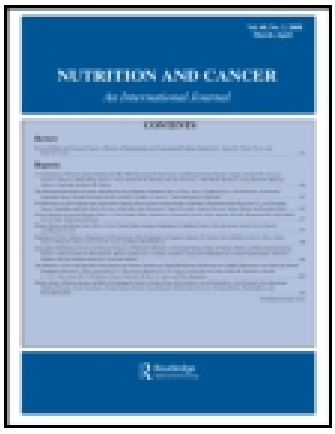

Nutrition and Cancer
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hnuc20

Cooking Methods and Esophageal Squamous Cell Carcinoma in High-Risk Areas of Iran

Roya Hakami [a], Arash Etemadi [a b], Farin Kamangar [a c], Akram Pourshams [a], Javad Mohtadinia [d], Mehdi Saberi Firoozi [a e], Nicholas Birkett [f], Paolo Boffetta [g h], Sanford M. Dawsey [b] & Reza Malekzadeh [a]

[a] Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences , Tehran , Iran

[b] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health , Bethesda , Maryland , USA

[c] Department of Public Health Analysis, School of Community Health and Policy, Morgan State University , Baltimore , Maryland , USA

[d] School of Health and Nutrition, Tabriz University of Medical Sciences , Tabriz , Iran

[e] Gastroentero-Hepatology Research Center, Shiraz University of Medical Sciences , Shiraz , Iran

[f] Department of Epidemiology and Community Medicine, University of Ottawa , Ottawa , Canada

[g] The Tisch Cancer Institute and Institute for Transitional Epidemiology, Mount Sinai School of Medicine , New York , New York , USA

[h] International Prevention Research Institute , Lyon , France

Published online: 13 Sep 2013.

To cite this article: Roya Hakami , Arash Etemadi , Farin Kamangar , Akram Pourshams , Javad Mohtadinia , Mehdi Saberi Firoozi , Nicholas Birkett , Paolo Boffetta , Sanford M. Dawsey & Reza Malekzadeh (2014) Cooking Methods and Esophageal Squamous Cell Carcinoma in High-Risk Areas of Iran, Nutrition and Cancer, 66:3, 500-505, DOI: 10.1080/01635581.2013.779384

To link to this article: http://dx.doi.org/10.1080/01635581.2013.779384

Nutrition and Cancer, 66(3), 500–505

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635581.2013.779384

Routledge
Taylor & Francis Group

Cooking Methods and Esophageal Squamous Cell Carcinoma in High-Risk Areas of Iran

Roya Hakami
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Arash Etemadi
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Farin Kamangar
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, and Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, Maryland, USA

Akram Pourshams
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Javad Mohtadinia
School of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran

Mehdi Saberi Firoozi
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, and Gastroentero-Hepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Nicholas Birkett
Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada

Paolo Boffetta
The Tisch Cancer Institute and Institute for Transitional Epidemiology, Mount Sinai School of Medicine, New York, New York, USA, and International Prevention Research Institute, Lyon, France

Sanford M. Dawsey
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Reza Malekzadeh
Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Address correspondence to Arash Etemadi, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Rockville, MD 20852, USA. Phone: +1-240-276-7197. Fax: +1-240-276-7837. E-mail: arash.etemadi@nih.gov

Cooking methods have been implicated in the etiology of gastrointestinal cancers, reflecting exposure to potential carcinogens as results of cooking. We used a validated food frequency questionnaire and a pretested cooking method questionnaire in 3 groups: 40 esophageal squamous cell carcinoma (ESCC) cases from a high-risk area in northeast of Iran, 40 healthy subjects from the same high-risk area, and 40 healthy subjects from a low-risk area in Southern Iran. We compared the frequency of boiling, grilling, and frying, and the frying score among these 3 groups. We also calculated "frying index" by multiplying the frequency of each fried food item by its frying score. Mean frying to boiling ratios were 18.2:1, 12.8:1, and 2.6:1 for cases, high-risk controls, and low-risk controls, respectively ($P < 0.01$). Reuse of cooking oil for frying was reported in 37.5% of the ESCC cases, 25% of high-risk controls, and 7.5% of low-risk controls ($P < 0.001$). Frying index was higher in the high-risk than in the low-risk controls ($P < 0.001$) and in cases than in the high-risk controls ($P < 0.05$) after adjusting for smoking, opium use, rural residence, education, and ethnicity. High-temperature cooking and frying may be associated with increased risk of ESCC in high-risk areas.

INTRODUCTION

Despite an apparent decline in its incidence, esophageal cancer is the most common cause of cancer death in Central Asian "esophageal cancer belt" region (1) including Golestan Province in northeastern Iran (2). Several risk factors, including low socioeconomic status (3), low intake of fruit and vegetables (4–6), and drinking hot tea (7) have been identified in this region, but these risk factors do not appear to fully account for the high rate of esophageal cancer seen in this area (8).

Cooking methods may be related to the risk of upper gastrointestinal tract cancers (9–12). According to American Cancer Society guidelines, high-temperature cooking methods (as in frying) give rise to a variety of mutagenic substances that are carcinogenic in experimental animals (13). Cooking meat at high temperatures results in formation of high amounts of PAHs (polycyclic aromatic hydrocarbons), and also high levels of HCAs (heterocyclic amines) (14, 15). Both of these groups of chemicals have been suggested to increase the risk of esophageal cancer (9, 16, 17). A recent study revealed high exposure to PAHs among never smokers in Golestan Province, which may be due to high nutritional intake or second-hand smoking (18).

In this study, we compare the cooking habits of esophageal cancer cases from the high-risk area of Golestan Province with control subjects from the same area, and also control subjects from Fars, a province in the center of Iran with very low incidence of ESCC (age-adjusted rate ~3/100,000/yr) of esophageal cancer (19).

MATERIAL AND METHODS

We selected 40 ESCC cases and 40 control subjects from Golestan Province (high-risk controls) and 40 control subjects from Fars Province (low-risk controls). Golestan cases and controls were selected from among those who were referred to Atrak Clinic, a referral upper gastrointestinal clinic (20). Controls from Fars Province were selected from subjects who were referred to the Gastrointestinal Research Center of Namazi Hospital, a referral hospital in Shiraz city, the capital of this Province.

All cases were histopathologically confirmed as having esophageal squamous cell tumors, had sufficiently good health to answer the questions, and were diagnosed within 6 mo prior to the interviews. Both control groups had no evidence of upper gastrointestinal tract malignancy on endoscopy, had no family history of esophageal cancer in first-degree relatives, and were matched for sex and age (±5 yr) to the cases. Those otherwise eligible case or control subjects who had changed their dietary habits over the past year because of disease or any other reasons were not included in the study.

All study subjects ($n = 120$) were interviewed face-to-face by a trained nutritionist. Food use over the previous year was assessed by a validated semiquantitative food frequency questionnaire (FFQ) (21). This FFQ was based on the usual frequency of consumption of each item in terms of times per day, week, month, or year. All values were later converted to times per week.

Cooking practices were assessed using a pretested questionnaire. The frequency of boiling, grilling, and frying food items per week was recorded. Because frying practices were especially important in this study, 2 indices, "frying score" and "frying index," were calculated. The frying score was recorded as 4 levels: not frying/not using (score 0), surface browning including sauté items (score 1), changing color (score 2), and browning (score 3); if an item was not consumed or was not fried at all, it was given a score of zero. The frying index was calculated by multiplying the frequency of consumption of each fried food item by its frying score, and summed over food items. *Fryboiling*, defined as frying and then boiling a food item or vice versa, was considered as a form of frying and contributed to calculation of frying score and frying index. Re-use of cooking oil for frying was also recorded.

Ever smoking, opium use, place of residence, and re-use of cooking oil for frying were compared between different groups using Fisher's Exact test. Frequency of frying score for each food item was compared among the groups using Kruskall-Wallis and Mann Whitney tests. The mean frequencies of cooking methods, and frying index were compared among the 3 groups using analysis of variance. To adjust for the effect of potential confounders (smoking, opium use, ethnicity, education, and rural residence) on frying index, multivariate regression was used. The Bonferroni-corrected post-hoc test was used to compare mean differences between the cases and high-risk controls and between high-risk and low-risk controls. To adjust for total amount of food intake, frying to boiling frequency ratios were calculated for each person and compared among the 3 groups. Statistical analysis was done using SPSS (version 19.0), and the level of significance was determined at 0.05.

RESULTS

The distribution of age, sex, smoking, opium use, place of residence, education, ethnicity, cooking fuel, and cooking methods by study groups are shown in Table 1. There were more smokers and opium users among cases. The results showed that, compared to high-risk controls, cases used boiling significantly less frequently (2.2 vs. 4.5 times/wk; $P < 0.01$) but their use of frying (14.6 vs. 13.4 times/wk; $P = 0.37$) and grilling (0.3 vs. 0.8 times/wk; $P = 0.18$) were not significantly different. Compared to the low-risk controls, high-risk controls used boiling less frequently (4.5 vs. 7.0 times/wk; $P < 0.05$) and frying more frequently (13.4 vs. 7.2 times/wk; $P < 0.01$), but there was no significant difference in grilling frequency (0.8 vs. 0.5 times/wk; $P = 0.5$). Mean frying to boiling ratios were 18.2:1, 12.8:1, and 2.6:1 for ESCC cases, high-risk controls, and low-risk controls, respectively ($P < 0.01$).

Reuse of cooking oil for frying was reported in 37.5% of the cases, 25% of high-risk controls, and 7.5% of low-risk controls ($P < 0.001$). Bonferroni-corrected P values were significant comparing high-risk and low-risk controls ($P = 0.01$). However, the difference between the cases and high-risk controls was not significant ($P = 0.06$) (Table 1).

As shown in Table 2, for most food items, frying at higher frying scores was more common in cases than in high-risk controls and also in high-risk controls than in low-risk ones. This difference was especially prominent for chicken and onion. In addition, frying index showed a significant difference among the groups (Table 1). Although the frequency of frying was similar, compared to the high-risk controls, cases used frying at higher scores more frequently, resulting in a higher overall frying index ($P < 0.05$). On the other hand, both the frequency of frying and frying at higher scores were more common among high-risk controls than the low-risk ones, and both of these contributed to the higher frying index in the high-risk controls ($P < 0.01$). As Table 3 shows, the association between frying index and study groups was still present after adjusting for smoking and opium. In the fully adjusted model, although the association in the ESCC cases was weakened, it was still statistically significant.

DISCUSSION

In the present study, ESCC cases used frying more than high-risk controls, and high-risk controls, in turn, more than low-risk controls. The American Cancer Society reported that high-temperature cooking methods (as in frying) give rise a wide variety of mutagenic substances that are carcinogenic in experimental animals (13). Differences in frying indices of the 3 groups in our study suggest that ESCC patients and high-risk controls were more exposed to the possible carcinogenic compounds produced by frying.

TABLE 1
Distribution of cases and controls for selected variables

Variable	Cases ($n = 40$)	High-risk controls ($n = 40$)	Low-risk controls ($n = 40$)
Age (yr), mean ± SD	62.5 ± 11.2	62.8 ± 11.2	62.3 ± 11.6
Sex (female)	21 (52.5)	21 (52.5)	21 (52.5)
Ever smoking	11 (27.5) [a]	3 (7.5)	1 (2.5)
Ever opium use	13 (32.5)	9 (22.5)	0 (0)[c]
Place of residence (urban)	10 (25)[b]	24 (60)	40 (100)[c]
Education (some education)	3 (7.5)[a]	12 (30)	31 (77.5)[c]
Ethnicity (non-Turkoman)	17 (42.5)	26 (65)	40 (100)[c]
Fuel for cooking (natural gas)	39 (97.5)	37 (92.5)	40 (100)
Total boiling (times/wk)	2.2 ± 2.5[b]	4.5 ± 4.2	7.0 ± 3.9[d]
Meat group	0.3 ± 1.1[b]	1.4 ± 3.2	1.3 ± 1.5
Vegetables	1.9 ± 2.1[a]	3.1 ± 2.7	5.7 ± 3.0[c]
Total frying (times/wk)	14.6 ± 5.1	13.4 ± 7.8	7.2 ± 3.9[c]
Meat group	3.2 ± 2.1	3.1 ± 2.5	3.0 ± 2.0
Vegetables	11.4 ± 4.4	10.3 ± 6.0	4.2 ± 2.7[c]
Total grilling (times/wk)	0.3 ± 0.7	0.8 ± 2.1	0.5 ± 1.4
Frying index (mean ± SD)	38.84 ± 14.96 [a]	29.84 ± 19.66	14.08 ± 8.54 [c]
Re-use of cooking oil for frying			
Use in next frying	15 (37.5)	10 (25)	3 (7.5)[c]
Use in the same food	19 (47.5)	17 (42.5)	8 (20)
No re-use	6 (15)	13 (32.5)	29 (72.5)

Meat group: meat, chicken, fish; vegetables: onion, potato, green leafy vegetables, eggplant. Values in the parentheses are percentages.
[a]$P < 0.05$. [b]$P < 0.01$, between cases and high-risk controls. [c]$P < 0.01$. [d]$P < 0.05$, between the 2 controls.

TABLE 2
Meat and vegetable frying scores in cases and controls

Variable	Category**	Frying score (number of subjects)* Cases ($n = 40$)	Golestan controls ($n = 40$)	Fars controls ($n = 40$)
Meat frying score	Score 3	15 (37.5)	9 (22.5)	3 (7.5)
	Score 2	14 (35)	10 (25)	14 (35)
	Score 1	0 (0)	6 (15)	16 (40)
	Score 0	11 (27.5)	15 (37.5)	7 (17.5)
Chicken frying score	Score 3	29 (72.5)[a]	12 (30)	4 (10)[b]
	Score 2	8 (20)	11 (27.5)	7 (17.5)
	Score 1	1 (2.5)	6 (15)	12 (30)
	Score 0	2 (5)	11 (27.5)	17 (42.5)
Fish frying score	Score 3	25 (62.5)	21 (52.5)	15 (37.5)
	Score 2	1 (2.5)	5 (12.5)	17 (42.5)
	Score 1	1 (2.5)	2 (2.5)	0 (0)
	Score 0	13 (32.5)	12 (30)	8 (20)
Leafy vegetables frying score	Score 3	18 (45)	12 (30)	5 (12.5)
	Score 2	6 (15)	14 (35)	23 (57.5)
	Score 1	0 (0)	3 (7.5)	4 (10)
	Score 0	16 (40)	11 (27.5)	8 (20)
Onion frying score	Score 3	25 (62.5)[a]	11 (27.5)	5 (12.5)
	Score 2	14 (35)	20 (50)	23 (57.5)
	Score 1	0 (0)	3 (7.5)	3 (7.5)
	Score 0	1 (2.5)	6 (15)	9 (22.5)
Potato frying score	Score 3	13 (32.5)	6 (15)	4 (10)
	Score 2	18 (45)	23 (57.5)	17 (42.5)
	Score 1	0 (0)	2 (5)	1 (2.5)
	Score 0	9 (22.5)	9 (22.5)	18 (45)
Eggplant frying score	Score 3	26 (65)	16 (40)	14 (35)
	Score 2	5 (12.5)	15 (37.5)	20 (50)
	Score 1	0 (0)	2 (5)	1 (2.5)
	Score 0	9 (22.5)	7 (17.5)	5 (12.5)

*Percentage of subjects in each frying score has been shown in parentheses.
**Scores: 0: not frying/not using, 1: surface browning, 2: changing color, 3: browning.
[a]$P < 0.001$, between cases and high-risk controls. [b]$P < 0.05$, between the 2 controls.

Based on surface browning by pan-frying, frying chicken at higher frying degrees was more common in the high-risk vs. the low-risk controls ($P < 0.05$) and in ESCC patients vs. high-risk controls ($P < 0.001$). Cooking meat at high temperatures produces HCAs by pyrolysis of proteins, amino acids or creatine (22). HCAs are clearly bioavailable from normal human diet. The proposed bioactivation pathway consists of N-hydroxylation by CYP1A2. The most active area of research for

TABLE 3
Regression analysis of the differences in frying index among study groups

Group	Coefficient for crude model (95% CI)	Adjusted for opium and smoking (95% CI)	Fully adjusted (95% CI)†
Low-risk control	−15.76 (−22.44, −9.08)**	−16.13 (−23.04, −9.22)**	−11.83 (−20.01, −3.64)**
High-risk control	1	1	1
ESCC case	9.00 (2.31, 15.68)**	10.11 (3.18, 17.05)**	7.70 (0.10–15.31)*

†adjusted for smoking, opium use, rural residence, ethnicity and education.
*$P < 0.05$. **$P < 0.001$.

HCAs focuses on colon cancer (23–26). In a study in Sweden, the association between HCA and esophageal squamous cell carcinoma was studied (9). HCA intake was estimated based on the frequency of consumption and degree of surface browning of commonly fried meats. They observed a 50–70% higher risk of esophageal squamous cell carcinoma among individuals in the highest compared to those in the lowest quartile levels of heterocyclic amines that was not statistically significant. In contrast, they found no association with the risk of adenocarcinoma of the esophagus, similar to another study in eastern Nebraska in which doneness level of meat was not associated with a significant trend in risk of esophageal adenocarcinoma (27). In a dietary exposure study in China, 7 meat-cooking methods (pan-fried fish, pork and chicken, deep fried chicken, as well as fish, roasted/barbecued pork, and grilled minced beef) contributed 90.1% of HCA intake in the Chinese population (28). In another study, pan-fried and cooked fish and chicken samples in Singapore Chinese households were analyzed for 5 HCAs (29). They found that pan-fried chicken produced more HCA, even with lower cooking surface temperature compared to pan-fried fish. Our findings of higher frying scores of chicken among ESCC cases and high-risk individuals are in line with these findings.

Previous studies have shown an increased risk of ESCC with higher consumption of boiled, as well as fried, red meat (30, 31). We did not see a similar association with boiled meat; this may be because in our study, boiled meat was not limited to red meat and could include chicken and fish as well. It may also have been due to differences in preparation and serving methods across different cultures, or the classification of these methods. For example, in our study, some participants reported fryboiling which is frying and then boiling the meat and this category was classified as frying; or individuals in the previous report (30) seem to have consumed boiled and stew meat at a high temperature, which may have contributed to its effect on esophageal mucosa.

We observed that 85% of ESCC patients, 67.5% of the high-risk controls, but only 27.5% of the low-risk controls reused fried oil that may contain some carcinogenic compounds. There are some studies (30–32) indicating that repeated frying produces numerous carcinogens including PAHs. Pandey et al. studied the potential carcinogenicity of repeated fish fried oil in rats, mice, and human hepatoma cell line, Hep G2. In a study (32) that aimed at assessing the role of repeated fish fried oil on hepatic cytochrome P450 (CYP) isozymes, benzo(a)pyrene metabolism, and DNA adduct formation in hepatic microsomes of rats, they observed several PAHs in repeated fish fried oil, increased reactive metabolites of PAHs through enhanced induction of cytochrome p450 isozymes, and subsequent binding to DNA following exposure to the repeated fish fried oil. In another study (33), single topical exposure of repeated fish fried oil for 24–72 h caused overexpression of p53 and p21WAF1 proteins in the skin cells of mice which was similar to that of benzo(a)pyrene exposure. The authors also studied the potential carcinogenic effect of fish fried oil on human hepatoma cell line, Hep G2 (34), and they observed a dose-dependent increase in ethoxyresorufin-O-deethylase and aryl hydrocarbon hydroxylase activity and reduced cell viability following treatment of cells with repeated fish fried oil extract. Their results support the carcinogenic possibility of reused fish fried oil.

In conclusion, this study adds to the current evidence for the possible carcinogenic role of high-temperature cooking and repeated oil use and may imply their role in ESCC pathogenesis in high-risk areas of Iran.

ACKNOWLEDGMENTS

This study was supported by funds from Tabriz University of Medical Science and Digestive Disease Research Center of Tehran University of Medical Science, Iran. It was also supported in part by the intramural research program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. We thank Dr. Yoosefi in Shiraz and Ms. Mohammadi and Ms. Goglani in Gonbad for their collaboration in this study.

REFERENCES

1. Eslick GD: Epidemiology of esophageal cancer. *Gastroenterol Clin North Am* **38**, 17–25, **vii**, 2009.
2. Semnani S, Sadjadi A, Fahimi S, Nouraie M, Naeimi M, et al.: Declining incidence of esophageal cancer in the Turkmen plain, eastern part of the Caspian littoral if Iran: a retrospective cancer surveillance. *Cancer Detect Prev* **30**, 14–19, 2006.
3. Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, et al.: Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. *Int J Epidemiol* **38**, 978–988, 2009.
4. Ghadirian P: Food habit of the people of the Caspian littoral of Iran in relation to esophageal cancer. *Nutr Cancer* **9**, 147–157, 1987.
5. Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, et al.: Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. *Br J Cancer* **39**, 293–309, 1979.
6. Hormozdiari H, Day NE, Aramesh B, and Mahboubi E: Dietary factors and esophageal cancer in the Caspian littoral of Iran. *Cancer Res* **35**, 3493–3498, 1975.
7. Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, et al.: Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ* **338**, b929, 2009.
8. Etemadi A, Abnet CC, Golozar A, Malekzadeh R, and Dawsey SM: Modeling the risk ofesophageal squamous cell carcinoma and squamous dysplasia in a high risk area in Iran. *Arch Iran Med* **15**, 18–21, 2012.
9. Terry PD, Lagergren J, Wolk A, Steineck G, and Nyren O: Dietary intake of heterocyclic amines and cancers of the esophagus and gastric cardia. *Cancer Epid Bio Prev* **12**, 940–944, 2003.
10. Galeon C, Pelucchi C, Talamini R, Levi F, Bosetti C, et al.: Role of fried foods and oral/pharyngeal and oesophageal cancers. *Br J Cancer* **92**, 2065–2069, 2005.
11. De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Muñoz N, et al.: Food groups and risk of squamous cell carcinoma of the esophagus: a case-control study in Uruguay. *Br J Cancer* **89**, 1209–1214, 2003.
12. De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Correa P, et al.: Meat consumption, cooking methods, mutagens, and risk of squamous cell carcinoma of the esophagus: a case-control study in Uruguay. *Nutr. Cancer* **64**, 294–299, 2012.

13. World Cancer Research Fund/American Institute for Cancer Research: *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective* 2007. Washington, DC: American Institute for Cancer Research. Retrieved from http://www.dietandcancerreport.org/?p=ER
14. Knize MG, Salmon CP, Pais P, and Felton JS: Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. *Adv Exp Med Biol* **459**, 179–193, 1999.
15. Sinha R, and Rothman N: Role of well-done, grilled red meat, heterocyclic amines (HCAs) in the etiology of human cancer. *Cancer Lett* **143**, 189–194, 1999.
16. Kamangar F, Strickland PT, Pourshams A, Malekzadeh R, Boffetta P, et al.: High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. *Anticancer Res* **25**, 425–428, 2005.
17. Hakami R, Mohtadinia J, Etemadi A, Kamangar F, Nemati M, et al.: Dietary intake of benzo(a)pyrene and risk of esophageal cancer in North of Iran. *Nutr.Cancer* **60**, 216–221, 2008.
18. Islami F, Boffetta P, van Schooten FJ, Strickland P, Phillips DH, et al.: Exposure to Polycyclic Aromatic Hydrocarbons Among Never Smokers in Golestan Province, Iran, an Area of High Incidence of Esophageal Cancer—a Cross-Sectional Study with Repeated Measurement of Urinary 1-OHPG in Two Seasons. *Front Oncol* **2**, 14, 2012.
19. Bagheri Lankarani K, Mowla A, Asadian F, Tabei SZ, and Panjeshahin MR: Changing Epidemiology of esophageal cancer in Fars province, Iran. *IJMS* **27**, 4–10, 2012.
20. Etemadi A, Golozar A, Kamangar F, Freedman ND, Shakeri R, et al.: Large body size and sedentary lifestyle during childhood and early adulthood and esophageal squamous cell carcinoma in a high-risk population. *Ann Oncol* **23**, 1593–1600, 2012.
21. Malekshah AF, Kimiagar M, Saadatian-Elahi M, Pourshams A, Nouraie M, et al.: Validity and reliability of a new food frequency questionnaire compared to 24h recalls and biochemical measurements: pilot phase of Golestan cohort study of esophageal cancer. *Eur J Clin Nutr* **60**, 971–977, 2006.
22. Goldman R, and Shields PG: Food mutagens. *J Nutr* **133**, 965S–973S, 2003.
23. Sinha R, Chow WH, Kulldorff M, Denobile J, Butler J, et al.: Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res* **59**, 4320–4324, 1999.
24. Cross AJ, and Sinha R: Meat related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen* **44**, 44–55, 2004.
25. Butler LM, Duguay Y, Millikan RC, Sinha R, Gagne JF, et al.: Joint effects between UDP-glucuronosyltransferase 1A7 genotype and dietary carcinogen exposure on risk of colon cancer. *Cancer Epidemiol Biomarkers Prev* **14**, 1626–1632, 2005.
26. Sinha R, Peters U, Cross AJ, Kulldorff M, Weissfeld JL, et al.: Meat, meat cooking methods and preservation, and risk for colorectal adenoma. *Cancer Res* **65**, 8034–8041, 2005.
27. Ward MH, Sinha R, Heineman EF, Rothman N, Markin R, et al.: Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. *Int J Cancer* **71**, 14–19, 1997.
28. Wong KY, Su J, Knize MG, Koh WP, and Seow A: Dietary exposure to heterocyclic amines in a Chinese population. *Nutr Cancer* **52**, 147–155, 2005.
29. Salmon CP, Knize MG, Felton JS, Zhao B, Seow A: Heterocyclic aromatic amines in domestically prepared chicken and fish from Singapore Chinese households. *Food Chem Toxicol* **44**, 484–492, 2006.
30. De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Brennan P, et al.: Food groups and risk of squamous cell carcinoma of the oesophagus: a case-control study in Uruguay. *Br J Cancer* **89**, 1209–1214, 2003.
31. De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Correa P, et al.: Meat consumption, cooking methods, mutagens, and risk of squamous cell carcinoma of the esophagus: a case-control study in Uruguay. *Nutr Cancer* **64**, 294–299, 2012.
32. Pandey MK, Yadav S, Parmar D, and Das M: Induction of hepatic cytochrome P450 isozymes, benzo(a)pyrene metabolism and DNA binding following exposure to polycyclic aromatic hydrocarbon residues generated during repeated fish fried oil in rats. *Toxicol Appl Pharmacol* **213**, 126–134, 2006.
33. Pandey MK, Dhawan A, and Das M: Induction of p53, p21 Waf1, orinithine decorboxylase activity, and DNA damage leading to cell-cycle arrest and apoptosis following topical application of repeated fish fried oil extract to mice. *Mol Carcinog* **45**, 805–813, 2006.
34. Pandey MK, Pant AB, and Das M: In vitro cytotoxicity of polycyclic aromatic hydrocarbone residues arising through repeated fish fried oil in human hepatoma Hep G2 cell line. *Toxicol In Vitro* **20**, 308–316, 2006.