institute. *Statistical analyses system. SAS user's guide: statistics*. 5th ed. Cary, North Carolina: SAS Institute, 1985.
- Cook DG, Shaper AG, Pocock SJ, Kussick SJ. Giving up smoking and the risk of heart attacks: a report from the British regional heart study. *Lancet* 1986;ii:1376-9.
- Stamford BA, Matter S, Fell RD, Sady S, Cresanta M, Papanek P. Cigarette smoking, exercise and high density lipoprotein cholesterol. *Atherosclerosis* 1984;52:73-83.
- Pietinen P, Uusitalo U, Vartiainen E, Tuomilehto J. Dietary survey of the FINMONICA project in 1982. *Acta Med Scand* 1988; suppl 728: 169-77.
- Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat: effects of cigarette smoking. *JAMA* 1989;261:1169-73.
- Vague P. *La différenciation sexuelle humaine. Ses incidences en pathologie*. Paris: Masson Editeur, 1953:386-96.
- Kaprio J, Koskenvuo M. A prospective study of psychological and socio-economic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and nonsmokers. *Journal of Clinical Epidemiology* 1988;41:139-50.
- Istvan J, Matarazzo JD. Tobacco, alcohol, and caffeine use: a review of their interrelationships. *Psychol Bull* 1984;95:301-26.

(Accepted 8 March 1989)

Intralesional tumour necrosis factor combined with interferon gamma in metastatic melanoma

S Retsas, M Leslie, D Bottomley

Medical Oncology Unit,
Westminster Hospital,
London SW1P 2AP
S Retsas, MD, consultant
medical oncologist
M Leslie, MRCP, registrar in
oncology
D Bottomley, MRCP, senior
house officer

Correspondence to:
Dr Retsas.

Br Med J 1989;298:1290-1

Recombinant tumour necrosis factor α and interferon gamma are cytokines that show synergistic antitumour activity in vitro against clonogenic human tumour cells.^{1,2} Remission rates of up to 40% after direct injection of recombinant tumour necrosis factor α into the tumour have been reported.² We looked at the therapeutic potential of these two cytokines used together in seven patients with advanced metastatic malignant melanoma.

Patients, methods, and results

The study was approved by the hospital ethical committee. Three women and four men with a median

age of 44 years (range 28 to 57) took part. All patients had progressive disease in more than two organ sites, which was distributed as follows: skin (seven patients), lymph nodes (three), lung (three), bone (two), and brain (one). They had all previously been treated with chemotherapy, with a median of five drugs (range four to 11), and three had also received interferon alfa. Cerebral and cutaneous metastases in one woman had previously responded to chemotherapy with the DJV3 combination (vindesine, dacarbazine, carboplatin, vinblastine, and vincristine), and another patient had had a prolonged remission with interferon alfa, as already reported.^{3,4}

The planned treatment regimen was recombinant interferon gamma 100 $\mu\text{g}/\text{m}^2$ body surface area intramuscularly thrice weekly, followed by injection of recombinant tumour necrosis factor α once weekly into the lesion at an initial dose of 5 $\mu\text{g}/\text{m}^2$ and increasing to a maximum of 150 $\mu\text{g}/\text{m}^2$ if tolerance permitted. Selected subcutaneous lesions were injected, repeatedly when possible, except in one patient who lacked a suitable lesion and was injected subcutaneously.