RESEARCH COMMUNICATION

Dietary Benzo[a]pyrene, Alcohol Drinking, and Risk of Breast Cancer: a Case-control Study in Uruguay

Alvaro L Ronco[1,2]*, Eduardo De Stefani[3] , Pelayo Correa[4], Hugo Deneo-Pellegrini[3], Paolo Boffetta[5], Gisele Acosta[3], Maria Mendilaharsu[3]

Abstract

In order to determine to the effect of benzo[a]pyrene (BaP) on breast cancer risk we conducted a case-control study in the time period 1996-2004. The study included 1,098 participants (460 cases and 638 controls). All the patients were drawn from the four major hospitals in Montevideo, Uruguay. Statistical analysis was performed using unconditional multiple logistic regression and the models included age, residence, urban/rural status, education, monthly income, body mass index, menopausal status, age at menarche, parity, smoking index, alcohol drinking, mate consumption, total energy, total vegetables and fruits, and BaP intake. The highest vs. the lowest quartile of BaP intake (OR 2.0, 95 % CI 1.2-3.3) was significantly associated with breast cancer risk. Alcohol drinking was also directly associated with breast cancer risk (OR 1.63, 95 % CI 1.19-2.23) and the joint effect of BaP and alcohol drinking showed an elevated risk of the disease (OR 3.32, 95 % CI 2.17-5.06). The present study suggests that elevated consumption of BaP could play an important role in the etiology of breast cancer. This effect is enhanced by the intake of alcohol.

Keywords: Benzo[a]pyrene - alcohol drinking - breast cancer - mutagens - DNA adducts

Asian Pacific J Cancer Prev, 12, 1463-1467

Introduction

Benzo[a]pyrene (BaP), a member of the chemicals known as polynuclear aromatic hydrocarbons (PAH), has been classified as a sufficient cause of cancer among animals and probably carcinogenic to humans (2A) according to the International Agency for Research on Cancer (IARC, 2004). BaP is present in drinking water, occupational exposures, tobacco and diet. In particular BaP is present in well-done red meat, fried poultry with skin, and fried eggs (Kazerouni et al., 2001). Several studies suggest that dietary BaP is a probable carcinogen for lung cancer (Lam et al., 2009), colorectal cancer (Sinha et al., 2005) and other cancer sites.

Uruguayan population is characterized by high consumption of red meat and is the country with the highest production of beef in the World (Matos and Brandani, 2002). The incidence rates of breast cancer (BC) in Uruguay are the highest among the South-American countries (Parkin et al., 2002), with age-standardized rates of 72.6 per 100,000 persons per year, respectively. Rates of cancers of the larynx, esophagus, lung, prostate, bladder and kidney are also high, especially among men (Parkin et al., 2002). While there is no doubt that smoking and high alcohol consumption contribute to the high rates of cancers of the lung, aerodigestive tract and some other cancers, there is increasing evidence that diet plays a major role in influencing cancer risk (WCRF, 2007). Also, the Uruguayan diet is characterized by a low intake of fruits, vegetables and whole grains (Buiatti and Sorso, 1993) and thus provides an interesting setting for investigating meat intake, meat mutagens, and cancer risk. Several previous studies conducted in this population suggested increased risk of multiple cancers including those of the upper aerodigestive tract (De Stéfani et al., 1998a), stomach (De Stéfani et al., 2004; 2009a), colorectum (Deneo-Pellegrini et al., 2005), breast (Ronco et al., 1996), kidney (De Stéfani et al., 1998b) and lung (Deneo-Pellegrini et al., 1996), with higher meat intake, a major source of BaP.

In a previous analysis we reported positive associations between a Western dietary pattern high in red and processed meat and the risk of several cancers (De Stéfani et al., 2008) and in other studies we reported elevated risks of several cancers with higher intake of total, red, processed and salted meat (Aune et al., 2009a; 2009b; De Stéfani et al., 2009b). To further expand upon these findings (high rates of cancer, high consumption of red meat, low intake of vegetables and fruits) we decided

[1]Departamento de Epidemiología y Métodos Científicos, Facultad de Medicina IUCLAEH, Maldonado, [2]Unidad de Oncología y Radioterapia, Hospital Pereira Rossell, Ministerio de Salud Pública, Montevideo, [3]Grupo de Epidemiología, Departamento de Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina UDELAR, Montevideo, Uruguay, [4]Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN, [5]Mount Sinai School of Medicine, New York, NY USA
**For correspondence: alronco@gmail.com*

to explore the association between benzo[a]pyrene consumption and BC risk in a case-control study in Uruguay.

Materials and Methods

Selection of cases

In the time period between 1996 and 2004 we conducted a case-control study on BC. All the cases were drawn from the four major public hospitals of Montevideo, representing 45 % of the general population. A total of 480 newly diagnosed and microscopically confirmed cancers of the breast were considered eligible for the study. In total 20 patients refused the interview, leaving a final total of 460 cases which were included in the study (response rate 95.7 %).

Selection of controls

In the same time period and in the same hospitals, 2,117 patients with diseases not related with smoking, drinking and without recent changes in their diet were considered eligible for this study. Sixty seven patients refused the interview, leaving a final total of 2,032 controls (response rate 96.0%). The number and percentage of each type of controls are shown in Table 1.

Interviews and questionnaire

All the participants were administered a structured questionnaire by four trained social workers. All the interviews of cases and controls were conducted in the hospitals shortly after admittance and no proxy interviews were conducted. The questionnaire contained the following sections: 1) socio-demographic characteristics (age, sex, residence, education), 2) a complete occupational history based in their jobs and its duration, 3) self-reported height and weight five years before the date of the interview, 4) a history of cancer in first degree relatives, 5) a complete history of tobacco smoking (age at start, age of quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), 6) a complete history of alcohol intake (age at start, age of quit, number of glasses per day or week, type of alcoholic beverage), 7) a complete history of mate (a local herbal tea), coffee and tea consumption (age at start, age of quit, number of cups ingested per day), 8) menstrual and reproductive events (age at menarche, age at menopause, breastfeeding, menopausal status, age at first livebirth, age of last livebirth, parity), and 8) a detailed food frequency questionnaire (FFQ) with 64 food items. This FFQ was considered as representative of the Uruguayan diet and allowed the estimation of total energy intake. Although the FFQ has not been validated, it has been tested for reproducibility with good results (Ronco et al., 2006).

Foods as a source of benzo[a]pyrene

A local Table of chemical composition of foods which included information on nitrates, nitrites, nitrosamines, heterocyclic amines and polycyclic aromatic hydocarbons was used in order to determinate the concentrations of BaP in several foods (Mazzei et al., 1995; Jackzsyn et al., 2004). The values are shown in nanograms per kilogram and the foods and its concentration in BaP are shown in the Table 2. The total BaP in the Uruguayan diet was log transformed and energy-adjusted using the residuals method (Willett and Stampfer, 1986) and then categorized in quartiles, according to the controls distribution.

Table 1. Distribution of Cases and Controls by Sociodemographics and Selected Risk Factors

Characteristics		Cases		Controls		p value
Age (years)	30-39	39	8.5	60	9.4	
	40-49	69	15.0	92	14.4	
	50-59	114	24.8	146	22.9	
	60-69	114	24.8	164	25.7	
	70-79	106	23.0	154	24.1	
	80-89	18	3.9	22	3.5	0.95
Residence	Montevideo	235	51.1	352	55.2	
	Other	225	48.9	286	44.8	0.18
Urban/rural	Urban	386	83.9	563	88.2	
status	Rural	74	16.1	75	11.8	0.04
Education	0-2	83	18.0	114	17.9	
(years)	3-5	150	32.6	214	33.5	
	6+	227	49.4	310	48.6	0.95
Income	≤142	155	33.7	252	39.5	
(US $)	143+	173	37.6	226	35.4	
	Unknown	132	28.7	160	25.1	0.13
Family	No	366	79.6	598	93.7	
history BC	Yes	94	20.4	40	6.3	<0.0001
Menopausal	Pre	86	18.7	140	21.9	
status	Post	374	81.3	498	78.1	0.19
Age	15+	47	10.2	82	12.9	
menarche	12-14	304	66.1	427	66.9	
	≤11	109	23.7	129	20.2	0.21
Nº Children	Nuliparae	93	20.2	80	12.5	
	1-2	183	39.8	240	39.6	
	3-4	112	24.4	160	25.1	
	5+	72	15.6	158	24.8	<0.0001
No. of patients		460	100.0	638	100.0	

Statistical methods

We used unconditional multiple logistic regression to estimate odds ratios of cancer for increasing levels of benzo[a]pyrene intake (Rothman et al., 2008). We used a multivariable model including the following covariates: age (continuous), residence (urban/rural), education (continuous), income (continuous), interviewer (categorical), menopausal status (premenopausal, postmenopausal), age at menarche (categorical), parity (categorical), alcohol intake (categorical), mate drinking (continuous), total energy intake (continuous) and BMI (continuous). Potential confounders (total vegetables, total fruits, total red meat) were included in the multivariate models based on review of the literature and from comparisons of cases vs. controls. Tests for linear trend were calculated by entering the categorical variables as continuous parameters in the models.

For direct comparison with other studies, we also analyzed benzo[a]pyrene consumption as a continuous variable and in this model, the unit of intake was set to one standard deviation. A two-tailed P-value of <0.05 was considered to be statistically significant. All statistical tests were carried out using STATA version 10.0 (Stata Corp, 2007).

Table 2. Odds Ratios of Breast Cancer for Alcoholic Drinks[1]

Characteristics		Cases/Controls	OR	96% CI
Alcohol status	Never	349/540	1.0	reference
	Ever	111/98	1.63	1.19-2.23
Beer	Abstainers	443/624	1.0	reference
	Drinkers	17/14	1.62	0.76-3.46
Wine	Abstainers	366/549	1.0	reference
	Drinkers	94/89	1.43	1.02-2.00
Hard liquor	Abstainers	446/629	1.0	reference
	Drinkers	14/9	1.92	0.80-4.63
Total alcohol	Never	349/540	1.0	reference
(ml/day)	1-27	41/38	1.55	0.96-2.51
	28+	70/60	1.67	1.14-2.46
	p-value for trend		0.005	
Years of	None	349/540	1.0	reference
drinking	1-32	53/53	1.46	0.95-2.23
	33+	58/45	1.83	1.18-2.82
	p-value for trend		0.004	
Cumulative	None	349/540	1.0	reference
	1-87	55/50	1.58	1.03-2.42
	88+	56/48	1.68	1.09-2.57
	p-value for trend		0.006	

[1]Adjusted for age, residence, urban/rural status, education, family history of breast cancer among first-degree relatives, body mass index, menopausal status, age at menarche, parity, mate drinking, and total energy intake

Table 3. Odds Ratios of Breast Cancer for Benzo[a] pyrene intake[1]

Characteristics		Cases/Controls	OR	96% CI
Premenopausal	I	17/44	1.0	reference
	II	16/34	1.33	0.50-3.58
	III	26/35	2.76	1.08-7.03
	IV	27/27	3.18	1.21-8.36
	p-value for linear trend			0.007
Postmenopausal	I	58/115	1.0	reference
	II	72/126	1.16	0.74-1.82
	III	92/126	1.41	0.91-2.19
	IV	152/131	2.09	1.38-3.17
	p-value for linear trend			<0.0001
Both strata	I	75/159	1.0	reference
	II	88/160	1.15	0.77-1.72
	III	118/161	1.52	1.03-2.24
	IV	179/158	2.16	1.49-3.14
p-value for linear trend		<0.0001		

1 Adjusted for age, residence, urban/rural status, education, family history of breast cancer among first-degree relatives, body mass index, menopausal status, age at menarche, parity, mate drinking, and total energy intake

Table 4. Joint Effect of Benzo[a]pyrene (BP) and Alcohol Drinking[1,2]

	Never		Ever			
BP/Alcohol	OR	95 % CI	OR	95 % CI	Total BaP	
Low	1.0	reference	0.44	0.15-1.26	1.0	reference
High	1.90	1.27-2.85	3.56	0.99-12.8	2.16	1.49-3.14
Total alc	1.0		1.65	1.11-2.44		

[1]Adjusted for age, residence, urban/rural status, education, family history of breast cancer among first-degree relatives, body mass index, menopausal status, age at menarche, parity, mate consumption, and total energy intake; [2]p-value for heterogeneity=0.01

Results

The distribution of cases and controls according to socio-demographic variables and selected risk factors is shown in Table 1. Compared with the controls, the cases were in general older and less educated, they also had a higher intake of cigarettes, alcohol and total meat, but a lower intake of fruits and vegetables. The ten top sources of BaP were listed as follows, eggs (7.49 nanograms/100 grams), chicken (4.60), beef (3.80), sausage (2.05), whole milk (1.5), hot dog (1.1), mate (1.05), cheese (0.91), winter squash (0.45),and black coffee (0.36).

Odds ratios of BC for alcohol drinking is shown in Table 2. Ever drinkers were associated with BC (OR 1.63, 95 % 1.19-2.23) compared with never drinkers. Also, consumption, duration, cumulative exposure of alcohol were directly associated with risk of BC (OR 1.83, 95 % CI 1.18-2.82).

The adjusted odds ratios for benzo[a]pyrene and BC with reference to menopausal status are given in Table 3. High consumption of benzo[a]pyrene was strongly associated with risk of BC (OR 2.26, 95 % CI 1.57-3.27, p-value for trend <0.0001). When BaP was stratified by menopausal status, the highest risk was observed among premenopausal women (OR 3.25, 95 % CI 1.24-8.54).

Joint effects of alcohol drinking and BaP are shown in Table 4. The category of high consumption of BaP and ever drinkers was associated with a risk of 3.56 (95 % CI 0.99-12.8) suggesting a multiplicative model. The p-value for heterogeneity was 0.01.

Discussion

In this large hospital-based case-control study we found increased risk of BC with high intake of BaP (benzo[a]pyrene) and a multiplicative model which included alcohol drinking and BaP.

The cancer site which has been most investigated previously in relation to BaP intake is colorectal cancer and our finding of an elevated risk with higher intake of BaP is consistent with previous studies (Butler et al., 2003; Cross and Sinha, 2004; Cross et al., 2007; Ward et al., 2007) and in the most recent report from the World Cancer Research Fund/American Institute for Cancer Research, the evidence that red and processed meat (major sources of BaP) increases colorectal cancer risk was judged to be convincing (WCRF, 2007). In experimental studies (Harris et al., 2009) saturated fat enhanced BaP-induced colon tumors in APCmin mice. In previous studies high intake of dietary BaP was associated with a doubling in risk of colon, rectal, and colorectal cancers. Thus, the results were consistent across subsites of large bowel cancer.

According to the recent monograph of the International Agency for Research on Cancer on Alcohol Consumption (IARC, 2010), more than 100 epidemiological studies—two thirds case–control and one third cohort—have evaluated the association between the consumption of alcoholic beverages and the risk for BC. There is robust evidence that alcoholic drinks are a cause of premenopausal and postmenopausal BC, something that was suggested by Willett et al almost 25 years ago (Willett

et al., 1987).

Reactive metabolites of alcohol, such as acetaldehyde may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation and the generation of free radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens (like BaP) into cells.

In the present study, dietary BaP was directly associated with risk of BC with a well-defined dose-response. Recent cohort studies on BC reported no association with heterocyclic amines from well-done fried red meat (WCRF, 2007). On the other hand, Mordukhovich et al found a positive association between PHA-related exposures and p53 mutations in BC (Mordukhovich et al., 2010). This recent study replicates the findings of the pool analysis of Gammon et al (2004). Furthermore, it has been found that ethanol enhances the formation of BaP-DNA adducts in human mammary epithelial cells (Barnes et al., 2000). This fact is of paramount importance, since it emphasizes a major step in breast carcinogenesis. Thus, BaP and alcohol appear to be major strong risk factors for BC and they act in, probably, as synergistic factors.

Mate consumption is consumed with the herb (or tea) diluted in large amounts of tap water (mean amount of 1 liter or more per cup). According to the California Environmental Protective Agency (Di Bartolomeis, 1997), drinking water contains 1 nanogram per liter/day. Thus, mate could contribute to the BaP loading of the diet. A rather recent study (Fagundes et al., 2006) found that mate contained BaP and elevated amounts of its urine metabolite 1-hydroxypyrene glucuronide (1-OHPG). Since mate preparation implies wood smoke and is linked with smoke and barbecued meat (Fagundes et al., 2006) it is possible that BaP could act as a carcinogen. Recently, Kamangar et al (2008) reported that very high concentrations of PAHs were found in yerba mate leaves and in hot and cold mate infusions suggesting that the carcinogenicity of mate may be related to its PAH content. In our study, mate was inversely associated with BC risk. In fact, mate has polyphenols and ascorbic acid which were inversely associated with risk of BC. These substances could counteract the effect of BaP in mate.

Our study has several potential limitations; as with any case-control study we cannot rule out the possibility of recall or selection biases. If the controls either consume or report their meat consumption differently than the general population biased results would occur. Participation rates were very high, thus minimizing the potential for selective participation according to lifestyle practices. Recall bias is a potential problem in case-control studies because of the retrospective assessment of diet. Nevertheless, the participants in this study were generally of low socioeconomic status, with little knowledge about the role of diet and meat intake in affecting cancer risk. This is likely to apply even more for the less common cancers. Meat intake (a major source of BaP) is not considered an unhealthy dietary habit in this population and this should have reduced the possibility for recall bias, but we cannot exclude the possibility that it may have been present. Further, we cannot exclude the possibility of residual confounding by unknown or unmeasured factors. We were not able to adjust for physical activity which is an important risk factor for several cancer sites, however, other studies found that the association between BaP intake and cancer risk remained significant even after adjustment for physical activity, suggesting that confounding from physical activity does not fully explain the findings. Also, we found that adjustment for other food groups strengthened rather than weakened the association between BaP intake and cancer risk. Finally, some of our findings may have been due to chance.

Our study has several strengths as well; the high BaP intake and the relatively large dietary variation in the Uruguayan population increased the power to detect significant associations. The rather strong ORs found in our study probably reflect the very high meat intake in this population, compared with other populations.

In conclusion, our findings provide further evidence that high BaP intake may increase BC risk and suggest that multiple cancer sites may be linked to high intake of this mutagen/carcinogen. Reducing the main sources of benzo[a]pyrene intake may be an important modifiable risk factor for several types of cancer.

Acknowledgements

This work was supported by a grant from International Agency for Research on Cancer, Lyon, France.

References

Aune D, Ronco A, Boffetta P, et al (2009a). Meat consumption and cancer risk: a multisite case-control study in Uruguay. *Cancer Therapy*, **7**, 174-87.

Aune D, De Stefani E, Ronco A, et al (2009b). Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pacific J Cancer Prev*, **10**, 429-436.

Barnes SL, Singletary KW, Frey R (2000). Ethanol and acetaldehyde enhance benzo[a]pyrene-DNA adduct formation in human mammary epithelial cells. *Carcinogenesis*, **21**, 2123-8.

Buiatti E, Sorso B (1993). Distribution of risk factors in Italy and in the host countries. In: Geddes M, Parkin DM, Khlat M, et al (editors). Cancer in Italian Migrant Populations. IARC Scientific Publications No. 123, Lyon, France, pp. 48-54.

Butler LM, Sinha R, Millikan RC, et al. (2003). Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am J Epidemiol*, **157**, 434-45.

Cross AJ, Sinha R (2004). Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen*, **44**, 44-55.

Cross AJ, Leitzmann MF, Gail MH, et al (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, **4**, e325.

De Stéfani E, Ronco A, Mendilaharsu M, et al (1998a). Case-control study on the role of heterocyclic amines in the etiology of upper aerodigestive cancers in Uruguay. *Nutr Cancer*, **32**, 43-8.

De Stéfani E, Fierro L, Mendilaharsu M, et al (1998b). Meat intake, 'mate' drinking and renal cell cancer in Uruguay: a case-control study. *Br J Cancer*, **78**, 1239-43.

De Stéfani E, Correa P, Boffetta P, et al (2004). Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. *Gastric Cancer*, **7**, 211-20.

De Stéfani E, Deneo-Pellegrini H, Boffetta P, et al (2008). Dietary patterns and risk of cancer: A factor analysis in Uruguay. *Int J Cancer*, **124**, 1391-7.

De Stéfani E, Aune D, Deneo-Pellegrini H, et al (2009a). Dietary patterns and risk of gastric cancer: A factor analysis in Uruguay. *Med Hypotheses Res*, **5**, 10-8.

De Stéfani E, Aune D, Boffetta P, et al (2009b). Salted meat consumption and the risk of cancer: a multisite case-control study in Uruguay. *Asian Pacific J Cancer Prev*, **10**, 853-7.

Deneo-Pellegrini H, De Stéfani E., Ronco A, et al (1996). Meat consumption and risk of lung cancer; a case-control study from Uruguay. *Lung Cancer*, **14**, 195-205.

Deneo-Pellegrini H, Boffetta P, De Stéfani E, et al (2005). Meat consumption and risk of colorectal cancer: a case-control study in Uruguay. *Cancer Therapy*, **3**, 193-200.

Di Bartolomeis M (editor) (1997). Public Health Goal for benzo[a]pyrene in drinking water. California Environmental Protective Agency, CA, pp. 1-42.

Fagundes RB, Abnet CC, Strickland PT, et al (2006). Higher urine 1-hidroxypyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking mate in healthy subjects from Rio Grande do Sul, Brazil. *BMC Cancer*, **6**, 139-45.

Gammon MD, Sagiv SK, Eng SM, et al (2004). Polynuclear aromatic hydrocarbons-DNA adducts and breast cancer: a pooled analysis. *Arch Environ Health*, **59**, 640-9.

Harris DL, Niaz MS, Morrow JD, et al (2009). Diet as a modifier of benzo[a]pyrene metabolism and benzo[a]pyrene-induced colon tumors in Apcminmice. In Obayashi Y, Isobe T, Suzuki S, et al (editors). Interdisciplinary studies on Environmental Chemistry-Environmental Research in Asia, TerraPub Publishers, Tokyo, pp 227-38.

International Agency for Research on Cancer (2004). Tobacco Smoke and Involuntary Smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83, IARC, Lyon.

International Agency for Research on Cancer (2010). Alcohol Consumption and Ethyl Carbamate. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 96, IARC, Lyon .

Jakszyn P, Agudo A, Ibañez R, et al (2004). Development of a food database of nitrosamines, heterocyclic amines, and polynuclear aromatic hydrocarbons. *J Nutr*, **134**, 2011-4.

Kamangar F, Schantz MM, Abnet CC, et al (2008). High levels of carcinogenic polycyclic aromatic hydrocarbons in mate drinks. *Cancer Epidemiol Biomarkers Prev*, **17**, 1262-8.

Kazerouni N, Sinha R, Hsu CH, et al (2001). Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food Chem Toxicol*, **39**, 423-36.

Lam TK, Cross AJ, Consonni D, et al (2009). Intakes of red meat, processed meat, and meat mutagens increase lung cancer risk. *Cancer Res*, **63**, 1-8.

Matos E, Brandani A (2002). Review on meat consumption and cancer in South America. *Mutat Res*, 506-507, 243-9.

Mazzei ME, Puchulu MR, Rochaix MA (1995). Tabla de composición química de alimentos. 2ª Edición. Centro de Nutrición Aplicada. Edit. El Ateneo, Buenos Aires.

Mordukhovich J, Rossner Jr P, Terry MB, et al (2010). Association between polynuclear aromatic hydrocarbons-related exposures and p53 mutations in breast cancer. *Env Healhh Perspect*, **118**, 511-8.

Parkin DM, Whelan SL, Ferlay J, et al (2002) (editors). Cancer Incidence in Five Continents vol. VIII. IARC Scientific Publications No. 155, Lyon, France.

Ronco A, De Stéfani E, Mendilaharsu M, et al (1996). Meat, fat, and risk of breast cancer. *Int J Cancer*, **65**, 328-31.

Ronco AL, De Stéfani E, Boffetta P, et al (2006). Food patterns and risk of breast cancer: A factor analysis study in Uruguay. *Int J Cancer*, **119**, 1672-8.

Rothman KJ, Greenland S, Lash TL (editors)(2008). Modern Epidemiology. Third Edition. Lippincott Williams and Wilkins, Phil, PA, pp. 303-27.

Sinha R, Kulldorff M, Gunter MJ, et al (2005). Dietary benzo[a] pyrene intake and risk of colorectal adenoma. *Cancer Epidemiol Biomarkers Prev*, **14**, 2030-4.

Stata Corp (2007). Stata Statistical Software. Release 10. College Station, TX.

Ward MH, Cross AJ, Divan H, et al (2007). Processed meat intake, CYP2A6 activity and risk of colorectal adenoma. *Carcinogenesis*, **28**, 1210-6.

Willett WC, Stampfer MJ (1986). Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*, **124**, 17-27.

Willett WC, Stampfer MJ, Colditz GA et al (1987). Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med*, **316**, 1174-80.

World Cancer Research Fund/American Institute for Cancer Research (2007). Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. AICR, Washington DC.