Cooked Meat and Risk of Breast Cancer—Lifetime Versus Recent Dietary Intake

Susan E. Steck, Mia M. Gaudet,† Sybil M. Eng,‡ Julie A. Britton,§ Susan L. Teitelbaum,§ Alfred I. Neugut,‖ Regina M. Santella,** and Marilie D. Gammon†*

Background: Polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) are carcinogens formed in or on the surface of well-done meat, cooked at high temperature.

Methods: We estimated breast cancer risk in relation to intake of cooked meat in a population-based, case-control study (1508 cases and 1556 controls) conducted in Long Island, NY from 1996 to 1997. Lifetime intakes of grilled or barbecued and smoked meats were derived from the interviewer-administered questionnaire data. Dietary intakes of PAH and HCA were derived from the self-administered modified Block food frequency questionnaire of intake 1 year before reference date. Unconditional logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Modest increased risk was observed among postmenopausal, but not premenopausal, women consuming the most grilled or barbecued and smoked meats over the life course (OR = 1.47; CI = 1.12–1.92 for highest vs. lowest tertile of intake). Postmenopausal women with low fruit and vegetable intake, but high lifetime intake of grilled or barbecued and smoked meats, had a higher OR of 1.74 (CI = 1.20–2.50). No associations were observed with the food frequency questionnaire-derived intake measures of PAHs and HCAs, with the possible exception of benzo(α)pyrene from meat among postmenopausal women whose tumors were positive for both estrogen receptors and progesterone receptors (OR = 1.47; CI = 0.99–2.19).

Conclusions: These results support the accumulating evidence that consumption of meats cooked by methods that promote carcinogen formation may increase risk of postmenopausal breast cancer.

(*Epidemiology* 2007;18: 373–382)

Polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) are 2 classes of carcinogens that are found in the human diet. PAHs can appear on or near the surface of foods from the smoke created by incomplete combustion of carbon and hydrogen in fat that has fallen onto hot coals (such as in grilling or barbecuing), or by contamination from air or water pollutants.[1] PAHs are found in a variety of food products, including grilled or barbecued meat, smoked meat, vegetables, fruits, yogurt, margarine, grains, and cereals.[1] HCAs are formed when amino acids pyrolyze in meat juice, and are particularly high in pan-fried, grilled and, to a lesser extent, broiled meat.[2] The method, temperature, and duration of cooking greatly affect the amount of HCAs found in meat products, with greater doneness associated with higher concentrations of HCAs.[3,4] HCAs and PAHs are known carcinogens in animals, and are involved in the development of mammary tumors.[5,6] Dietary intake of these compounds has been consistently linked to colorectal cancer,[7] and has been linked to breast cancer in a few epidemiologic studies,[8,9] but not all.[10]

Several epidemiologic studies have observed positive associations between recent intake of well-done cooked meat and breast cancer,[11–13] whereas other studies have not.[14–16] None of the previous studies assessed lifetime intake of cooked meat, which may be the more relevant time frame of exposure in carcinogenesis. Additionally, many of the studies were limited in their ability to estimate dietary intake of specific carcinogens from cooked meat because the exposure assessment method relied on food frequency questionnaires (FFQs) without specific questions related to meat preparation techniques or doneness preference.

This large population-based study was undertaken to address the hypothesis that breast cancer risk may be associated with dietary intake of PAHs, HCAs, and meat, according to cooking methods and level of doneness. We assessed intake both recently and throughout the lifetime. Further, we looked for possible interactions with fruit and vegetable intake, based on the possibility that these foods may mitigate

Submitted 8 February 2006; accepted 1 December 2006.

From the *Departments of Nutrition and †Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC; ‡Global Epidemiology, Worldwide Safety and Risk Management, Pfizer, Inc., New York, NY; §Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY; ¶Department of Epidemiology, Mailman School of Public Health; ‖Department of Medicine, College of Physicians and Surgeons; and **Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY.

This work was supported in part by grants from the National Cancer Institute, the National Institutes of Environmental Health and Sciences, and the American Institute for Cancer Research (Grant nos. CA/ES66572, P30ES10126, P30ES09089, CA58233, 1K07CA102640-01, AICR-03B091).

Correspondence: Susan E. Steck, Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, 2221 Devine Street, Room 231, Columbia, SC 29208. E-mail: ssteck@sc.edu.

ISSN: 1044-3983/07/1803-0373
DOI: 10.1097/01.ede.0000259968.11151.06

the carcinogenic effects of PAHs and HCAs, as shown in animal models.[17,18]

METHODS

Institutional Review Board approval was obtained by all collaborating institutions. The study was conducted in accordance with national and institutional guidelines for the protection of all study participants.

Study Design and Population

The Long Island Breast Cancer Study Project is a population-based case-control study funded by the National Cancer Institute and the National Institute of Environmental Health Sciences in response to a federal mandate (Public Law 103-43, June 10, 1993) that a case-control study be conducted on Long Island, New York to examine the relationship between environmental exposures and breast cancer. Methods have been described in detail previously.[19] Cases (n = 1508; 82% of eligible cases) were identified through pathology/cytology records of 33 institutions; they included residents of Nassau and Suffolk counties, newly diagnosed with breast cancer between 1 August 1996 and 31 July 1997. Population-based controls (n = 1556; 63% of eligible controls) were identified using random digit dialing for women under the age of 65 years and by Center for Medicare and Medicaid Services (formerly known as Health Care Financing Administration) rosters for women 65 years and older. Controls were frequency-matched to the expected age distribution of cases by 5-year age group. All participants signed informed consent forms before enrolling in the study.

Exposure Assessment

An in-home questionnaire that lasted on average 101 minutes was administered to each subject by a trained interviewer. The questionnaire elicited information on demographic factors, current and past residences, occupational history, environmental exposures, reproductive history, menstruation and menopause history, contraceptive and hormone use, medical history, body size, physical activity, family history of disease, alcohol consumption, and smoking history (questionnaire available at http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html). This main questionnaire also included assessment of intake of 4 categories of grilled/barbecued and smoked meats over each decade of life since the teenage years (Section C. Residential History, pages 19–20 of the questionnaire on the Web site). Among the respondents who completed the main questionnaire, 98% of breast cancer cases and 98% of controls also completed a self-administered Block FFQ (detailed below), including approximately 100 food items that assessed diet in the previous year.

Exposure Indices Calculated

Lifetime Intake of Grilled or Barbecued and Smoked Foods

As previously described,[20] variables quantifying lifetime consumption of grilled/barbecued and smoked foods were constructed based on 1) data collected in the main questionnaire that focused on past lifetime consumption and 2) a checklist that focused on consumption in the 4 weeks before the interview. In the main questionnaire, women were queried about their consumption patterns over 6 decades of life (<20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60+ years) for 4 different groups of PAH-containing foods: smoked beef, lamb, and pork; grilled/barbequed beef, lamb, and pork; smoked poultry or fish; and, grilled/barbequed poultry or fish. The average of the 6 (or fewer) decades was calculated to derive an average lifetime consumption of these 4 PAH-containing food groups.

Values were missing for <2% of respondents for each of the 24 groups (6 decades of consumption × 4 food groups), which translated to 9%–10% of respondents missing the values for the 4 derived averages. Most of missing values were restricted to a single decade of reported consumption. Imputations for the missing values were derived by multiple regression[21] using data from women with complete data to predict the missing variables in each of the 24 groups. In addition, regression analyses were performed separately by the decade of age at interview because of concerns about possible cohort effects. For example, to predict average consumption of smoked beef, lamb, and pork between the ages of 20 and 29 years, for women in their 30s at reference, multiple regression was conducted using subjects in their 30s at reference to construct a model:

$$\text{Beef consumption during ages 20–29 years} = \alpha + \beta_1\,(\text{beef consumption under age 20 years}) + \beta_2\,(\text{beef consumption during ages 30–39 years}) + \varepsilon$$

These regression coefficients, β_1 and β_2, were then used to impute beef consumption for all women in their 30s who were missing only beef consumption during the decade 20 to 29 years of age. These steps were repeated for other women missing only 1 interval of consumption within each food category. To correct for artificially minimized standard errors for the odds ratios (ORs) produced when using imputations, the standard errors obtained using imputed data were inflated back to the lower sample-size level. This imputation strategy reduced the amount of missing intake data in the following manner: lifetime grilled/barbecued beef, lamb, or pork consumption reduced from 9% to 3%; lifetime intake of grilled/barbecued poultry or fish from 10% to 3%; lifetime smoked beef, lamb, or pork consumption from 9% to 3%; lifetime intake of smoked poultry or fish from 10% to 5%; and lifetime consumption of all 4 types of food combined from 15% to 5%.

The results obtained from this imputed data set were not materially different from those obtained from the data set in which missing consumption values were simply dropped, although, as expected, confidence intervals were wider for the latter data set (data not shown). Sensitivity analyses revealed that substitution of more crudely derived imputations (for example the highest or lowest observed values) did not substantially affect the observed ORs (data not shown). Thus, the results based on models with the more precisely estimated regression coefficients imputed for the missing values are shown.

HCA and Benzo(α)pyrene Indices

Calculation of these exposure indices was based on data collected as part of the Block FFQ,[22] which was modified to include a detailed assessment of frequency, preparation techniques, and doneness levels for 5 items (hamburgers, steak, pork, poultry, and fish).[23] Frequency of intake was categorized as never, <1 per month, 1 per month, 2–3 per month, 1–2 per week, 3–4 per week, 5–6 per week, and at least 1 time per day. For each meat and fish item, participants were asked, "how often during the last 12 months, did you eat meat . . . grilled or barbequed, pan-fried, (not deep-fat-fried), oven-broiled, oven-baked, microwaved, and other (specify: _____)." Levels of doneness were categorized as rare/medium, well-done, or very well-done. Frequency of cooking methods for each food item was converted to the common denominator of times per week. Responses to the frequency and portion sizes of food items were translated into daily intakes (in grams) for each food item using the National Cancer Institute DietSys program, version 3.[24]

We examined 1 PAH [benzo(α)pyrene] and 3 HCAs [2-amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQX,)]. The values per gram of food item were each applied to consumption (in grams) of hamburger, steak, pork, bacon, sausage, fried chicken, and other types of poultry using a modification of the method developed by Sinha.[3,4,25,26]

PAH and HCA values for meats vary with cooking method, level of doneness, and consumption of the skin for poultry items.[1] To translate participants' responses into daily intake in grams for each meat item, cooking method weights were created based on the percent of time a women used each specific cooking method. These weights were then multiplied to the HCA and benzo(α)pyrene values unique to that cooking method and doneness level. Weighted HCA and benzo(α)pyrene levels for each cooking method were then summed across cooking methods for each meat item. The resulting number of nanograms of HCA or benzo(α)pyrene per 1 g for each meat item was multiplied by the woman's intake (in grams) of that meat item.

Women who did not respond to a meat item's doneness level and frequency of intake were assumed to be nonconsumers of that item (assigned to 0). Among the minimal number of remaining women with missing data for the cooking method section, HCA and benzo(α)pyrene values for the missing meat item were set to missing; this was done for 28 hamburger responses [14 cases (0.9%), 14 controls (0.9%)], 28 steak responses [14 cases (0.9%), 14 controls (0.9%)], 44 pork responses [24 cases (1.6%), 20 controls (1.3%)], and 36 chicken responses [15 cases (1.0%), 21 controls (1.4%)]. The FFQ did not specifically ask cooking methods for steaks or roasts, so the frequency of cooking methods for "beef, including hamburger" was assigned to steaks or roasts. Cooking methods for bacon and sausage were also not specifically queried, so cooking methods reported for pork were assigned to bacon and sausage. In the control population, the categories "Don't know" and missing values for doneness of meat items were assumed to be the most common doneness response. For hamburger [22 (1.6%) cases, 35 (2.4%) controls] and steak [44 (1.7%) cases, 29 (2.0%) controls], missing values were assigned the medium doneness level that was selected by greater than 50% of controls. For pork, 41 (3.3%) cases and 51 (2.9%) controls, and for poultry, 28 (1.9%) cases and 40 (2.7%) controls were assigned the "well" doneness selected by greater than 50% of controls.

Covariate Assessment

The following variables were studied with regard to confounding or effect modification: 1) from the main questionnaire, reference age (defined as date of diagnosis for cases and date of identification for controls), menopausal status, race, education, age at first birth, parity, age at menarche, history of breast-feeding, use of oral contraceptives, use of hormone replacement therapy, family history of breast cancer, smoking status, physical activity, body mass index, alcohol intake; and 2) from the FFQ, consumption of energy, fruits and vegetables, and single and multiple vitamin use. Stratified analyses were performed to test for heterogeneity by stage of disease and estrogen receptor/progesterone receptor (ER/PR) status as previously described.[19]

Statistical Methods

The main exposure variables were total and average lifetime intake of grilled/barbecued and smoked meats estimated from the main questionnaire, and estimated intake of total benzo(α)pyrene, benzo(α)pyrene from meat only, benzo(α)pyrene from sources other than meat, and each of the 3 HCAs, all based on FFQ responses as described above. These variables were categorized into quantiles (deciles, quintiles, quartiles, tertiles, or dichotomous) based on menopause-specific distributions among the controls to assess the best representation of the data. Because the findings were similar regardless of the quantile chosen, we used tertiles to improve power during stratified analyses. Unconditional logistic regression was used to calculate ORs and 95% confidence intervals (CIs) of breast cancer in relation to tertiles of the main exposure variables. Crude ORs and corresponding 95% CIs adjusting only for age were calculated, as well as adjusted ORs controlling for potential confounders.

Effect modification on the multiplicative scale was evaluated by comparing the ORs for meat intake variables across strata of covariates and testing for heterogeneity. We created interaction terms between meat intake variables and covariates, and conducted a likelihood ratio test to compare the model with the interaction terms to the reduced model containing only the individual variables. We assessed additive interaction by computing interaction contrast ratios using the hypothesized lowest risk category of low meat intake and high fruit and vegetable intake as the common referent and comparing all other joint categories of meat and fruit and vegetable intake to this common referent. In these data, menopausal status was not an effect modifier on a multiplicative scale. Nonetheless, because we[27] and others[28] have found breast cancer risk in relation to diet to vary with menopause, and because there was some indication that the lifetime cooked

meat results varied with menopausal status, we present all analyses stratified by menopausal status.

We assessed confounding with backward elimination, beginning with a full model. A covariate remained in the model if the OR of the reduced model (without the covariate) changed by more than 10% when compared with the OR of the full model. Tests for trend were calculated by setting each tertile equal to the median value and treating these 3 median tertile values as a continuous variable.

RESULTS

Breast cancer risk among postmenopausal women was elevated in relation to measures of both total and average

TABLE 1. Adjusted* ORs and 95% CIs for Breast Cancer by Intake of Grilled/Barbecued and Smoked Meats Over the Woman's Lifetime (Assessed From Main Questionnaire) in the Long Island Breast Cancer Study Project, 1996–1997

Intake†		Premenopausal				Postmenopausal			
Range	Median	Cases No. (%)	Controls No. (%)	OR	(95% CI)	Cases No. (%)	Controls No. (%)	OR	(95% CI)
Grilled/barbecued beef, pork, and lamb									
Average over lifetime									
0–13‡	3	119 (25)	134 (27)	1.00		391 (40)	415 (43)	1.00	
14–48	28	145 (31)	145 (29)	1.09	(0.72–1.63)	327 (33)	302 (32)	1.21	(0.93–1.57)
49–364	79	203 (43)	215 (44)	0.96	(0.66–1.40)	271 (27)	244 (25)	1.28	(0.96–1.71)
P for trend				$P = 0.47$				$P = 0.18$	
Total over lifetime									
0–630‡	219	124 (27)	137 (29)	1.00		289 (32)	316 (35)	1.00	
631–2162	1358	175 (38)	186 (39)	0.98	(0.67–1.42)	261 (28)	266 (30)	1.18	(0.89–1.57)
2163–17,217	3640	158 (35)	155 (32)	0.85	(0.57–1.26)	366 (40)	310 (35)	1.32	(1.01–1.72)
P for trend				$P = 0.24$				$P = 0.10$	
Smoked ham, pork, and lamb									
Average over lifetime									
0–21‡	1	229 (49)	240 (48)	1.00		469 (48)	499 (51)	1.00	
22–52	38	140 (30)	160 (32)	1.06	(0.75–1.52)	281 (29)	270 (28)	1.25	(0.96–1.63)
53–364	97	98 (21)	99 (20)	0.96	(0.63–1.47)	233 (24)	208 (21)	1.13	(0.84–1.51)
P for trend				$P = 0.88$				$P = 0.35$	
Total over lifetime									
0–810‡	323	163 (43)	155 (40)	1.00		187 (25)	215 (30)	1.00	
811–2277	1490	132 (35)	153 (39)	0.97	(0.68–1.39)	240 (31)	215 (30)	1.45	(1.09–1.93)
2278–24,253	3750	82 (22)	81 (21)	0.94	(0.60–1.47)	332 (44)	298 (40)	1.30	(0.99–1.69)
P for trend				$P = 0.29$				$P = 0.22$	
Total grilled/barbecued and smoked meats									
Average over lifetime									
0–54‡	24	91 (20)	111 (23)	1.00		324 (35)	373 (41)	1.00	
55–137	89	169 (38)	170 (36)	1.24	(0.83–1.86)	320 (34)	274 (30)	1.48	(1.13–1.93)
138–1092	208	191 (42)	197 (41)	1.13	(0.76–1.68)	295 (31)	259 (29)	1.35	(1.02–1.79)
P for trend				$P = 0.89$				$P = 0.12$	
Total over lifetime									
0–2562‡	1164	153 (34)	166 (34)	1.00		280 (29)	330 (35)	1.00	
2565–6081	4264	161 (35)	181 (38)	0.98	(0.68–1.40)	287 (30)	272 (30)	1.47	(1.11–1.95)
6085–51,652	9448	143 (31)	136 (28)	1.03	(0.68–1.54)	390 (41)	330 (35)	1.47	(1.12–1.92)
P for trend				$P = 0.98$				$P = 0.02$	
Average over previous decade of life									
0–48‡	12	109 (24)	126 (26)	1.00		395 (41)	418 (45)	1.00	
49–140	96	161 (35)	146 (30)	1.05	(0.70–1.56)	312 (32)	278 (30)	1.31	(1.00–1.70)
142–1092	220	185 (41)	216 (44)	0.88	(0.60–1.30)	254 (26)	234 (25)	1.20	(0.90–1.60)
P for trend				$P = 0.52$				$P = 0.27$	

*Adjusted for age, energy intake, fruit and vegetable intake, and multivitamin supplement use.
†Average indicates the number of times consumed per year; total indicates the total number of times consumed.
‡Reference category.

lifetime intake of grilled/barbecued and smoked meats (as assessed in the main questionnaire; Table 1). Compared with women in the lowest tertile, ORs for total lifetime intake among women in the second and third tertile were both 1.47 (95% CI = 1.11–1.95 and 1.12–1.92, respectively); the corresponding results for average lifetime intake were similar (OR = 1.48 [CI = 1.13–1.93] and 1.35 [CI = 1.02–1.79], respectively). Modest increased risks among postmenopausal women were also observed in relation to average and total lifetime intake of grilled/barbecued beef, pork, and lamb, and in relation to total lifetime intake of smoked ham, pork, and lamb. No associations were observed for any of the lifetime cooked meat intake variables among premenopausal women (Table 1). Further, no associations were observed for intakes of grilled/barbecued poultry or smoked fish among pre- or postmenopausal women (data not shown).

We also examined the association between breast cancer and intake of cooked meat by decade of life (data not shown). For postmenopausal women, although some individual associations were noted, no clear patterns emerged to suggest differential risk by intake in specific decades of life. In general, associations between the various cooked meat variables and breast cancer risk were spread throughout the lifetime. When examining associations by decade of life in premenopausal women, a few associations were observed in the second but not the third tertiles of intake.

As shown in Table 2, intakes of benzo(α)pyrene and HCAs in the previous year (as assessed by the FFQ) were not associated with increased risk of breast cancer. Contrary to our hypothesis, for premenopausal women, a reduced risk of breast cancer was observed in women in the third tertile of intake of 2 HCAs (MeIQx and DiMeIQx) compared with

TABLE 2. Adjusted* ORs and 95% CIs for Breast Cancer by Intake of Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines in the Previous Year (Assessed From FFQ)

Intake†		Premenopausal				Postmenopausal			
Range	Median	Cases No. (%)	Controls No. (%)	OR	(95% CI)	Cases No. (%)	Controls No. (%)	OR	(95% CI)
Total BaPs from food									
0–56‡	42	142 (32)	159 (33)	1.00		336 (35)	318 (34)	1.00	
57–84	70	156 (35)	160 (34)	1.20	(0.79–1.81)	347 (36)	296 (32)	1.22	(0.89–1.67)
85–411	107	150 (33)	156 (33)	1.15	(0.68–1.94)	281 (29)	324 (34)	1.01	(0.68–1.50)
P for trend				$P = 0.52$				$P = 0.92$	
BaPs from meat									
0‡	0	208 (46)	219 (46)	1.00		568 (59)	552 (59)	1.00	
1–3	1	112 (25)	124 (26)	0.75	(0.51–1.11)	226 (23)	224 (24)	0.91	(0.70–1.20)
4–189	11	128 (29)	132 (28)	0.91	(0.62–1.32)	170 (18)	162 (17)	1.07	(0.79–1.46)
P for trend				$P = 0.71$				$P = 0.51$	
BaPs from foods other than meat									
0–54‡	41	153 (33)	182 (37)	1.00		357 (36)	316 (33)	1.00	
55–80	67	165 (36)	158 (32)	1.27	(0.82–1.97)	342 (34)	317 (33)	0.95	(0.69–1.32)
81–406	100	139 (31)	152 (31)	1.04	(0.56–1.92)	294 (30)	335 (34)	0.88	(0.58–1.34)
P for trend				$P = 0.99$				$P = 0.37$	
PhIP									
0‡	0	152 (34)	139 (29)	1.00		385 (40)	377 (40)	1.00	
1–14	4	115 (26)	153 (32)	0.58	(0.39–0.87)	290 (30)	299 (32)	0.75	(0.57–0.99)
15–942	58	181 (40)	183 (39)	0.83	(0.57–1.21)	289 (30)	262 (28)	0.92	(0.70–1.22)
P for trend				$P = 0.97$				$P = 0.76$	
MeIQx									
0‡	0	135 (30)	117 (25)	1.00		334 (35)	334 (36)	1.00	
1–11	4	159 (36)	170 (36)	0.78	(0.52–1.15)	335 (35)	324 (34)	0.90	(0.69–1.19)
12–323	25	154 (34)	188 (39)	0.60	(0.40–0.91)	295 (30)	280 (30)	0.94	(0.71–1.25)
P for trend				$P = 0.007$				$P = 0.96$	
Di MeIQx									
0‡	0	208 (46)	212 (45)	1.00		534 (55)	512 (55)	1.00	
1–2	1	152 (34)	141 (30)	1.02	(0.71–1.46)	275 (29)	274 (29)	0.86	(0.66–1.12)
3–40	5	88 (20)	122 (25)	0.59	(0.38–0.91)	155 (16)	152 (16)	0.91	(0.66–1.26)
P for trend				$P = 0.003$				$P = 0.70$	

*Adjusted for age, energy intake, fruit and vegetable intake, and multivitamin supplement use.
†ng per day.
‡Reference category.

TABLE 3. Adjusted* ORs and 95% CIs for Postmenopausal Breast Cancer by Intake of Grilled/Barbecued and Smoked Meats Over the Women's Lifetime (Assessed From Main Questionnaire) Stratified by Fruit and Vegetable Intake

Intake†		Low Fruit and Vegetable Intake				High Fruit and Vegetable Intake			
Range	Median	Cases No. (%)	Controls No. (%)	OR	(95% CI)	Cases No. (%)	Controls No. (%)	OR	(95% CI)
Grilled/barbecued beef, pork and lamb									
Average over lifetime									
0–10‡	2	211 (35)	197 (38)	1.00		136 (37)	173 (41)	1.00	
11–40	24	198 (32)	159 (31)	1.42	(0.98–2.05)	115 (32)	117 (28)	1.37	(0.90–2.08)
41–364	67	202 (33)	159 (31)	1.37	(0.95–1.98)	113 (31)	133 (31)	1.14	(0.75–1.73)
P for trend				$P = 0.24$				$P = 0.66$	
Total over lifetime									
8–537‡	181	160 (28)	154 (32)	1.00		101 (30)	135 (34)	1.00	
540–2197	1343	190 (33)	163 (34)	1.37	(0.95–1.97)	99 (30)	125 (32)	1.05	(0.68–1.60)
2201–17,217	3683	223 (39)	163 (34)	1.48	(1.03–2.13)	133 (40)	134 (34)	1.29	(0.86–1.54)
P for trend				$P = 0.23$				$P = 0.35$	
Smoked ham, pork and lamb									
Average over lifetime									
0–20‡	1	268 (44)	250 (47)	1.00		184 (51)	233 (54)	1.00	
21–52	38	185 (30)	157 (30)	1.54	(1.08–2.18)	102 (28)	109 (26)	1.07	(0.72–1.60)
53–364	98	155 (26)	120 (23)	1.28	(0.87–1.87)	75 (21)	86 (20)	1.04	(0.66–1.64)
P for trend				$P = 0.27$				$P = 0.60$	
Total over lifetime									
10–1010‡	391	138 (29)	125 (31)	1.00		86 (32)	111 (36)	1.00	
1013–2632	1784	160 (33)	145 (35)	1.56	(1.08–2.25)	89 (33)	91 (30)	1.19	(0.77–1.82)
2637–24,253	4400	186 (38)	137 (34)	1.31	(0.91–1.89)	92 (34)	106 (34)	1.04	(0.68–1.60)
P for trend				$P = 0.47$				$P = 0.95$	
Total grilled/barbecued and smoked meats									
Average over lifetime									
0–46‡	19	177 (30)	172 (35)	1.00		101 (29)	145 (36)	1.00	
47–122	80	188 (32)	154 (32)	1.67	(1.15–2.42)	126 (37)	125 (31)	1.27	(0.85–1.92)
123–1092	189	219 (38)	159 (33)	1.56	(1.08–2.26)	116 (34)	132 (33)	1.14	(0.75–1.73)
P for trend				$P = 0.19$				$P = 0.26$	
Total over lifetime									
0–2553‡	1025	170 (29)	178 (36)	1.00		104 (30)	142 (35)	1.00	
2574–6514	4456	192 (32)	162 (32)	1.84	(1.27–2.67)	118 (34)	129 (31)	1.15	(0.76–1.73)
6533–51,652	10,094	232 (39)	159 (32)	1.74	(1.20–2.50)	127 (36)	140 (34)	1.15	(0.76–1.74)
P for trend				$P = 0.07$				$P = 0.23$	
Average over previous decade of life									
0–29‡	8	197 (33)	187 (37)	1.00		120 (34)	159 (39)	1.00	
30–108	64	195 (33)	160 (32)	1.47	(1.02–2.12)	118 (33)	120 (29)	1.44	(0.96–2.18)
109–1092	208	202 (34)	155 (31)	1.35	(0.93–1.97)	117 (33)	130 (32)	1.32	(0.87–2.01)
P for trend				$P = 0.34$				$P = 0.28$	

*Adjusted for age, energy intake, and multivitamin supplement use.
†Average indicates the number of times consumed per year; total indicates the total number of times consumed.
‡Reference category.

women in the first tertiles. Among postmenopausal women, no associations were observed with regard to benzo(α)pyrene and HCA indices.

As shown in Table 3, when the results among postmenopausal women were further stratified by fruit and vegetable intake (as assessed in the FFQ), the increased risk of breast cancer associated with the highest tertile of lifetime consumption of grilled/barbecued and smoked meats was limited to women in the lowest category of fruit and vegetable intake (*P* value for multiplicative interaction = 0.25). The increased risk associated with intake of smoked ham, pork, and lamb was also limited to consumers of low fruit and vegetable diets. No associations between benzo(α)pyrene or HCA intake and breast cancer were observed in either high or low consumers of fruits and vegetables for postmenopausal women (Table 4). There was no evidence for additive inter-

TABLE 4. Adjusted* ORs and 95% CIs for Postmenopausal Breast Cancer by Intake of Polycyclic Aromatic Hydrocarbons and Heterocyclic Amines in the Previous Year (Assessed From FFQ) Stratified by Fruit and Vegetable Intake

Intake†		Low Fruit and Vegetable Intake				High Fruit and Vegetable Intake			
Range	Median	Cases No. (%)	Controls No. (%)	OR	(95% CI)	Cases No. (%)	Controls No. (%)	OR	(95% CI)
Total BaPs from food									
0–56‡	41	316 (53)	279 (53)	1.00		19 (5)	39 (9)	1.00	
57–85	70	222 (37)	184 (35)	1.10	(0.78–1.55)	134 (37)	124 (30)	1.47	(0.73–2.98)
86–309	107	61 (10)	57 (11)	1.10	(0.63–1.93)	211 (58)	255 (61)	1.09	(0.52–2.26)
P for trend				$P = 0.32$				$P = 0.29$	
BaPs from meat									
0‡	0	353 (59)	305 (59)	1.00		214 (59)	247 (59)	1.00	
1–2	1	119 (20)	117 (22)	0.77	(0.53–1.12)	78 (21)	78 (19)	1.30	(0.83–2.03)
3–126	8	127 (21)	98 (19)	1.03	(0.70–1.52)	72 (20)	93 (22)	0.93	(0.60–1.44)
P for trend				$P = 0.59$				$P = 0.55$	
BaPs from foods other than meat									
0–55‡	41	350 (57)	289 (54)	1.00		21 (6)	39 (9)	1.00	
56–81	67	206 (33)	186 (35)	0.88	(0.62–1.25)	132 (35)	126 (29)	1.35	(0.62–2.95)
82–280	101	63 (10)	59 (11)	0.89	(0.50–1.58)	220 (59)	268 (62)	1.03	(0.45–2.31)
P for trend				$P = 0.56$				$P = 0.35$	
PhIP									
0‡	0	231 (39)	192 (37)	1.00		153 (42)	185 (44)	1.00	
1–13	3	181 (30)	181 (35)	0.72	(0.50–1.03)	99 (27)	109 (26)	0.77	(0.50–1.17)
14–839	51	187 (31)	147 (28)	0.93	(0.64–1.34)	112 (31)	124 (30)	0.91	(0.60–1.38)
P for trend				$P = 0.60$				$P = 0.94$	
MeIQx									
0‡	0	201 (34)	166 (32)	1.00		132 (36)	168 (40)	1.00	
1–10	4	204 (34)	201 (39)	0.69	(0.48–1.00)	118 (33)	111 (27)	1.29	(0.84–1.99)
11–247	24	194 (32)	153 (29)	0.90	(0.61–1.33)	114 (31)	139 (33)	0.98	(0.64–1.50)
P for trend				$P = 0.63$				$P = 0.57$	
Di MeIQx									
0‡	0	327 (55)	270 (52)	1.00		206 (56)	242 (58)	1.00	
1–2	1	179 (30)	175 (34)	0.80	(0.57–1.13)	96 (26)	99 (24)	0.94	(0.62–1.42)
3–34	5	93 (15)	75 (14)	0.99	(0.64–1.54)	62 (17)	77 (18)	0.81	(0.50–1.30)
P for trend				$P = 0.81$				$P = 0.36$	

*Adjusted for age, energy intake, and multivitamin supplement use.
†ng per day.
‡Reference category.

action for any of the meat variables with fruit and vegetable intake. Additionally, we examined the interactions shown in Tables 3 and 4 for premenopausal women separately, and found no joint effects between any of the meat intake variables and fruit and vegetable intake (data not shown).

Our large sample size allowed for examination of effects within joint categories of estrogen- and progesterone-receptor status in postmenopausal women. The risk of breast cancer among postmenopausal women consuming high amounts of grilled/barbecued meats over their lifetime was similar for ER+/PR+ and ER−/PR− tumors (data not shown). We found no strong associations for any of the benzo(α)pyrene or HCA intake variables assessed from the FFQ across categories of ER/PR status (data not shown), with the exception of a positive association observed in ER+/PR+ cases (OR = 1.47; CI = 0.99–2.19; *P* for trend = 0.07) in the highest tertile of benzo(α)pyrene from meats intake when compared with those in the lowest tertile. No consistent associations were observed for meat intake variables within ER+/PR− and ER−/PR+ tumors, though the small numbers of cases within these categories limited our power to detect associations within these groups (data not shown).

Analyses stratified by stage of diagnosis (in situ versus invasive) revealed slight differences in effect estimates for lifetime intake variables, although these were inconsistent across different intake variables (data not shown). For example, the increased risk associated with total grilled/barbecued beef, lamb, or pork was slightly higher for in situ cases, compared with invasive cancers, in postmenopausal women (for third tertile compared with the first tertile, the OR for in situ cancer was 1.41 [95% CI = 0.79–2.52] and for invasive cancers it was 1.23 [0.92–1.66]). In contrast, for total smoked

ham, lamb, or pork, the increased risk was higher for invasive cancer (OR = 1.43; CI = 1.01–2.03) than for in situ cases (1.04; 0.53–2.05). No differences in effect estimates between in situ and invasive cancer were observed in the levels of benzo(α)pyrene and HCA intake in the year before interview (data not shown).

DISCUSSION

Using data from a large population-based case-control study, we examined associations of breast cancer risk with lifetime intake of grilled/barbecued and smoked meats, and also with intake of benzo(α)pyrene and HCAs in the previous year. Modest positive associations were found for high lifetime intake of grilled/barbecued and smoked meats in postmenopausal women. These associations were strongest among women with low consumption of fruits and vegetables. The associations did not appear to differ substantially by tumor stage or hormone receptor status.

We found no consistent associations between breast cancer and high dietary intake of HCAs or benzo(α)pyrene in the previous year among pre- or postmenopausal women. Two other studies of recent diet and breast cancer risk found no associations with cooked or processed meat,[14,29] and 2 large prospective studies of up to 18 years of follow-up found no associations between meat intake and breast cancer, although detailed information related to cooking methods and doneness preferences were not collected.[15,16] In contrast, intake of very well-done cooked red meat was associated with increased risk of breast cancer in 1 case-control study,[12] and intake of well-done deep-fried red meat in the previous 5 years was highly associated with increased risk of breast cancer, particularly in women at high body mass indexes in another study.[11]

We found high lifetime intake of grilled/barbecued and smoked meats was associated with increased risk of breast cancer among women consuming few fruits and vegetables. We previously reported an inverse association between fruit and vegetable intake and postmenopausal breast cancer in this population.[27] Experimental studies suggest that chemopreventive constituents of fruits and vegetables, such as isothiocyanates and chlorophyllin, may protect against PAH- and HCA-induced genotoxicity.[17,18] Our results support laboratory findings in animal models that fruits and vegetables may confer some protection against the harmful effects of cooked meat intake.

In animal models, benzo(α)pyrene and HCAs are potent mammary carcinogens. Their mechanism of action is believed to be through direct damage to DNA (formation of DNA adducts).[5] However, more recently, there is evidence from cell culture experiments that 1 HCA (PhIP, but not MeIQx) may be estrogenic.[30] The majority of epidemiologic and animal model evidence supports a causal relationship between estrogen levels and breast cancer risk. Thus, it is surprising that we did not observe increased risk for breast cancer with increasing intake of HCAs, and in particular, PhIP. One possible explanation may be that intake in the year before diagnosis is not representative of a woman's lifetime intake of HCA-related foods. Most cancers are believed to be slow-growing, developing over a lifetime with initiating events occurring possibly as early as adolescence. A few studies have attempted to retrospectively assess adolescent diet and examine associations with breast cancer,[31–34] with few significant findings. One study by Baer et al[35] reported positive associations of intake of total meat, red meat, and hot dogs with risk of proliferative benign breast disease. The numbers of questions relating to diet are usually limited in these studies, and none has attempted to assess meat cooking methods in adolescence or over the lifetime.

Also surprising were the inverse associations between the third tertile of MeIQx and DiMeIQX intake as compared with the first tertiles and breast cancer among premenopausal women. Another study found decreased risk of breast cancer for the highest quartile of PhIP intake as compared with the lowest quartile (which was attenuated after adjustment for chicken intake), and nonsignificant decreased risk for the highest quartiles of MeIQx and DiMeIQx as compared with the lowest quartile in premenopausal and postmenopausal women combined.[10] Chicken is a major contributor to PhIP intake. The authors suggest this may partially explain the inverse associations for PhIP because white meat may help support proper immune function, or may be a surrogate for other healthy lifestyle factors. However, 2 other studies found either no effect of DiMeIQX and MeIQX and an increased risk with PhIP intake in women aged 55–69 years,[8] or increased risks in postmenopausal women with high intakes of MeIQx and PhIP and no associations in premenopausal women.[9] The ranges of estimated HCA intake in these studies were similar to ours. Foods high in MeIQx are pan-fried hamburger, sausage, and steak cooked well-done or very well-done, whereas DiMeIQx has been detected in small quantities in pan-fried very well-done steak and in pan-fried and grilled/barbecued chicken.[4,36] Thus, the inverse associations in premenopausal women in our study are unexplained and may be due to chance.

Using an in-person, interviewer-administered questionnaire, we indirectly assessed dietary intake of PAHs by asking about intake of 4 types of meat prepared either as grilled/barbecued or smoked during each decade of life. Our results based on these measures must be interpreted with care because the lifetime meat intake questionnaire has not been validated. Although the validity of recall of lifetime intake of cooked meats has not been directly addressed in the literature, we can extrapolate from other studies that have attempted to validate long-term recall of dietary intake. These studies have reported modest correlations between dietary assessments at one point in time, and recall of the same diet 11–24 years later (average correlations for food and nutrient intakes ranged from 0.23 to 0.59).[26,37–41] Recall of adolescent diet in adulthood as compared with maternal reporting has also been examined in the Nurses' Health Study II, and moderate correlations were observed (correlations ranged from 0.13 to 0.59).[42] Misclassification of exposure, when the variable is multilevel, may result in bias toward or away from the null. An additional concern is that the accuracy of long-term recall may have differed by case or control status; however, this is unlikely for the following reasons. First, previous validation

studies of long-term recall of diet have not found differential recall between cancer cases and controls.[40,41,43] Second, to assess whether preconceived notions of breast cancer etiology would bias a women's recall of meat intake, we examined the participants' responses to what they believed caused breast cancer. Few women listed meat intake as a causal factor, and among these women there was no case-control difference. Therefore, recall bias is unlikely to have a strong influence on our results.

Given the known measurement error in FFQs, nondifferential misclassification of cooked meat intake variables may be another explanation for our findings of no association between recent intake of benzo(α)pyrene and HCAs and breast cancer. Unlike some studies showing positive associations,[8,12] we did not use color photographs of meat cooked to varying levels of doneness, but instead relied on written descriptions of doneness preference, which may be a less accurate means of collecting these data. Additionally, some meat items that do not have similar HCA or PAH values were grouped together in the food questionnaire. For example, steaks and roasts were grouped in "beef (steaks, roasts, etc., including on sandwiches)." However, the content of HCAs and PAHs in meats is highly dependent on cooking methods, so the fact that we used reported frequency of the cooking methods to assign HCA and PAH values to the meat items should have improved our estimation of intake of these carcinogens over the basic FFQ. We also did not specifically ask cooking methods for bacon and sausage, but instead assigned the reported cooking methods for pork to that of bacon and sausage. As the true cooking methods for these different meat items may vary considerably (eg, pan-frying for bacon and sausage vs. oven-broiling or baking for pork) and the corresponding HCA and benzo(α)pyrene content of bacon is different depending on whether the meat is oven-broiled or pan-fried,[1,3] this assumption may have led to misclassification of exposure.

Due to the lack of validation of methods to assess long-term dietary recall, it is possible that current diet, if correlated with recall of long-term diet, could confound the relationship between lifetime intake and breast cancer.[35] We examined the correlation between intake of grilled/barbecued beef, pork, and lamb from the lifetime intake questionnaire with intake of grilled and barbecued beef and pork on the FFQ. The Spearman correlation coefficient between intake before age 20 and intake in the year before interview was weak ($r = 0.25$), whereas the correlation between intake in the previous decade and intake in the year before interview was stronger ($r = 0.53$). Similar results were found for poultry and fish, and the results did not differ greatly between cases and controls. These correlations support the findings from Baer et al[35] that current diet is not strongly correlated with long-term recall of diet.

Given that we did not collect data on overall lifetime dietary intake (especially lifetime total meat intake irrespective of the cooking methods), we cannot exclude the possibility that our observed results may be due to other potentially correlated dietary factors, such as lifetime total meat intake or lifetime total fat intake, rather than the specific cooking methods of meat that were queried. We examined confounding by all known risk factors for breast cancer. However, there may have been residual confounding by exposures measured with error, such as other dietary intake variables, lifetime physical activity, or alcohol use. It is unlikely, though, that residual confounding could fully account for our findings.

Our study supports a role in postmenopausal breast cancer etiology for lifetime intake, but not more recent intake, of meats cooked in ways that enhance PAH formation, particularly among women consuming few fruits and vegetables. Future investigation into this area in larger studies may provide useful information on the contribution of these dietary exposures to breast cancer etiology.

ACKNOWLEDGMENTS

For their valuable contributions to the Long Island Breast Cancer Study Project, the authors thank: members of the Long Island Breast Cancer Network; the 31 participating institutions on Long Island and in New York City, NY; our National Institutes of Health collaborators, Gwen Collman, National Institutes of Environmental Health Sciences; G. Iris Obrams, formerly of the National Cancer Institute; members of the External Advisory Committee to the population-based case-control study: Leslie Bernstein, (Committee chair) Gerald Akland, Barbara Balaban, Blake Cady, Dale Sandler, Roy Shore, and Gerald Wogan, as well as other collaborators who assisted with various aspects of our data collection efforts including Steve Stellman, Maureen Hatch, Mary Wolff, Geoff Kabat, Gail Garbowski, H. Leon Bradlow, Martin Trent, Ruby Senie, Carla Maffeo, Pat Montalvan, Gertrud Berkowitz, Margaret Kemeny, Mark Citron, Freya Schnabel, Allen Schuss, Steven Hajdu, and Vincent Vinciguerra.

REFERENCES

1. Kazerouni N, Sinha R, Hsu CH, et al. Analysis of 200 food items for benzo[*a*]pyrene and estimation of its intake in an epidemiologic study. *Food Chem Toxicol*. 2001;39:423–436.
2. Knize MG, Salmon CP, Pais P, et al. Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. *Adv Exp Med Biol*. 1999;459:179–193.
3. Sinha R, Knize MG, Salmon CP, et al. Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. *Food Chem Toxicol*. 1998;36:289–297.
4. Sinha R, Rothman N, Salmon CP, et al. Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem Toxicol*. 1998;36:279–287.
5. Snyderwine EG, Venugopal M, Yu M. Mammary gland carcinogenesis by food-derived heterocyclic amines and studies on the mechanisms of carcinogenesis of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). *Mutat Res*. 2002;506/507:145–152.
6. el-Bayoumy K, Chae YH, Upadhyaya P, et al. Comparative tumorigenicity of benzo[a]pyrene, 1-nitropyrene and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine administered by gavage to female CD rats. *Carcinogenesis*. 1995;16:431–434.
7. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen*. 2004;44:44–55.
8. Sinha R, Gustafson DR, Kulldorff M, et al. 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, a carcinogen in high-temperature-cooked meat, and breast cancer risk. *J Natl Cancer Inst*. 2000;92:1352–1354.
9. De Stefani E, Ronco A, Mendilaharsu M, et al. Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. *Cancer Epidemiol Biomarkers Prev*. 1997;6:573–581.

10. Delfino RJ, Sinha R, Smith C, et al. Breast cancer, heterocyclic aromatic amines from meat and *N*-acetyltransferase 2 genotype. *Carcinogenesis*. 2000;21:607–615.
11. Dai Q, Shu XO, Jin F, et al. Consumption of animal foods, cooking methods, and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2002;11:801–808.
12. Zheng W, Gustafson DR, Sinha R, et al. Well-done meat intake and the risk of breast cancer. *J Natl Cancer Inst*. 1998;90:1724–1729.
13. Hermann S, Linseisen J, Chang-Claude J. Nutrition and breast cancer risk by age 50: a population-based case-control study in Germany. *Nutr Cancer*. 2002;44:23–34.
14. Gertig DM, Hankinson SE, Hough H, et al. *N*-acetyl transferase 2 genotypes, meat intake and breast cancer risk. *Int J Cancer*. 1999;80: 13–17.
15. Missmer SA, Smith-Warner SA, Spiegelman D, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. *Int J Epidemiol*. 2002;31:78–85.
16. Holmes MD, Colditz GA, Hunter DJ, et al. Meat, fish and egg intake and risk of breast cancer. *Int J Cancer*. 2003;104:221–227.
17. Dingley KH, Ubick EA, Chiarappa-Zucca ML, et al. Effect of dietary constituents with chemopreventive potential on adduct formation of a low dose of the heterocyclic amines PhIP and IQ and phase II hepatic enzymes. *Nutr Cancer*. 2003;46:212–221.
18. Conaway CC, Wang CX, Pittman B, et al. Phenethyl isothiocyanate and sulforaphane and their *N*-acetylcysteine conjugates inhibit malignant progression of lung adenomas induced by tobacco carcinogens in A/J mice. *Cancer Res*. 2005;65:8548–8557.
19. Gammon MD, Neugut AI, Santella RM, et al. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res Treat*. 2002;74:235–254.
20. Gammon MD, Santella RM, Neugut AI, et al. Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. *Cancer Epidemiol Biomarkers Prev*. 2002;11:677–685.
21. Selvin S. *Statistical Analysis of Epidemiologic Data*. New York: Oxford University Press; 1996.
22. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. 1986;124:453–469.
23. Potischman N, Swanson CA, Coates RJ, et al. Intake of food groups and associated micronutrients in relation to risk of early-stage breast cancer. *Int J Cancer*. 1999;82:315–321.
24. HHHQ-DietSys Analysis Software, version. 3. 0. Bethesda, MD: National Cancer Institute; 1999.
25. Sinha R, Rothman N. Exposure assessment of heterocyclic amines (HCAs) in epidemiologic studies. *Mutat Res*. 1997;376:195–202.
26. Bakkum A, Bloemberg B, van Staveren WA, et al. The relative validity of a retrospective estimate of food consumption based on a current dietary history and a food frequency list. *Nutr Cancer*. 1988;11:41–53.
27. Gaudet MM, Britton JA, Kabat GC, et al. Fruits, vegetables, and micronutrients in relation to breast cancer modified by menopause and hormone receptor status. *Cancer Epidemiol Biomarkers Prev*. 2004;13: 1485–1494.
28. Ambrosone CB, McCann SE, Freudenheim JL, et al. Breast cancer risk in premenopausal women is inversely associated with consumption of broccoli, a source of isothiocyanates, but is not modified by GST genotype. *J Nutr*. 2004;134:1134–1138.
29. Ambrosone CB, Freudenheim JL, Sinha R, et al. Breast cancer risk, meat consumption and *N*-acetyltransferase (NAT2) genetic polymorphisms. *Int J Cancer*. 1998;75:825–830.
30. Lauber SN, Ali S, Gooderham NJ. The cooked food derived carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine is a potent oestrogen: a mechanistic basis for its tissue-specific carcinogenicity. *Carcinogenesis*. 2004;25:2509–2517.
31. Hislop TG, Coldman AJ, Elwood JM, et al. Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev*. 1986;9:47–58.
32. Pryor M, Slattery ML, Robison LM, et al. Adolescent diet and breast cancer in Utah. *Cancer Res*. 1989;49:2161–2167.
33. Potischman N, Weiss HA, Swanson CA, et al. Diet during adolescence and risk of breast cancer among young women. *J Natl Cancer Inst*. 1998;90:226–233.
34. Frazier AL, Ryan CT, Rockett H, et al. Adolescent diet and risk of breast cancer. *Breast Cancer Res*. 2003;5:R59–R64.
35. Baer HJ, Schnitt SJ, Connolly JL, et al. Adolescent diet and incidence of proliferative benign breast disease. *Cancer Epidemiol Biomarkers Prev*. 2003;12:1159–1167.
36. Sinha R, Rothman N, Brown ED, et al. High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo- [4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. *Cancer Res*. 1995;55:4516–4519.
37. Wu ML, Whittemore AS, Jung DL. Errors in reported dietary intakes. II. Long-term recall. *Am J Epidemiol*. 1988;128:1137–1145.
38. Lindsted KD, Kuzma JW. Long-term (24-year) recall reliability in cancer cases and controls using a 21-item food frequency questionnaire. *Nutr Cancer*. 1989;12:135–149.
39. Sobell J, Block G, Koslowe P, et al. Validation of a retrospective questionnaire assessing diet 10–15 years ago. *Am J Epidemiol*. 1989; 130:173–187.
40. Byers TE, Rosenthal RI, Marshall JR, et al. Dietary history from the distant past: a methodological study. *Nutr Cancer*. 1983;5:69–77.
41. Jensen OM, Wahrendorf J, Rosenqvist A, et al. The reliability of questionnaire-derived historical dietary information and temporal stability of food habits in individuals. *Am J Epidemiol*. 1984;120:281–290.
42. Maruti SS, Feskanich D, Colditz GA, et al. Adult recall of adolescent diet: reproducibility and comparison with maternal reporting. *Am J Epidemiol*. 2005;161:89–97.
43. Friedenreich CM, Slimani N, Riboli E. Measurement of past diet: review of previous and proposed methods. *Epidemiol Rev*. 1992;14:177–196.