

Charcoal cigarette filters and lung cancer risk in Aichi Prefecture, Japan

Joshua E. Muscat,^{1,5} Toshiro Takezaki,³ Kazuo Tajima⁴ and Steven D. Stellman²

¹Department of Health Evaluation Sciences, Penn State Cancer Institute, Division of Population Sciences, Penn State College of Medicine, Room C3739, MC H069, 500 University Drive, Hershey, PA 17033, ²Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032, USA; ³Department of International Island and Community Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8544, and ⁴Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden Chikusa-ku, Nagoya 464-8681, Japan

(Received January 13, 2005/Revised March 9, 2005/Accepted March 11, 2005/Online publication May 16, 2005)

The lung cancer mortality rate has been lower in Japan than in the United States for several decades. We hypothesized that this difference is due to the Japanese preference for cigarettes with charcoal-containing filters, which efficiently absorb selected gas phase components of mainstream smoke including the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. We analyzed a subset of smokers (396 cases and 545 controls) from a case-control study of lung cancer conducted in Aichi Prefecture, Japan. The risk associated with charcoal filters (73% of all subjects) was evaluated after adjusting for age, sex, education and smoking dose. The odds ratio (OR) associated with charcoal compared with 'plain' cigarette filters was 1.2 (95% confidence intervals [CI] 0.9, 1.6). The histologic-specific risks were similar (e.g. OR = 1.3, 95% CI 0.9, 2.1 for adenocarcinoma). The OR was 1.7 (95% CI 1.1, 2.9) in smokers who switched from 'plain' to charcoal brands. The mean daily number of cigarettes smoked in subjects who switched from 'plain' to charcoal brands was 22.5 and 23.0, respectively. The findings from this study did not indicate that charcoal filters were associated with an attenuated risk of lung cancer. As the detection of a modest benefit or risk (e.g. 10–20%) that can have significant public health impact requires large samples, the findings should be confirmed or refuted in larger studies. (*Cancer Sci* 2005; 96: 283–287)

Most cigarette brands that are manufactured and sold in Japan contain activated carbon (charcoal) granules embedded in the filter. The charcoal filter efficiently absorbs gas phase toxins in mainstream smoke including hydrogen cyanide, formaldehyde, ammonia and crotonaldehyde. Under standard US Federal Trade Commission (FTC) machine-smoking conditions, selected Japanese cigarettes with charcoal filters delivered similar yields of carbon monoxide and nicotine but substantially lower yields of the pulmonary carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone than selected American filter cigarettes.⁽¹⁾ The charcoal filter possibly limits the adverse health effects from smoking, but direct claims of risk reduction have not been made as empiric evidence is lacking. The charcoal also absorbs volatiles that flavor the cigarette and consequently the bland flavor and taste is considered unacceptable to American consumers. Japanese smokers perceive the taste as smoother than American brands.⁽²⁾ Charcoal cigarettes make up <1% of all cigarette sales in the United States and about 70% in Japan. (Before 1981 there was no information on sales data in Japan. Since 1981, the annual market share of charcoal cigarettes has risen slightly from about 68% to over 70%.)

The higher smoking prevalence in Japanese men compared with American men, but lower rates and risk of lung cancer, has long been considered a 'paradox'.^(3–6) It has been suggested that Japanese cigarettes are less toxic than Western brands. Because both charcoal filter cigarettes and 'plain' filter cigarettes are smoked in Japan, we determined the risk of lung cancer associated

with filter type in a Japanese population. The overall methods for this study were described previously.⁽⁵⁾

Materials and Methods

Subject recruitment. We conducted a case-control study of cigarette smoking and lung cancer in Aichi Prefecture, the third largest metropolitan area in Japan. Aichi Prefecture has over five million residents, including two million in its largest city, Nagoya, and 300 000 in Okazaki City.⁽⁷⁾ The Aichi Cancer Center, National Nagoya Hospital, First Red Cross Hospital, Aichi Prefecture Hospital and several smaller hospitals recruited newly diagnosed incident patients with histologically confirmed lung cancer. The hospital staff, physicians, nurses and study interviewers identified eligible patients between 1993 and 1998 from surgical schedules and admission rosters. The case eligibility included an age of 20–81 years, no previous diagnosis of lung, oral, kidney, bladder or pancreas cancer, and ability to participate and provide informed consent. The staff abstracted information on the diagnosis and histology from the pathology reports and medical records. The response rate was approximately 90%.

The study included both hospital controls and community-based controls. The eligibility criteria of the two control groups were the same as for cases except that the hospital controls were admitted for non-malignant diseases or conditions unrelated to cigarette smoking. A patient with a non-tobacco-related cancer was selected only if there were no other available control. The controls were identified from admission rosters and matched to cases by age (within 5 years), sex, hospital and date of interview (± 4 months). The patient's physician was contacted to obtain consent for the interview. The controls were grouped by ICD-9 code categories. These included genitourinary system disorders such as kidney calculus and renal failure (37% of controls), digestive system disorders such as hernia, cholelithiasis and cirrhosis (16%), symptoms, signs and ill-defined conditions (13%), injuries and poisoning (11%), musculoskeletal and connective tissue diseases (11%), diabetes and other endocrine disorders (6%), nervous system disorders (4%) and cancer (2%). The response rate was approximately 90% but because physician consent was not obtained for all controls, the sample size of hospital controls was smaller than that for cases.⁽⁵⁾

We selected community controls using a stratified sampling scheme that was based on the age (within 5 years), sex and residential district of the hospital where the cases were admitted. Within each stratum, two controls were selected randomly from the Aichi Prefecture electoral records that are kept in Nagoya

⁵To whom correspondence should be addressed. E-mail: jmuscat@hmc.psu.edu

Table 1. Characteristics of smokers in cases, hospital controls and community controls, Aichi Prefecture, Japan

Subject characteristic	Cases n = 396 (%)	Hospital controls n = 224 (%)	Community controls n = 321
Sex			
Men	348 (87.9)	201 (89.7)	280 (87.2)
Women	48 (12.1)	23 (10.3)	41 (12.8)
Mean age in years	61.5 ± 9.9	57.0 ± 10.1	61.6 ± 10.0
Mean years of education	11.1 ± 2.9	11.8 ± 2.9	12.0 ± 2.9
Smoking status			
Current	297 (75.0)	135 (60.3)	177 (55.1)
Former	99 (25.0)	89 (39.7)	144 (44.9)
Histology			
Adenocarcinoma	168 (42.5)		
Squamous cell carcinoma	109 (27.6)		
Small cell carcinoma	91 (23.0)		
Other/mixed	28 (6.9%)		

and Okazaki City. Each electoral record includes name, mailing address and birth date. The interviewers placed telephone calls to enlist participation. The telephone numbers were obtained from the information service of the telephone company. Forty percent of the community controls were interviewed. The same study interviewer assigned to a case patient made an appointment to visit the control subject at home.

All subjects signed an informed consent form that was approved by their respective hospital's Institutional Review Board. After consent was obtained, subjects were interviewed in person using a structured questionnaire that contained detailed items on smoking history including cigarette brand, years of smoking, cigarettes per day (cpd) and year of smoking cessation.

Statistical analysis. This analysis included subjects who reported smoking cigarettes regularly, defined as at least one cigarette per day for one or more years. Never smokers were excluded. The sample included 396 cases, 224 hospital controls and 321 community controls. The cigarette box label identifies whether the brand is manufactured with a charcoal filter. Of 1133 ever smokers, 941 (82.7%) of the current and former smokers reported that their most recent brand was a filter cigarette (82.7%). One hundred and ninety-two (17.3%) reported that their most recent brand was a non-filter cigarette or could not identify the filter type. These subjects were not included in the analysis.

Univariate analysis of the data included means and standard deviations. Odds ratios (OR) and 95% confidence intervals (CI) were derived from unconditional logistic regression analysis. The main effect variable was coded as '1' for charcoal filters and '0' for 'plain' cigarettes. The OR were adjusted for sex, age, education, smoking status and pack-years of smoking. We also modeled the risk adjusted for sex, age, education and years since quitting smoking. In the latter analysis, index variables were created for years since quitting smoking (<5, 6–10, 11–20 and >20), with current smokers serving as the referent group. Histologic-specific risks were calculated using smoking and other information from the entire control group. All statistical tests were two-sided.

For subjects who smoked more than one brand in their lifetime, we carried out an analysis based on the two most recent types of cigarettes smoked. The main effect variables were classified as 'charcoal only' or 'mixed' (e.g. charcoal and 'plain'). The referent group was 'plain only.' Those subjects who reported that their most recent brand was a filter cigarette but that their second most recent brand was a non-filter cigarette were further excluded.

Results

The distribution of sex, age, education and smoking history are shown in Table 1. Almost 90% of both cases and controls were men, reflecting the historically low prevalence of smoking among Japanese women. The average age was approximately 61 years in cases and 60 years in controls. Controls had a higher mean level of education. Seventy-five percent of cases, 60% of hospital controls and 55% of community controls were current smokers. The most common histopathologic types of lung cancer were adenocarcinoma (43%), squamous cell carcinoma (28%) and small cell carcinoma (23%).

The characteristics of the subjects were compared by cigarette filter type and are shown in Table 2. For 680 subjects (73%), the most recent brand of cigarette was a charcoal brand whereas for 257 subjects (27%) it was a 'plain' brand. Data on cigarette amount was missing for four subjects. Current smokers were more likely to smoke charcoal brands than former smokers. There were few differences in filter preference by sex, age and education (Table 2).

The overall OR associated with the most recent brand of cigarette was 1.2 (95% CI 0.9, 1.6, Table 3) for charcoal versus 'plain'. The OR was 1.1 (95% CI 0.7, 1.7) when the analysis was limited to cases and hospital controls only, and 1.3 (95% CI 0.9, 1.9) when the analysis was limited to cases and community controls only. In a model that substituted years since quitting for pack-years and smoking status, the overall OR associated with charcoal filter versus 'plain' filter was 1.1 (95% CI 0.8, 1.6; Table 3). In an analysis limited to men only, the OR for charcoal filter versus 'plain' filter was 1.1 (95% CI 0.8, 1.6). In histologic-specific analyses, the risk associated with charcoal versus 'plain' filter of the most recent brand of cigarette was 1.3 (95% 0.9–2.1) for adenocarcinoma, 1.2 (95% CI 0.7, 2.1) for squamous cell carcinoma, and 0.6 (95% CI 0.4, 1.1) for small cell carcinoma (Table 3).

In an examination of the two most recent cigarette brands smoked, 198 of the 941 smokers of filter cigarettes smoked a non-filter brand previously. Of the remaining 743, 361 were classified as smoking charcoal brands only (this number includes 45 subjects whose smoking history was only one brand of charcoal cigarette), 259 smoked both 'plain' and charcoal brands, and 123 smoked 'plain' brands (this number includes 44 subjects whose smoking history was only one brand of 'plain' cigarettes). Subjects who smoked both charcoal and plain brands were classified as 'switchers.' In the majority of cases, the switchers were smokers who changed from smoking a 'plain'

Table 2. Characteristics of smokers by case-control status and filter type (e.g. charcoal vs 'plain'), Aichi Prefecture, Japan

Subject characteristic	Cases		Controls	
	Charcoal <i>n</i> = 304 (%)	'Plain' <i>n</i> = 92 (%)	Charcoal <i>n</i> = 379 (%)	'Plain' <i>n</i> = 166 (%)
Sex				
Men	261 (85.9)	87 (94.6)	331 (87.3)	150 (90.4)
Women	43 (14.1)	5 (5.4)	48 (12.7)	16 (9.6)
Mean age in years	61.2 ± 10.0	62.6 ± 9.5	58.8 ± 10.3	61.6 ± 9.4
Mean years of education	11.0 ± 2.6	11.2 ± 3.5	11.9 ± 2.9	12.0 ± 2.8
Smoking status				
Current	235 (77.3)	62 (67.4)	257 (67.8)	55 (33.1)
Former	69 (22.7)	30 (32.6)	122 (32.2)	111 (66.9)
Cigarettes per day	28.3 ± 15.1	31.6 ± 16.4	24.9 ± 14.7	25.5 ± 17.4

Based on the most recent brand of cigarette.

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for filter type and lung cancer histology

Cigarette filter	All		AC		SCC		SmCC	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Most recent brand (<i>n</i> = 941)								
'Plain'	1.0		1.0		1.0		1.0	
Charcoal	1.2	0.9, 1.6	1.3	0.9, 2.1	1.2	0.7, 2.1	0.6	0.4, 1.1
Last two brands (<i>n</i> = 743)								
'Plain' only	1.0		1.0		1.0		1.0	
Mixed	1.7	1.1, 2.9	2.1	1.1, 4.0	2.5	1.0, 6.3	0.6	0.3, 1.5
Charcoal only	1.4	0.8, 2.2	1.6	0.8, 3.1	1.6	0.6, 4.1	0.6	0.3, 1.3

Odds ratios were adjusted for sex, age, education, smoking status (current vs former) and pack-years. The odds ratio was 1.1 (95% CI 0.8–1.6) after adjustment for sex, age, education, cigarette amount and years since quitting. Odds ratios associated with the last two brands of cigarettes were based on 743 subjects (includes 654 subjects who smoked two brands, 45 subjects who smoked only one brand of charcoal and were classified as charcoal only, and 44 subjects who smoked only one brand of 'plain' cigarettes and were classified as 'plain' only). AC, adenocarcinoma; SCC, squamous cell carcinoma; SmCC, small cell carcinoma.

Table 4. Average number of cigarettes smoked per day (cpd) for the two most recent brands

Cigarette history	Filter type	<i>n</i>	cpd	Filter type	<i>n</i>	cpd
Most recent brand	Charcoal	543	27.2 ± 15.0	'Plain'	111	24.3 ± 13.9
Previous brand	'Plain'	220	25.1 ± 13.0	Charcoal	32	25.0 ± 12.2
	Charcoal	316	26.1 ± 13.8	'Plain'	78	24.0 ± 14.6

A few subjects had missing data for cpd on the previous brand smoked.

brand to a charcoal brand. Only 32 subjects switched from a charcoal to a 'plain' brand. Many switchers had a history of smoking three brands. In nearly all cases, the third most recent brand was also a 'plain' cigarette. Only nine subjects reported switching from a charcoal to a 'plain' back to a charcoal brand. Excluding the subjects whose second previous brand was a non-filter cigarette, the overall OR for the last two brands was 1.4 (95% CI 0.8, 2.2) for charcoal only versus 'plain' only, and 1.7 (95% CI 1.1, 2.9) for mixed versus 'plain' only (Table 3). Similar findings were observed in separate analyses using hospital controls only and community controls only (data not shown). A significant increased risk for adenocarcinoma of the lung was observed in subjects who switched from 'plain' to charcoal versus subjects whose last two brands were 'plain' cigarettes (Table 3).

The mean number of cigarettes per day in smokers who smoked two or more brands is shown separately for subjects who smoked charcoal brands only, mixed smokers, and 'plain' brands only (Table 4). The mean number of cigarettes smoked per day was 27.2 for charcoal brands and 24.3 for 'plain' brands. For smokers of charcoal brands that had switched from a previous brand, the mean number of cigarettes smoked per day

increased by approximately one to two, regardless of the filter type of the previous brand.

Discussion

The introduction of filter cigarettes into the US market approximately 50 years ago was anticipated to reduce the future incidence rate of lung cancer. There are conflicting findings on whether this occurred in smokers who switched from high-tar cigarettes to low-tar cigarettes.⁽⁸⁾ In Japan, the risk of lung cancer for those who smoked filter cigarettes all their life compared with subjects who smoked both non-filter and filter cigarettes was 0.70 (95% CI 0.4–1.2).⁽⁹⁾ These findings indicate that while filtration substantially reduces exposure to tobacco carcinogens, the possible benefits might be lower than anticipated because of compensatory smoking behaviors.

Another technological approach to reduce the hazards from smoking is the development of a more efficient filtration system than that provided by a typical acetate filter.⁽¹⁰⁾ The charcoal filter reduces exposure to several gas phase volatile compounds under FTC machine-smoking conditions. Selected Japanese charcoal brands deliver 30% lower yields of both tar and CO,

25% lower benzo(a)pyrene (8.5 vs 11.4 ng/cig), 58% lower tobacco-specific nitrosamines (245 vs 580 ng/cig) and similar levels of nicotine.⁽¹⁾ Some disadvantages of the charcoal filter compared with typical acetate filters are increased gas phase concentration of the lung carcinogen isoprene, possibly increased production of reactive free radicals,⁽¹¹⁾ and manufacturing defects that contaminate the filter surfaces with charcoal granules.⁽¹²⁾

The delivery of tobacco smoke toxins from cigarettes with acetate filters tends to be greater under human smoking conditions than FTC machine-smoking conditions. These comparisons have not been conducted for charcoal cigarettes but suggest that the reduction in gas phase components associated with the charcoal filter might not be as high as under machine-smoking conditions. Within a single charcoal cigarette the levels of delivered toxins are much higher in the last puffs because the charcoal becomes inactive and deabsorbs gas phase compounds.⁽¹¹⁾ Consequently, the possible impact of charcoal filters on lung cancer risk might be affected by smoking behaviors such as number of puffs per cigarette and puff volume. Because the charcoal filter technology varies from brand to brand and is under continuous technological development,⁽¹³⁾ the filtration efficiency, taste, aftertaste and possibly puffing habits might vary from one brand to another.

The current study did not find a reduced risk of lung cancer associated with charcoal filters. The strengths of our study included the high response rate in cases and hospital controls, a similar histologic distribution of lung cancer to that reported in a prospective study⁽¹⁴⁾ and a similar percentage of subjects that smoked charcoal filter cigarettes as that reported in national sales data. The daily smoking amount increased slightly from the previous brand to the current brand, which is consistent with Japanese cigarette consumption statistics that show small annual increases in the average cpd.^(15,16)

One limitation was that, as expected, the response rate among the community controls was lower than for hospital controls, although not atypical for elderly Japanese citizens contacted by telephone. The response rate of community controls in a study of colorectal cancer conducted in Fukuoka, Japan was 60%.⁽¹⁷⁾ Although the response rate was somewhat lower here, we previously evaluated response bias for this community control group and reported few differences in years of smoking and cpd compared to population-based smoking surveys in Japan.⁽⁵⁾ The current analysis also found few differences in the proportion of

community versus hospital controls that smoked charcoal cigarettes. Self-reported smoking information such as cpd, years of smoking and year started is usually reported accurately. Still, there is little data on the reliability of self-reported information on brand name. One study found that the validity of self-reported cigarette brands was 74%.⁽¹⁸⁾ In this study, the five most commonly reported brands corresponded to the rankings of Japanese national sales data (data not shown). Seventeen percent of subjects reported that the most recent cigarette smoked was a non-filter brand. This compares to 7.5% reported elsewhere.⁽⁹⁾ However, our data included current and former smokers whereas Marugame *et al.* examined current smokers only.⁽⁹⁾ The effects of residual confounding in smokers who switched from non-filter to filter cigarettes is another potential source of error. We excluded smokers whose two most recent brands were non-filter cigarettes but it was not possible to exclude subjects who smoked a non-filter during their early smoking years.

In summary, charcoal filter tips were not associated with a reduced lung cancer risk but this finding should be confirmed or refuted in further investigations because of their potential public health impact. The charcoal filter is one of several possible factors that might be associated with the lower smoking-associated risk of lung cancer in Japan. Other explanations include a lower baseline risk of lung cancer in Japanese non-smokers than in American smokers,⁽⁶⁾ low saturated fat intake,⁽¹⁹⁾ high fish consumption^(20,21) and high green tea intake.⁽²²⁾ Green tea and other foods such as black tea and cruciferous vegetables inhibit cytochrome P4502E1 (CYP2E1) activity *in vitro* and in animals⁽²³⁾ and may contribute to the lower CYP2E1 activity in Japanese men than in Caucasian men.⁽²⁴⁾ Recent data also show that the 1960–1997 lung cancer incidence rates were similar between Japan and Japanese immigrants to Hawaii after several generations,⁽²⁵⁾ despite the lower prevalence of smoking in Japanese immigrants.^(26,27) These data indicate that the Western diet may be important in explaining ethnic differences in lung cancer. There is no information on changes in the types of cigarettes preferred by Japanese immigrants to the US but this information would be useful in helping to explain these epidemiologic patterns.

Acknowledgments

The USPHS Grants CA-68387, CA-17613 and the Verum Foundation provided the financial support. The authors thank the many physicians, nurses, staff and subjects who participated in the study.

References

- 1 Djordjevic MV, Eixarch L, Bush LP, Hoffmann D. A comparison of the yields of selected components in the mainstream smoke of the leading US and Japanese cigarettes. *Proceedings of the 1996 CORESTA Congress*; 6 Nov 1996, Yokohama Japan. 1996; 200–17.
- 2 Morrison CC, Wingate DE, Beard KA, Winkler LS, Simmons DF, Rogers JC, Borgerding MF. The effects of cigarette design modifications on selected mainstream vapor phase smoke constituent yields. *Proceedings of the 49th Tobacco Chemist Research Conference*; 24–27 Sep 1995. Lexington, KY, p. 44.
- 3 Wynder EL, Hirayama T. Comparative epidemiology of cancers of the United States and Japan. *Prev Med* 1977; **6**: 567–4.
- 4 Wynder EL, Fujita Y, Harris RE, Hirayama T, Hiyama T. Comparative epidemiology of cancer between the United States and Japan. A second look. *Cancer* 1991; **67**: 746–63.
- 5 Stellman SD, Takezaki T, Wang L, Chen Y, Citron ML, Djordjevic MV, Harlap S, Muscat JE, Neugut AI, Wynder EL, Ogawa H, Tajima K, Aoki K. Smoking and lung cancer risk in American and Japanese men: an international case-control study. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1193–9.
- 6 Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S, Study Group JPHC. Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women: the JPHC study. *Int J Cancer* 2002; **99**: 245–51.
- 7 Japanorama [website on the internet]. Japanese Cities Ranked by Population. 2001. [Cited Feb 2000.] Available from URL: http://www.japanorama.com/zip/cities_by_pop.pdf.
- 8 Thun MJ, Burns DM. Health impact of 'reduced yield' cigarettes: a critical assessment of the epidemiological evidence. *Tob Control* 2001; **10** (Suppl 1): 4–11.
- 9 Marugame T, Sobue T, Nakayama T, Suzuki T, Kuniyoshi H, Sunagawa K, Genka K, Nishizawa N, Natsukawa S, Kuwahara O, Tsubura E. Filter cigarette smoking and lung cancer risk: a hospital-based case-control study in Japan. *Br J Cancer* 2004; **90**: 646–51.
- 10 Hoffmann D, Djordjevic MV, Brunnemann K. Changes in cigarette design and composition over time and how they influence the yields of smoking constituents. *Natl Insts Health/Natl Cancer Inst Smoking Tobacco Control Monograph* 1996; **7**: 15–37.
- 11 Brunnemann KD, Kagan MR, Cox JE, Hoffmann D. Analysis of 1,3-butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. *Carcinogenesis* 1990; **11**: 1863–8.
- 12 Pauly JL, Stegmeier SJ, Mayer AG, Lesses JD, Streck RJ. Release of carbon granules from cigarettes with charcoal filters. *Tob Control* 1997; **6**: 33–40.
- 13 Bombick DW, Bombick BR, Ayres PH, Putnam K, Avalos J, Borgerding MF, Doolittle DJ. Evaluation of the genotoxic and cytotoxic potential of mainstream whole smoke and smoke condensate from a cigarette containing a novel carbon filter. *Fundam Appl Toxicol* 1997; **39**: 11–17.
- 14 Yoshimi I, Ohshima A, Ajiki W, Tsukuma H, Sobue T. A comparison of trends in the incidence rate of lung cancer by histological type in the Osaka

- Cancer Registry, Japan and in the Surveillance, Epidemiology and End Results Program, USA. *Jpn J Clin Oncol* 2003; **33**: 98–104.
- 15 Sato H, Araki S. Yields and daily consumption of cigarettes in Japan in 1969–96. *J Epidemiol* 2000; **10**: 7–15.
 - 16 Yamaguchi N, Mochizuki-Kobayashi Y, Utsunomiya O. Quantitative relationship between cumulative cigarette consumption and lung cancer mortality in Japan. *Int J Epidemiol* 2002; **29**: 963–8.
 - 17 Yin G, Kono S, Toyomura K, Hagiwara T, Nagano J, Mizoue T, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and colorectal cancer. The Fukuoka Colorectal Cancer Study. *Cancer Sci* 2004; **95**: 908–13.
 - 18 Peach H, Shah D, Morris RW. Validity of smokers' information about present and past cigarette brands – implications for studies of the effects of falling tar yields of cigarettes on health. *Thorax* 1986; **41**: 203–7.
 - 19 Wynder EL, Taioli E, Fujita Y. Ecologic study of lung cancer risk factors in the US and Japan, with special reference to smoking and diet. *Jpn J Cancer Res* 2002; **83**: 418–23.
 - 20 Mulder I, Jansen MC, Smit HA, Jacobs DR Jr, Menotti A, Nissinen A, Fidanza F, Kromhout D. Role of smoking and diet in the cross-cultural variation in lung-cancer mortality: the Seven Countries Study. Seven Countries Study Research Group. *Int J Cancer* 2000; **88**: 665–71.
 - 21 Nakaji S, Yoshioka Y, Mashiko T, Yamamoto Y, Kojima A, Baxter GD, Sugawara K. Explanations for the smoking paradox in Japan. *Eur J Epidemiol* 2003; **18**: 381–3.
 - 22 Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF, Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer* 1997; **70**: 255–8.
 - 23 Kim RB, Yamazaki H, Chiba K, O'Shea D, Mimura M, Guengerich FP, Ishizaki T, Shimada T, Wilkinson GR. *In vivo* and *in vitro* characterization of CYP2E1 activity in Japanese and Caucasians. *J Pharmacol Exp Ther* 1996; **279**: 4–11.
 - 24 Marchand LL, Wilkinon GR, Wilkens LR. Genetic and dietary predictors of CYP2E1 activity: a phenotyping study in Hawaii Japanese using chlorzoxazone. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 495–500.
 - 25 Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 2004; **14**: 431–9.
 - 26 Health and Welfare Statistics Association. National trend of nutrition intake in Japan. *J Health Welfare Stat* 1996; **43**: 96–105. Special issue.
 - 27 Ueshima H, Okayama A, Saitoh S, Nakagawa H, Rodriguez B, Sakata K, Okuda N, Choudhury SR, Curb JD, INTERLIPID Research Group. Differences in cardiovascular disease risk factors between Japanese in Japan and Japanese Americans in Hawaii: the INTERLIPID study. *J Hum Hypertens* 2003; **17**: 631–9.