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Ecologic Study of Lung Cancer Risk Factors in the U.S. and Japan, with Special Reference to Smoking and Diet

Ernst L. Wynder,[1,4] Emanuela Taioli[1,2] and Yasuyuki Fujita[3]

[1]American Health Foundation, 320 East 43 Street, New York, N.Y. 10017, USA, [2]National Research Council, ITBA, Via Ampere 56, 20100 Milano, Italy and [3]Department of Public Health, Jichi Medical School, Minamikawachi-machi, Tochigi-ken 329-04, Japan

Lung cancer mortality rates among United States and Japanese males were compared and related to smoking and dietary data. Mortality rates increased from 1950 to 1985 in both countries, but the absolute values are consistently lower in Japan (38.2 deaths/100,000 in 1985) than in the U.S. (72.2/100,000). The proportion of smokers is higher in Japan than in the U.S. since 1955. Japanese males start smoking considerably later than U.S. males, but smoke a higher quantity of cigarettes per day. Available information on inhalation practices and yield and type of cigarettes smoked showed no differences among the two countries large enough to account for the differences in mortality rates. Further data in this regard should be obtained. Dietary data show that fat consumption (as percentage of calories) is consistently higher in the U.S. than in Japan from 1950 (40% vs. 7.9%) through 1985 (43.5% vs. 24.5%). A linear relationship is observed between lung cancer mortality and fat intake. Our data support the hypothesis that dietary habits may modulate the carcinogenic effects of tobacco smoking.

Key words: Lung cancer — Ecologic study — Diet

The effects of cigarette smoking, the principal causative factor for lung cancer, are likely to be modulated by other factors, both exogenous and endogenous. Experimental as well as epidemiological studies suggest that dietary fats can enhance the effect of tobacco smoke on the pathogenesis of lung cancer, and that the regular intake of fruits and vegetables is associated with a lower risk.[1–9] Previous ecological studies carried out in our Institute suggested an association between dietary fat and lung cancer.[10, 11] International comparisons across countries could help to define a possible role of diet in the development of lung cancers. To examine the relationship between, diet, smoking, and lung cancer further, we performed an ecologic analysis on data from the U.S. and Japan, two countries with distinct food intakes and smoking habits, and a comparable quality of vital statistics.

MATERIALS AND METHODS

Age-specific lung cancer mortality rates in U.S. white males and Japanese males in the years 1950 through 1985 have been extracted from national statistics data.[12–16] Age-standardized mortality rates, using the 1970 U.S. population as a standard, have been calculated.

Fat intake, expressed as a percentage of total calories during the years 1950 through 1985, and the types of fat consumed (expressed in g/day/person) in the period 1956–1985, have been drawn from national statistics data for the U.S.[15] and Japan.[16, 17]

The proportion of male smokers from 1955 through 1985 and the number of cigarettes/day in the years 1965 through 1985 have been excerpted from U.S.[18, 19] and Japanese surveys.[20–22] Age at starting smoking was derived from a Japanese survey (I. Kato, personal communication) and from our hospital-based data on tobacco-related cancers (E. Taioli, unpublished data).

To allow an adequate induction period, fat intake and the proportion of smokers in each year were compared with mortality rates for lung cancer 10 years later.

RESULTS

Mortality data: Mortality rates for male lung cancer increased from 1950 to 1985 in both the U.S. (from 21.9 to 72.2 deaths/100,000) and Japan (from 3.3 to 38.2 deaths/100,000), with the absolute values in Japan consistently lower (Fig. 1). Age-specific mortality rates were increasing in Japan from 1955 through 1985, especially in the older age groups. In the U.S., the rates increased from 1955 to 1975 in all the age groups. In the period 1975–1985, age-specific mortality rates were stable or slightly decreasing in the younger age groups (Fig. 2), while they were stable or still increasing in the older groups (Fig. 3).

Smoking habits: A higher proportion of smokers has been observed among Japanese males than U.S. males since 1955 when data were first available (75.9% vs.

[4] To whom reprint requests should be addressed.

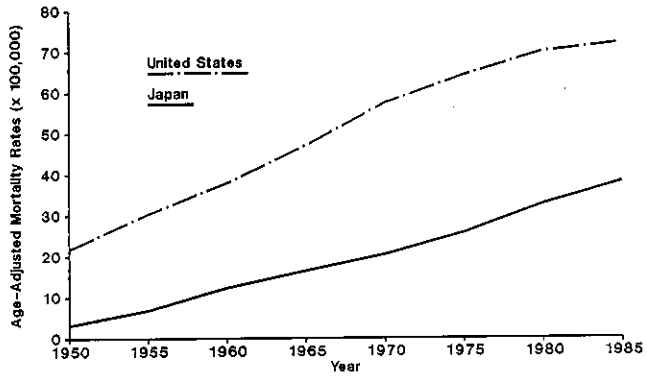

Fig. 1. Mortality rates for lung cancer among males in the U.S. and Japan (1950–1985). Source: References 12–14.

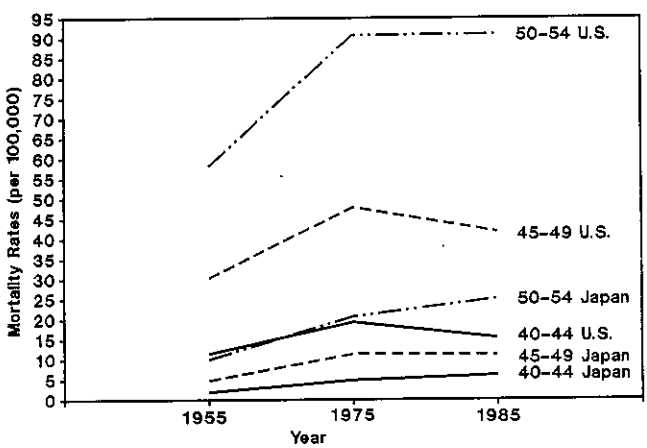

Fig. 2. Age-specific lung cancer mortality rates in the U.S. and Japanese males. Source: References 12–16.

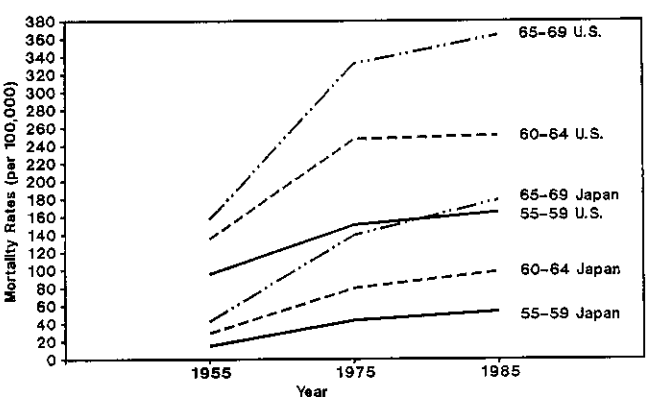

Fig. 3. Age-specific lung cancer mortality rates in the U.S. and Japanese males. Source: References 12–16.

Table I. Trend in the Proportion of Smokers and Number of Cigarettes Smoked per Day in U.S. and Japanese Males

Year	% Smokers		No. cigarettes/day	
	U.S.	Japan	U.S.	Japan
1955	54.2	75.9	—	—
1960	—	80.5	—	—
1965	51.1	82.3	—	19.4
1970	43.5	77.5	20.0	20.9
1975	41.9	76.2	21.2	23.8
1980	38.3	70.2	21.7	24.6
1985	33.2	64.6	22.8	24.6

Source: References 19–22.

Table II. Distribution of Age of Starting Cigarette Smoking among Current and Ex-smokers

Age at interview	n	Age of starting smoking			
		≤14 (%)	15–19 (%)	20–24 (%)	25+ (%)
Among the Japanese male population					
40–49	4462	0.2	32.6	61.5	5.7
50–59	4089	0.5	29.7	61.4	8.3
60–69	2572	0.2	18.7	70.5	10.7
70–79	1371	0.3	14.9	65.1	19.8
Among U.S. hospital-based sample					
40–49	1030	21.4	56.2	17.9	4.5
50–59	2435	19.3	56.6	17.9	6.2
60–69	2612	18.4	49.7	21.5	10.4
70–79	728	16.2	49.3	22.7	11.8

Source: Personal communication, and unpublished data.

54.2% in 1955). The proportion of smokers in Japan increased until 1970, when a decline began, while in the U.S., the number of smokers has declined since 1955, and is now about half of that observed in Japan (33.3% vs. 64.6% in 1985). The mean number of cigarettes per day was also slightly lower in the U.S. than in Japan for all the years considered (Table I). Among men over age 40, Japanese men tended to start smoking considerably later than U.S. men. About 60% of the Japanese men versus 18% of U.S. men started smoking between 20 to 24 years of age (Table II).

Tar and nicotine levels decreased from 1970 to 1980 in both U.S. and Japanese cigarettes (Table III). The market share of filter-tipped cigarettes was 51% in the U.S. and 3% in Japan in 1960; in 1982, the proportion of filter-tipped cigarettes sold in the U.S. and Japan was similar (Table III).

Dietary data: Fat consumption, as a percentage of total calories, was consistently higher in the U.S. than in

Table III. Changes in Tar and Nicotine Content of Cigarettes in the U.S. and Japan, 1970 and 1980, and Percentage Filter Cigarettes

	1970	1980
Tar (mg)		
U.S.	20.0	14.0
Japan	21.5	16.0
Nicotine (mg)		
U.S.	1.5	1.0
Japan	1.7	1.0

Filter cigarettes (%)	1960	1970	1982
U.S.	51.0	79.0	93.0
Japan	3.0	90.0	98.0

Source: References 19, 21, 23.

Japan in the years 1950–1985, even though the Japanese increased their fat intake considerably during this time period (+210%) (Table IV).

Analysis of the various types of fat consumed in the two countries indicated that the U.S. is characterized by a high intake of all types of fat, without great variation in the period considered (Table V). On the contrary, Japanese data showed an increased consumption of all types of fat, especially of saturated fat, starting from 1965 to 1980: +212% in individual intakes of monounsaturated, +75% of polyunsaturated, and +140% of saturated fats. The ratio of polyunsaturated to saturated fats has increased in the U.S. to 0.5:1, while it has remained about 1:1 in Japan. Vegetable consumption was also higher in the U.S. than in Japan in all the years under review (Table VI).

Table IV. Trend in per Capita Fat Consumption (Percentage of Calories) in U.S. and Japan

Year	U.S.	Japan
1950	40.0	7.9
1955	41.5	8.7
1960	41.5	10.6
1965	41.6	14.8
1970	42.3	18.7
1975	41.9	22.3
1980	41.8	23.6
1985	43.5	24.5

Source: References 14, 15.

Table VI. Trend in Vegetables Consumption in U.S. and Japan (g/day/person)

Year	U.S.	Japan
1950	—	242
1955	—	246
1960	—	214
1965	252	219
1970	306	249
1975	302	247
1980	308	241
1985	318	262

Source: References 15, 17.

Table V. Trend in Fatty Acid Consumption in U.S. and Japan

Year	Cholesterol	Monounsaturated fatty acid	Polyunsaturated fatty acid	Saturated fatty acid	P/S ratio
	(g/day/person)				
U.S.					
1960	560	58	20	60	0.33
1970	540	64	27	59	0.46
1975	500	61	27	54	0.50
1980	500	63	31	58	0.53
1985	500	61	33	61	0.54
Japan					
1956	214	8	8	5	1.61
1960	260	9	9	6	1.47
1965	356	16	11	8	1.31
1970	420	22	13	10	1.27
1975	452	25	13	12	1.15
1980	434	25	14	12	1.13

Source: References 15, 16.

The relationship between cigarette smoking, fat consumption, and lung cancer in the two countries has been analyzed by comparing smoking and fat intakes in the years 1955 through 1975 to age-adjusted mortality rates recorded 10 years and 20 years later (Fig. 4).

The percentage of smokers does not relate well to the relevant comparative lung cancer mortality in the two countries (Fig. 4), while fat intake showed a linear relationship with mortality among the Japanese population (Fig. 5).

DISCUSSION

Lung cancer mortality rates throughout the last 30 years have been significantly higher in the U.S. than in Japan, while the proportion of male smokers in the U.S.

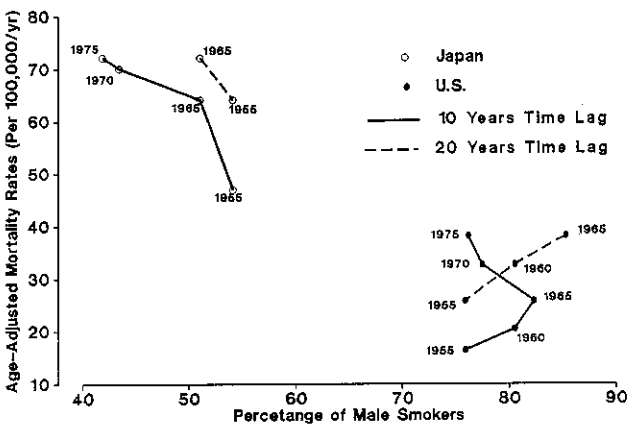

Fig. 4. Relationship between lung cancer mortality and smoking in males in the U.S. and Japan (1955–1975). Source: References 12–16.

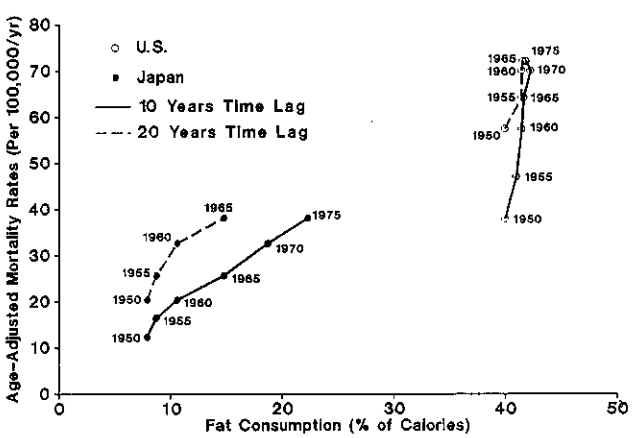

Fig. 5. Relationship between lung cancer mortality and fat consumption in males in the U.S. and Japan (1950–1975). Source: References 12, 13, 22.

was consistently lower than in Japan since 1955. Of course, in Japan, cigarette smoking is also the principal cause of lung cancer, as is true elsewhere in the world. However, available information about inhalation practices and yield and type of cigarette smoked, suggest that possible differences in these variables between the U.S. and Japan cannot fully explain the difference in mortality rates of lung cancer.[23]

U.S. and Japanese males showed considerable differences in the age at which they start smoking, with the U.S. males starting smoking significantly earlier than the Japanese. In the U.S. population, we found that an early age of starting smoking is positively associated with the number of cigarettes smoked per day later in life (Fig. 6). The relationship between age of starting smoking and number of cigarettes smoked per day does not appear to apply to the Japanese data. In fact, Japanese males start smoking significantly later than U.S. males but smoke a higher number of cigarettes.

The intercountry association between dietary fat and lung cancer, reported earlier,[10] has been supported by an intracountry comparison between northern and southern Italy,[11] and is now further strengthened by a U.S.-Japan comparison that includes detailed data of cigarette consumption.

Experimental studies provide possible mechanistic explanations for an effect of dietary fat on tobacco-induced lung carcinogenesis. There is epidemiological evidence that dietary fat can influence the development of hormone-related cancers and colon cancer.[24, 25] Experimentally, tumor-enhancing effects of fat have been observed for different sites such as the mouse skin,[26] rat mammary gland,[27] colon,[28] and pancreas.[29]

Several mechanisms have been proposed to account for the effect that dietary fat has on cancer risk (Table VII).

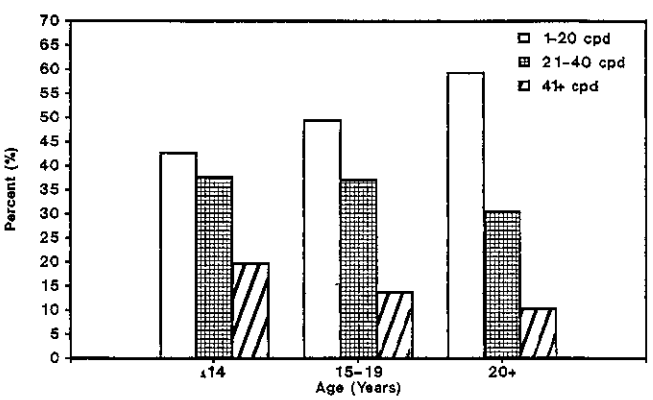

Fig. 6. Relationship between age of starting smoking and amount of cigarettes smoked per day among males in the United States. Source: Unpublished data.

Table VII. The High-fat Effect: Mechanisms

Biologic system	Reference	Mechanism
Endocrine	Cohen, Cancer Res. 41, 1981	Prolactin
	Siiterii *et al.*, Ann. NY Acad. Sci. 464, 1986	Free estrogen
		Sex hormone binding globulin
	Rose *et al.*, JNCI 78, 1987	Bioactive prolactin
Autocrine	Karmali, Ca 33, 1984	Prostagladins
Immune	Plescia *et al.*, PNAS 72, 1975	Natural killer cells
	Thomas & Erickson, JNCI 74, 1985	Natural killer cells
Oncogene activities	Tsai *et al.*, Science 293, 1989	*ras* gene
Gut bacteria	Adlercreutz, Gastroenterol, 86, 1984	Dietary precursors converted to estrogen-like compounds
	Goldin *et al.*, N. Engl. J. Med. 307, 1982	
Membrane structure	Cave & Jurkowski, JNCI 73, 1984	Prolactin receptor
Lipid peroxides	Petrakis *et al.*, Cancer Res. 41, 1981	Cholesterol epoxide

Various xenobiotics found in tobacco smoke, such as benz[*a*]pyrene, can be activated in the presence of various polyunsaturated fatty acids (PUFA).[30] Also, the activity of certain specific enzymes of the membrane-bound cytochrome P-450 class may be modulated by fat type and amount. These systems produce the reactive electrophilic metabolites of carcinogens like benzo[*a*]-pyrene and related hydrocarbons, and of the tobacco-specific nitrosamines in tobacco smoke.[31]

A high-fat intake may activate metabolic systems that affect the translocation and amplification of the activated oncogenes,[32] and alter the fatty acid composition of the cell membrane, which, in turn, can affect membrane fluidity, as well as membrane-bound receptor activity.[33]

Reactions of polyunsaturated fats with molecular oxygen and their metabolism to prostaglandins can promote free radical formation that, in turn, can result in damage to vital cell structures including the cell membrane and DNA.[33]

Animal studies show diets high in polyunsaturated fats to be both immunosuppressive and promoters of chemical tumorigenesis,[34] effects that appear to be mediated via eicosanoids. Natural killer (NK) cell activity does appear to be negatively effected by PUFA, and investigations in humans indicate that lowering dietary fat to 20% of calories may enhance NK cell activity.[35]

Fruits and vegetables have been suggested to reduce the risk of lung cancer in Japan,[36] but differences in male lung cancer rates among the U.S. and Japan cannot be accounted for by differences in intake of fruits and vegetables. During the period 1965–1985, U.S. intake of vegetables was slightly higher and increased more than in Japan (+26% in the U.S. vs. +20%). This change is too small to exert any influence on the trend in lung cancer mortality in the two countries.

The Japanese data suggest that a low fat diet, less than 25% of calories, reduces the importance of the type of fat consumed. The ratio of polyunsaturated to saturated fats (P:S ratio) (Table V) is considerably higher in Japan than in the U.S. The total amount of fat, therefore, appears to be the key rather than the P:S ratios.

Finally, in Japan as in the U.S., lung cancer would be an uncommon disease in the absence of cigarette smoking. Despite the limitations of ecologic studies,[37] the observation that a high-fat diet is associated with a higher mortality for lung cancer deserves mechanistic and preventive consideration, especially now that the Japanese population shows an increasing tendency toward a higher fat diet.

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REFERENCES

1) Kroes, R., Beems, R. B., Bosland, M. C., Bunnik, G. S. and Sinkeldam, E. J. Nutritional factors in lung, colon, and prostate carcinogenesis in animal models. *Fed. Proc.*, **45**, 136–141 (1985).

2) Beems, R. B. and van Beer, L. Modifying effect of dietary fat on benzo(a) pyrene-induced respiratory tract tumors in hamster. *Carcinogenesis*, **5**, 413–417 (1984).

3) Charest, M., Rossignol, G. and Castonguay, A. In vitro

and in vivo modulation of the bioactivation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in hamster lung tissues. *Chem.-Biol. Interact.*, **71**, 265–278 (1989).
4) Hirayama, T. Diet and cancer. Feasibility and importance of prospective cohort study. *In* "Diet and Human Carcinogenesis," ed. J. V. Joossens, pp. 191–198 (1985). Elsevier, Amsterdam.
5) Pisani, P., Berrino, F., Macaluso, M., Pastorino, U., Crosignani, P. and Baldasseroni, A. Carrots, green vegetables and lung cancer: a case-control study. *Int. J. Epidemiol.*, **15**, 463–468 (1986).
6) Shekelle, R. B., Lepper, M., Liu, S., Maliza, C., Raynor, W. J., Jr., Rossof, A. H., Paul, O., Shryock, A. M. and Stamler, J. Dietary vitamin A and the risk of cancer in the Western Electric study. *Lancet*, **ii**, 1186–1190 (1981).
7) Kvale, G., Bjelke, E. and Gart, J. J. Dietary habits and lung cancer risk. *Int. J. Cancer*, **31**, 319–322 (1983).
8) Ziegler, R. G., Mason, T. J., Stemhagen, A., Hoover, R., Schoenberg, J. B., Gridley, G., Virgo, D. W. and Fraumeni, J. F. Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am. J. Epidemiol.*, **123**, 1080–1093 (1986).
9) Byers, T. E., Graham, S., Haughey, B. P., Marshall, J. R. and Swanson, M. K. Diet and lung cancer risk: findings from the Western New York Diet Study. *Am. J. Epidemiol.*, **125**, 351–363 (1987).
10) Wynder, E. L., Hebert, J. R. and Kabat, G. C. Association of dietary fat and lung cancer. *J. Natl. Cancer Inst.*, **79**, 631–637 (1987).
11) Taioli, E., Nicolosi, A. and Wynder, E. L. Possible role of diet as a host factor in the etiology of tobacco-induced lung cancer. *Int. J. Epidemiol.*, **20**, 611–614 (1991).
12) Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare of Japan. "Vital Statistics 1950–1985" (1952–1987). Kosei Tokei Kyokai, Tokyo.
13) McFay, F. W., Hanson, M. R. and Miller, R. W. Cancer mortality in the United States: 1950–1977. *Natl. Cancer Inst. Monogr.*, No. 59 (1982).
14) National Cancer Institute. "Annual Cancer Statistics Review Including Cancer Trends: 1950–1985" (1988). US Dept Health & Human Services, Bethesda, MD.
15) US Bureau of the Census. "Statistical Abstract of the United States: 1989 (109th Ed.)" (1989). Washington DC.
16) Health Promotion and Nutrition Section, Ministry of Health and Welfare. "Kokumin-Eiyo-no Genjo (National Nutrition Survey 1950–1985)" (1952–1987). Daiichi Shuppan, Tokyo (in Japanese).
17) Ueshima, H. and Asakura, S. National trends in intake of lipids, Japan 1956–1980. *Jpn. J. Public Health*, **31**, 325–330 (1984).
18) USPHS, Office on Smoking and Health. "The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General" (1983). US Dept. Health & Human Services, Rockville, MD.
19) Centers for Disease Control. Cigarette smoking in the United States, 1986. *Mortal. Morb. Weekly Rep.*, **36**, 581–585 (1987).
20) Tominaga, S. "Smoking in Japan," ed. S. Tominaga and K. Aoki, pp. 27–35 (1982). University of Nagoya Press, Nagoya.
21) Ministry of Health and Welfare, Japan. Japanese Government (ed). "Smoking and Health. Report of Health Effect of Smoking" (1987). Tokyo.
22) The Annual Report of the Japan Tobacco and Salt Public Corporation, Vol. 124 (1982).
23) Wynder, E. L. and Hirayama, T. Comparative epidemiology of cancers of the United States and Japan. *Prev. Med.*, **6**, 567–594 (1977).
24) Cohen, L. A. Fat and endocrine-responsive cancer in animals. *Prev. Med.*, **16**, 668–674 (1987).
25) Reddy, B. S. Dietary fat and colon cancer: animal models. *Prev. Med.*, **16**, 460–467 (1987).
26) Watson, A. F. and Bellanby, E. Tar cancer in mice. II. The condition of the skin when modified by external treatment or diet, as a factor in influencing the cancerous reaction. *Br. J. Exp. Pathol.*, **11**, 311–322 (1930).
27) Carroll, K. K. Which fat/How much fat — animals. *Prev. Med.*, **16**, 510–515 (1987).
28) Galloway, D. J., Owen, R. W., Jarrett, F., Boyle, P., Hill, M. J. and George, W. D. Experimental colorectal cancer: the relationship of diet and faecal bile acid concentration to tumor induction. *Br. J. Surg.*, **73**, 233–237 (1986).
29) Longnecker, D. S., Wiebkin, P., Schaeffer, B. K. and Roebuck, R. D. Experimental carcinogenesis in the pancreas. *Int. Rev. Exp. Pathol.*, **26**, 177–229 (1984).
30) Gelboin, H. Benzo(a)pyrene metabolism, activation and carcinogenesis: role of the regulation of mixed function oxidases and related enzymes. *Physiol. Rev.*, **60**, 1–17 (1980).
31) Hoffmann, D. and Hecht, S. H. Advances in tobacco carcinogenesis. *Hand. Exp. Pharmacol.*, **94**, 63–182 (1990).
32) Kumar, R., Sitzaurat, S. and Barbacid, M. Activation of *ras* oncogenes preceding the onset of neoplasia. *Science*, **248**, 1101–1103 (1990).
33) Insull, W., Jr. Dietary fats and lipids of adipose tissue and cell membranes in carcinogenesis. *Prev. Med.*, **16**, 481–484 (1987).
34) Karmali, R. A. Eicosanoids in neoplasia. *Prev. Med.*, **16**, 493–502 (1987).
35) Barone, J., Hebert, J. R. and Reddy, M. M. Dietary fat and natural-killer cell activity. *Am. J. Clin. Nutr.*, **50**, 861–867 (1989).
36) Hirayama, T. Nutrition and cancer — a large scale cohort study. *Progr. Clin. Biol. Res.*, **206**, 299–311 (1986).
37) Morgenstern, H. Uses of ecologic analysis in epidemiologic research. *Am. J. Public Health*, **72**, 1336–1344 (1982).